Chapter 4. Clinical science and care incorporating the development of a European Platform for Clinical Research in Diabetes (EPCRD)

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Section A. Introduction

Clinical science and care of diabetes presents a major challenge for strategic mapping. The strategy must take into account *all* aspects of research into the care of people with diabetes mellitus, and it must include a multiprofessional dimension. Within DIAMAP the research Goals for clinical science and care are extensions of the Goals and priorities of other groups in the project and the translation of these into improving the lives of people with diabetes. The possible 'menu' of clinical and clinical science topics is huge. The group deliberately prioritised a number of areas (and omitted others) with the aim of focussing attention on options that could truly alter the delivery and quality of care for people with diabetes throughout their lives. The fragmentation of care, the inequality of access to care throughout Europe as a whole and the vulnerability of many special groups, due to geography, age or ethnicity, are major themes. Hypoglycaemia is prioritised as it remains a major fear of patients, a source of morbidity and mortality and an obstacle to metabolic control. Another major focus is paediatric diabetes, presented in a new context of disease staging and the start of the life-course. All aspects of diabetes in women of reproductive age are highlighted, again in the context of lifelong care, and the implications for both mother and child and the progression of health risks in the offspring in later life. Mental health is prioritised as is quality of life with diabetes care. Ageing itself is highlighted, with the increasing insight that diabetes is itself a disease of early ageing. There is also a focus on treatments for severe or morbid obesity, in recognition both of the stark implications of the modern obesity pandemic for the prevalence of insulin-resistant type 2 diabetes, and the rapid progress in the field of bariatric surgery, where much more research is needed to define risks, benefits and costs to patients and society.

While the major diabetes trials of the past two decades have changed clinical practice, many questions remain unanswered and new questions have arisen. The epidemiology of diabetes has continued to evolve rapidly, with marked increases in prevalence especially in Asia, and in ethnic sub-populations in Europe. A recurring theme is the impact of diabetes on vulnerable sub-groups This problem is growing as a result of factors such as immigration and increased longevity.

Defining treatment targets more directly according to the specifics of the patient, including disease phase (see also 'staging' of disease in children), life-phase (age) and the presence or absence of complications is a natural extension of the findings of the recent tight control studies, such as Action to Control Cardiovascular Risk in Diabetes (ACCORD), where more aggressive metabolic approaches in older, more complex patients led to some increase in adverse events. Hypoglycaemia remains one of the most important limitations to quality of life for people with diabetes and a key adverse outcome of treatment, in both type 1 (where it is much more frequent) and type 2 diabetes (where it is less frequent, but potentially more dangerous in patients with underlying complications). Greater understanding and development of new technologies including insulin pumps and glucose sensors, as well as the educational approaches (including the incorporation of telehealth) needed to make these treatments effective and the cost implications are cornerstones for diabetes research. A range of clinical research programmes could result from the topics emerging from this area of study.

The wide variability in the actual care provided to patients with diabetes across the continent of Europe is acknowledged within this road map. Vulnerable sub-groups exist in all countries and regions; however, *overall* access to education, care and specific therapies also depends on geographic location. Health records should be addressed, as well as variability in the itinerary of care (from primary care to specialist and back) in different countries and regions. This research approach is

novel when applied across Europe but would lead to important insights into the unequal and excess mortality and morbidity associated with diabetes in certain regions and sub-populations. Integrating the itinerary of care across Europe would help to address the challenge presented by gestational diabetes and type 2 diabetes in women, along with the devastating consequences in future generations of children.

Children with diabetes are a vulnerable group, and paediatric diabetes research has struggled to advance, partly because of fragmentation of the specialty and the small numbers of patients per clinic. A new challenge is the appearance and rapid increase in type 2 diabetes in obese children and adolescents. This is addressed by DIAMAP in discussing the paediatric research strategy in terms of *staging* of diabetes in relation to age, duration of disease, reserve of beta cell insulin secretion, and presence of complications and/or co-morbidities. This approach encompasses the accelerated prevalence of both type 1 and type 2 diabetes in children and adolescents, and provides a platform for research in all variants of childhood diabetes. An additional priority is the somewhat neglected field of transition of care between paediatric care and adult diabetes care. This a key phase during the life of a young person with diabetes, where the patient often gets 'lost' in the gap between two very different types of clinical service. Much more research and attention is needed to improve this period of the life of young patients.

Conversely, the European population in general is ageing, and incidence of diabetes increases rapidly with advancing years. This will have an increasingly negative impact upon society and the economy if not addressed now. Ageing itself is a research theme in its own right, and is especially relevant to diabetes research, since diabetes often causes acceleration of ageing, particularly in vascular tissues.

There is potential to markedly reduce costs of care and to improve the quality of life for patients in long-term institutional care if an integrated research approach is taken. There is an overwhelming need for diabetes registries, for improved information systems and for integration and standardisation. The resistance to large-scale clinical research in the traditional clinical setting hinders any progress in the area.

Inexorable decline in beta cell insulin secretion is the key parameter leading to progression of all forms of diabetes, although the techniques for measuring this process in human beings have been inadequate and remain at best rather inexact. Mathematical modelling has played an important role in clinical research in this area over the past 30 years. Better test algorithms that can be conducted at the bedside to calculate islet cell mass and function, along with the use of mathematical methods to integrate islet-related metrics in the context of multiple other variables, such as insulin sensitivity, and hepatic and renal function, remain important research goals that would support clinical science and care in diabetes.

Taken as a whole, the Clinical Science and Care sub-group sought not only to draw together these diverse research pathways but also examine them in the context of the quality of life of the patient, along with an analysis of societal and economic benefit. Such a strategy could be undertaken on a large European scale if a European Platform for Clinical Research in Diabetes (EPCRD, *see* Goal 4.1) could be created and supported by the European research institutions. Many clinical research questions can *only* be answered with a broad trans-national approach.

Section B. Scientific advances and major challenges

This is an outline of the main scientific advances over the past decades that may serve as platforms for research maps for the future. These are grouped under six main thematic areas:

Diabetes Care

- Education: the development of structured educational approaches for patients with diabetes, such as Dose Adjustment for Normal Eating (DAFNE), Diabetes Education and Self-Management for Ongoing and Newly Diagnosed (DESMOND). This is still an area under development and includes the field of age-appropriate education for vulnerable sub-groups such as children, pregnant women, and patients with disability. This field is in fact in its infancy, and much more research will be required to develop educational tools and systems that 'fit' the lives of real people across the huge spectrum of ages, ethnicity, and cultural and dietary traditions.
- Settings of care: the development of integrated care systems for people with diabetes, between specialists and primary care physicians.
- Multidisciplinary and multi-target oriented care of diabetes, as demonstrated in the Steno studies for type 2 diabetes and in the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes.
- Quality of Life: newer methods to evaluate the effects of diabetes, its complications and its treatment on quality of life. Patient-oriented outcomes that matter (POEMS).
- Diabetes registries: developed in various regions, with multiple benefits for care, but not yet in widespread use nationally or internationally.

Diabetes Control and Complications

- The DCCT and the Epidemiology of Diabetes Interventions and Complications Study (EDIC) in type 1 diabetes. The original landmark DCCT study proved that intensive glycaemic control reduced microvascular complications of diabetes. The EDIC follow-up of this cohort proved the extended benefit of intensive control over time to reduce macrovascular complications.
- UK Prospective Diabetes Study (UKPDS) and follow-up studies in type 2 diabetes. This landmark study proved the benefit of glycaemic and blood pressure control in patients with type 2 diabetes. UKPDS also posed the challenge of solving the problem of macrovascular disease prevention in type 2 diabetes, which is clearly more complicated than glucose control alone.
- Studies of lipid lowering: the Heart Protection Study and the Collaborative Atorvastatin Diabetes Study (CARDS), among others, provided clear evidence for the substantial benefit of statins in low-density lipoprotein lowering in type 2 diabetes. Less clear has been the question of fibrates and the question of triglycerides/HDL manipulation in preventing complications.
- Multi-target tight control studies in type 2 diabetes, including the cluster of Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) studies, all reporting during the same period. These studies posed the dilemma of possible harm of over-tight glycaemic control (particularly with insulin) in older subjects with cardiovascular disease.
- Recent evidence indicates that some categories of patients may not benefit from a tight glycaemic approach, and may be safer when treated to less rigorous glucose targets. More research is required to understand how these targets should be adjusted to take account of age, prior cardiovascular complications and other factors that may influence this treatment approach.
- Endpoint studies of new drugs: including A Diabetes Outcome Progression Trial (ADOPT), Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE). More studies of this type are needed to provide knowledge about the medium- to long-term effects of new therapies on disease progression and disease complications as well as quality of life.
- Longer term studies of insulin therapies: such as the recent 4T study, formally comparing three insulin regimes over 3 years in type 2 diabetes.
- Trials of therapies to treat blood pressure and prevent nephropathy: starting with the landmark study of angiotensin-converting enzyme inhibition by Lewis in 1993, there have been a large number of these studies, many including sub-groups with diabetes and some specifically studying only patients with diabetes.

Diabetes in special sub-populations

- Pregnancy and gestational diabetes mellitus (GDM): including the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study, the Australian Carbohydrate Intolerance Study

in Pregnant Women (ACHOIS) study, the Confidential Enquiry into Maternal and Child Health (CEMACH) Report, Metformin in Gestational Diabetes (MiG) trial and the Glyburide Trial.
- Paediatrics: including European Collaborative Paediatric Groups [Better control in Pediatric and Adolescent diabetes: working to create Centres of Reference (SWEET); Pedpumps, Hvidore-Group], studies by the International Society for Paediatrics and Adolescent Diabetes (ISPAD).
- Morbidly obese patients: The new and growing field of bariatric surgery for the treatment of type 2 diabetes.

Diabetes and novel technologies
- Insulin pump therapy: pumps have evolved rapidly since 1980, becoming much smaller and with more sophisticated software and hardware.
- Glucose sensors and continuous glucose monitoring (CGM) devices: sensors have improved but remain a niche area and are not widely available to patients. Non-invasive sensors are still under development.
- The connection of CGM with continuous subcutaneous insulin infusion (CSII) by a mathematical algorithm to form an 'artificial pancreas' is an ultimate goal of diabetes research. Meanwhile, progress towards a commercially available closed-loop system has moved forward recently in three areas:
  - technologies to 'shut-off' the insulin infusion as hypoglycaemia develops
  - hybrid systems incorporating pre-meal boluses with a closed-loop system to reduce daytime glucose variability and
  - a closed-loop system with enhanced algorithms to reduce glucose variability and the risk of hypoglycaemia overnight.
- Stem cell technologies and transplantation: islet transplantation had been the main hope in this field (with the aim of curing type 1 diabetes). The Edmonton protocol for islet transplantation and immunosuppression showed very promising initial results, but long-term clinical results beyond 5 years have been disappointing. Ultimately, demand for islet transplantation far exceeds supply. Two to three whole pancreases are required to treat one patient, and for example only 6,000 pancreases are donated annually in the whole United States. Stem cell technology holds promise for the treatment of type 1 diabetes, but many obstacles remain, including questions around immunosuppression, regulation of the transplanted cells' secretory functions and the danger of cancer.
- Laboratory standardisation: the standardisation of HbA1c (and many other assays such as insulin, lipids) and the development of alternative metrics of ongoing metabolic control, such as average blood glucose, are key new developments that will change diabetes care in the next decade.
- The field of mathematical modelling in the physiology and pathophysiology of diabetes has been pioneered in the last 30 years. This is now an established research area with the potential to greatly improve the accuracy and convenience of phenotyping patients in terms of insulin secretion and action, and to support the newer technologies including all of those listed above.

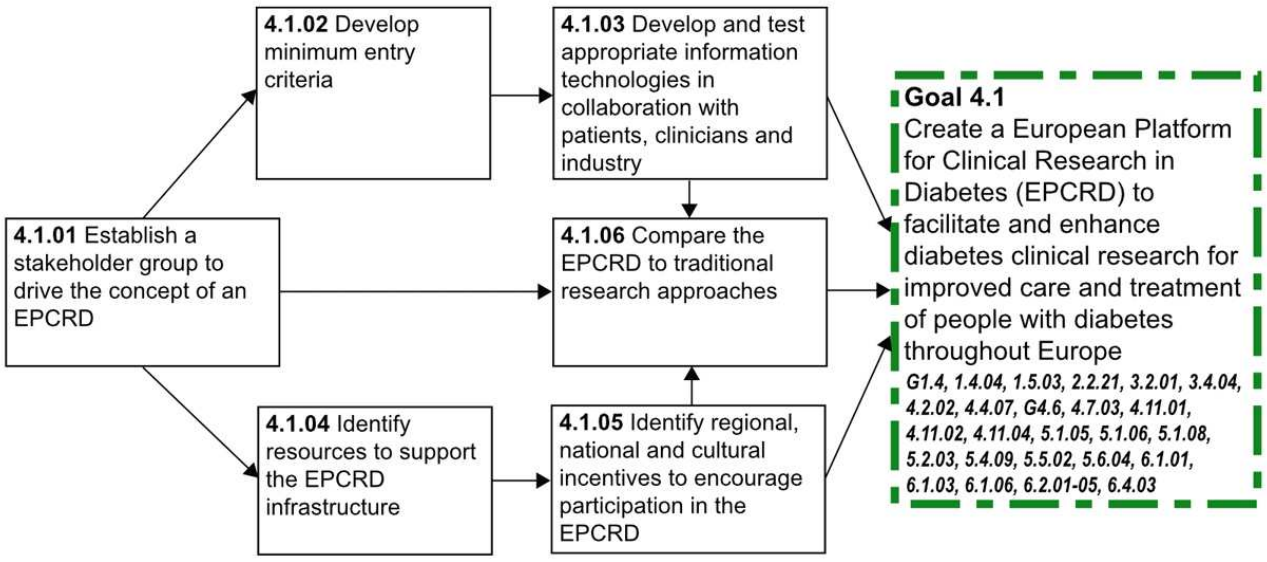
Whole-body physiology in patients with diabetes
- The development of 'gold standard' methods to measure insulin action (the hyperinsulinaemic clamp technique), insulin secretion (the hyperglycaemic clamp and several other methods) and other parameters of whole body metabolism are landmark advances in the past 30 years. The challenge now is to translate these research approaches to newer, more convenient and patient-friendly methods to study whole body metabolism in larger numbers of patients to support the aim of individualising therapy.

Prevention of diabetes
- Type 2 diabetes has been shown to be preventable in several large studies, particularly the landmark Finnish Diabetes Prevention Study and the National Institutes of Health Diabetes Prevention Program (NIH DPP).
- Many obesity intervention studies (lifestyle and drug therapies) by their design constitute diabetes prevention studies.
- Major epidemiological studies, such as Diabetes Epidemiology: Collaborative analysis of Diagnostic Criteria in Europe (DECODE), have delineated and more precisely defined the 'prediabetes' population(s) and have laid the foundations for future prevention studies. This field has also developed methods for the estimation of risk of developing diabetes (for example, the FINDRISK score), which may ultimately replace blood testing for initial screening at a population level.
- Type 1 diabetes prevention remains elusive; while there have been a number of negative trials, several newer approaches are under study.

Section C. Road map reports

Links between Goals and Milestones in the DIAMAP report are noted within the text and also in the diagrams in *italics*. Roadblocks are listed below the diagrams and described at the end of the chapter and shown in red circles. Goals and Milestones considered a priority are indicated with a broken green line.

Goal 4.1 Create a European Platform for Clinical Research in Diabetes (EPCRD) to facilitate and enhance diabetes clinical research for improved care and treatment of people with diabetes throughout Europe



Roadblock 1. Ethical guidelines: in particular regarding data sharing and transfer, collection and use of biological materials including DNA

Roadblock 2. Variation, lack of standardisation or international consensus across Europe in laboratory conditions, measurement techniques, sample handling and clinical diagnoses and practice

Introduction and background

Within the European Union there are increasing numbers of adults and children with diabetes. Despite guidelines and consensus statements related to approaches, targets and therapies, across Europe there remains huge variation in the quantity and quality of diabetes-related clinical research and health care available for people with diabetes. This variability in research activity and service delivery is a consequence of many factors, the most significant being the social and cultural differences among countries, differences in clinical governance, and lack of structured networks of interested parties with commonly agreed goals.

Aims and objectives

The aims of the European Platform for Clinical Research in Diabetes (EPCRD) are to:

- Facilitate and enhance clinical diabetes research with the purpose of improving care and treatment for people with diabetes.
- Facilitate access to data and biological samples by providing a uniform agreed and ethically approved infrastructure to permit sample and data sharing across multiple national and international security barriers.
- Improve access to structured education and training for European diabetes researchers and healthcare professionals engaging in research activity, and for people living with diabetes.
- Create centrally determined governance structures in line with current ethical guidelines.
- Facilitate access to information and online databases of clinical studies and trials, thus encouraging participation by interested volunteers (with diabetes and without). The closer dialogue between professionals and research participants is intended to encourage greater understanding of the science.
- Streamline the processes for dissemination of research findings through a dedicated communication channel including a

consultation process with people with diabetes and the public.
- Encourage investment by and participation of industry, facilitating access to a large number of research subjects and to scientists from sub-specialties. Funding of industry-initiated trials could be standardised across Europe supporting the concept of the 'European diabetes patient'. The use of such a market approach to clinical research has the potential to drive down costs to increase the competitiveness of Europe as a clinical trial location.

Advantages of an EPCRD
A large population of people with diabetes with variations in genetic and ethnic background (and family members) could be made accessible to clinical (and basic) researchers and the sponsors of research by participation in a network with a centralised point of entry. The DIAMAP road maps have repeatedly mentioned as roadblocks the need for registries of people with diabetes, networks of specialist researchers, access to biobanks and human biological material (especially in relation to the rarer complications) and the need for more standardised evidence-based treatment guidelines. The majority of roadblocks are addressed within the Horizontal Issues report by engaging with organisations or individuals external to the research community. However, it was felt strongly that diabetes research would be enhanced if the clinical research community itself could drive a collaborative initiative as it deals with the consequences of research upon treatment and care delivery (this Goal is linked with many Goals and Milestones throughout the road maps).

European clinical research has limitations compared with the United States in that access to large numbers of people with diabetes and healthy volunteers with specific characteristics in single centres is difficult. Clinical research, from small studies to large-scale pharmaceutical trials, or research into health service provision is more laborious and less representative than it could be because of the number of countries, languages and organisational cultures. The EPCRD would facilitate research in such situations.

Limitations of an EPCRD
The roadblocks list the limitations of an EPCRD, mainly concerning privacy of data and difficulties of data and sample transfer across borders. Also, participation is likely to vary in different countries, which may cause a cultural imbalance. The establishment of an EPCRD should ideally be piloted in a small number of locations, with operations directed from a central office, before any wider scale network could be envisaged.

Characteristics and essential functions of an EPCRD
There are many existing networks and study groups that are investigator-led, focussed upon specific research areas and funded by individual membership, research grants or the pharmaceutical industry. Such networks have developed a way of exchanging, learning and sharing of research ideas and best practices across Europe. Often these networks disperse when the grant comes to an end. This proposal is to access these networks and experience and to develop a more extensive and all-encompassing network with a central point of organisation.

The concept of a European Platform for Clinical Research in Diabetes (EPCRD) is based on the understanding that people living with diabetes and their families will find it relatively easy to understand its value to improve diabetes care. The support of the European population is essential and offers a significant opportunity for transparency in determining how diabetes research budgets are spent. The key to the success of the EPCRD is the role and consent of the individual person with diabetes. Modern technology has revolutionised the access to all sources of information for individuals, across all traditional borders of language and to some extent culture and education. Individual patients and their representative organisations will provide the impetus and drive to develop the EPCRD, once the network is initiated.

The following are necessary for the EPCRD to operate, and would need to be established before and during the EPCRD road map development.
- A central physical secretariat from which the administration, finance and communications could be directed with a central office staff.
- A legal basis would need to be established to facilitate operations; however, to contain initial costs the secretariat could be shared with another diabetes organisation. It is envisaged that much of the work could be carried out in a 'virtual' environment by staff situated remote from the physical secretariat.
- A management structure comprising a Scientific Board with decision-making strategy for research (as opposed to administrative) issues would provide guidance for ethics, consent, security and other governance issues concerning data and biological material collection and storage, location and use of biobanks (when established), professional training and education, and structure to manage telehealth initiatives

- The Scientific Board would direct proposals for research funding.
- Other diabetes organisations that have created networks would be engaged in dialogue such as JDRFI, to exchange expertise and appreciation of potential roadblocks.
- Criteria for involvement of the research and health care professionals, research locations such as hospitals and general practices, along with voluntary entry by patients and research volunteers would be decided by the Scientific Board.

Milestone 4.1.01. Establish a stakeholder group to drive the concept of an EPCRD
The EPCRD could not function without core stakeholder involvement and investment of time, expertise and funding. A core group is necessary for initial contacts and leading the discussions to initiate the enterprise. Engagement from the beginning would be with patient organisations [for example through the International Diabetes Federation (IDF-Europe)] as participation will be voluntary and such organisations have good connections across Europe.

Representatives from the diabetes scientific and clinical communities, patient groups, pharmaceutical and biotechnology industries, and also individuals with a background in the media would be approached as the success of research initiatives is dependent upon dissemination and translation of the findings into the relevant clinical areas. National based groups would be created eventually to liaise with the central office.

Milestone 4.1.02. Develop minimum entry criteria
Entry criteria would be determined for individual researchers, hospitals or general practices to become a part of the collaboration and to publicise the network, collect and record the data of patients willing to participate.

Governance structures would be developed to cover all aspects of clinical trials from developing the hypotheses, creating the protocols, developing standardised operating procedures, securing funding and ethics approval, the running of studies and dissemination of the findings.

Milestone 4.1.03. Develop and test appropriate information technologies in collaboration with patients, clinicians and industry
The EPCRD is based on the concept that much of the data would be handled by a 'virtual' research unit that would require collaboration between researchers and clinicians, people living with diabetes, and industry. It is likely that there would be a role for qualitative researchers in enhancing this aspect of the project.

As it is envisaged to connect experts in particular fields in many different locations, this would provide the ideal opportunity to develop audiovisual media (telehealth) in teaching, especially of research techniques, consultation and sharing of best practice.

An additional potential benefit of this approach would be a database that would allow a much greater understanding of the impact of (for example) introducing new therapies into the diabetes community. It may be possible for people with diabetes to report back the impact (or otherwise) of a new therapy on surrogate (e.g. HbA1c), personal (i.e. socio-economic), or clinical (rates of complications) outcomes. This information would be invaluable for health economic and health commissioning considerations.

Regular dialogue could be established between the EPCRD and the bodies governing testing and licensing of medicines within Europe such as the European Medicines Agency and other bodies such as the European Forum for Good Clinical Practice.

Milestone 4.1.04. Identify resources to support the EPCRD infrastructure
There are already tested and functioning models of academic and industry (also looking beyond the pharmaceutical industry) partnerships to support research as well as patient organisations. Such partnerships could be fostered within the EPCRD to support research and to develop new ideas. If a synergy between academia and industry could be created this would resolve many of the roadblocks identified within the DIAMAP road maps. Developing new funding streams and methods of financial support is important, in part because funding is finite and is already stretched between competing organisations and projects.

Milestone 4.1.05. Identify regional, national and cultural incentives to encourage participation in the EPCRD
There appears to be significant variation in the delivery of diabetes care across Europe. The EPCRD would allow for comparisons to be made between different methods of healthcare delivery using quantitative and qualitative methods, which would allow for national considerations.

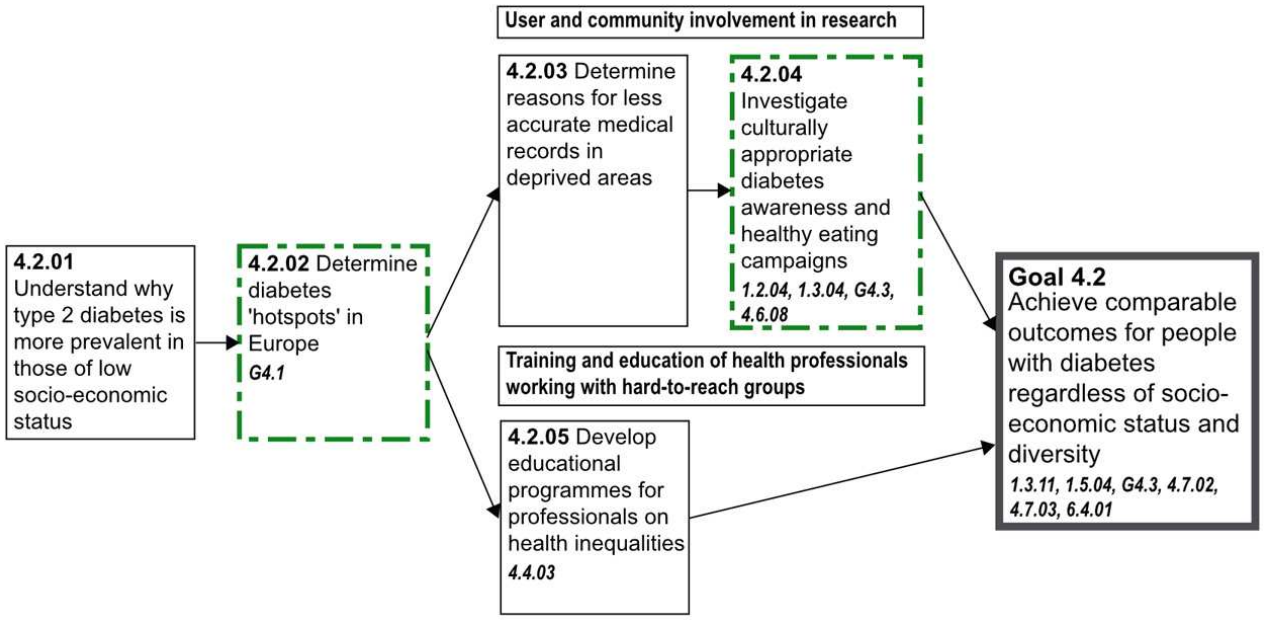
Developing a network of people with diabetes would be extremely attractive to those countries that do not have access to registries, and would

offer those countries that do have registries the possibility to augment the data and to access, for example, information on rare conditions.

Milestone 4.1.06. Compare the EPCRD to traditional research approaches

The EPCRD should be continuously evaluated to ensure that it remains true to its original aims and that it compares well with more traditional methods of locating research subjects and managing research administration. It must be emphasised that it is not proposed that the EPCRD should take over research that would otherwise be carried out at the national level. It must provide added value with evidence that the approach is cost-effective, that people with diabetes support the EPCRD and that positive aspects of national delivery of diabetes healthcare are enhanced.

Goal 4.2. Achieve comparable outcomes for people with diabetes regardless of socio-economic status and diversity



Roadblock 3. Practical and ethical challenges of locating research participants among diverse groups

Introduction and background

There are now many European studies indicating links between prevalence of diabetes and socio-economic status, with lower income groups being disproportionately affected by type 2 diabetes. These lower income groups are also likely to have high immigration populations e.g. the Marolles area of Brussels. They are also likely to have a higher incidence of obesity (of which type 2 diabetes is a consequence). Deprived populations such as these are also less likely to be well educated, less likely to take up the health services available, and appear to be less likely to even locate those services. Many deprived populations may also be older adults with restricted incomes, mobility and social standing. It has been noted with regards to diabetes management that such populations are less likely to have accurate medical records documenting HbA1c, cholesterol and smoking status although the reasons for this disparity with higher income groups are not clear. Deprived populations also tend to have more micro- and macrovascular disease – especially retinopathy and cardiovascular disease – and many present with higher HbA1c levels than national averages.

Many European countries are experiencing economic and budgetary constraints with higher unemployment in the face of an economic burden of care for diabetes and its complications that is likely to rise substantially. This has been recognised recently by the World Health Organization (WHO) that has indicated the growing negative impact of chronic diseases, such as diabetes, in terms of national social and economic wealth.

The importance of addressing such problems early, before expensive complications drain health services and affect European productivity, is crucial. It is also noted that research approaches likely to succeed in tackling these issues are those that involve all major agencies and, most importantly the targeted populations, through a focussed public and patient involvement strategy (*see also* Milestones 1.3.11, 1.5.04, 4.7.02, 4.7.03, 6.4.01 and Goal 4.3).

Milestone 4.2.01. Understand why type 2 diabetes is more prevalent in those of low socio-economic status

The higher incidence of diabetes in deprived populations is likely to be multifactorial including: age; belonging to an immigrant or ethnic sub-group; being in a lower socio-economic group; being obese; having limited education. If comparable incidence and prevalence of diabetes among all social groups is to be achieved these sub-groups should be the target for specific research.

Milestone 4.2.02. Determine diabetes 'hotspots' in Europe
In the first instance, areas in Europe where incidence of diabetes is higher than the European average should be determined so that research can be targeted to areas of most need. This can be achieved by developing an international diabetes registry situated at the point of health service provision that can capture demographic information, such as socio-economic status, ethnicity and age and which could feed into a European research database. Such a database would require very detailed consent, encryption and security features and could best be managed by the EPCRD (*see also* Goal 4.1).

Track 1. User and community involvement in research

Milestone 4.2.03. Determine reasons for less accurate medical records in deprived areas
Comparative research is required to determine why medical records in socially deprived areas are not as complete as those in more affluent regions. Qualitative data should be collected from people with diabetes on their health services experience. It would be important to follow the 'diabetes treatment pathway and patient journey' for the medical records and personal histories of patients so that disparities can be viewed from their perspective. Such a qualitative research programme would ideally include comparison of regional and institutional resources. Deprived populations at higher risk of developing type 2 diabetes may benefit from screening programmes for the condition and other health promotion campaigns and preventative strategies.

Milestone 4.2.04 Investigate culturally appropriate diabetes awareness and healthy eating campaigns
Cultural approaches: Health awareness programmes, especially in terms of weight management must be researched first to ensure they are culturally appropriate, and engage those at risk in how they should be conducted. For example, in certain religions, physical exercise can only be taken with same-sex attendees. Such research strategies need to be multi-agency and engage local community leaders and groups if they are to be effective. A good example is a programme of exercise for overweight women through Bangladeshi folk dancing. Research also needs to focus on culturally specific training for health professionals involved in diabetes management of ethnic minority groups. For example, in the past health professionals in the UK have denied the importance of Ramadan and instructed people with diabetes to ignore their religious beliefs and not to fast during this period. Recent research has indicated that people will put their religion before guidance from the physician and the assumption that people will fast has initiated a number of protocols that advise people how to do so effectively with diabetes (*see also* Milestones 1.3.04, 4.6.08 and Goal 4.3).

Role of local authorities and planners: A very broad research perspective towards improving health for such communities should be adopted. For example if physical activity is difficult due to lack of local facilities then health promotion campaigns need to engage more readily with town planners and local government to collaborate with other stakeholders to provide a safe appropriate environment. A research project that proposes to increase the use of bicycles for transport and pleasure needs local agencies to agree to make cycle lanes that are safe and therefore likely to be used. Research strategies that aim to improve the health of deprived populations, must adopt a culturally sensitive, multi-agency inclusive approach that should involve people from the local community in planning, development and evaluation (*see also* Milestone 1.2.04).

Alternative communication strategies: If successful campaign strategies can be identified, tested and validated through research they can be transferred to other population groups and adapted to the specific cultural group as appropriate. One example is ethnic minority diabetes story telling – a different way of imparting health messages, which may be more appropriate than more formal European education techniques and are highly valued by local inhabitants. School children can also be excellent ambassadors in immigrant populations for healthy eating and exercise; if such research could be conducted in schools, health messages are then taken home for the benefit of all family members.

Older sub-groups: Older people are also a hard-to-reach group due to several factors. Many may be supported by extended family, but a growing number live in isolation, such as when their children leave rural areas to work in towns or move to other countries within Europe in search of better prospects. If older people are from immigrant groups they may not speak the national language or they may already reside in residential homes. The higher incidence of diabetes and complications in this group is expensive for health budgets especially for in-patient care. Several areas here require research intervention, including social research to bring older adults to the top of the agenda. In the past, studies have labelled older adults as a 'burden' and discussed the 'ageing time

bomb'; this has had a negative impact on older populations who are then less likely to seek the healthcare they need. To encourage healthy ageing, qualitative enquiry needs to recall the usefulness of older people in society and how they can successfully manage their diabetes with the correct assistance. Knowledge of diabetes in residential homes for older adults is known to be inadequate especially by transient staff who may lack understanding of the risks and danger of hypoglycaemia and complications. Promotion of residential work with older adults as a valuable career pathway also needs to be explored (*see also* Goal 4.3).

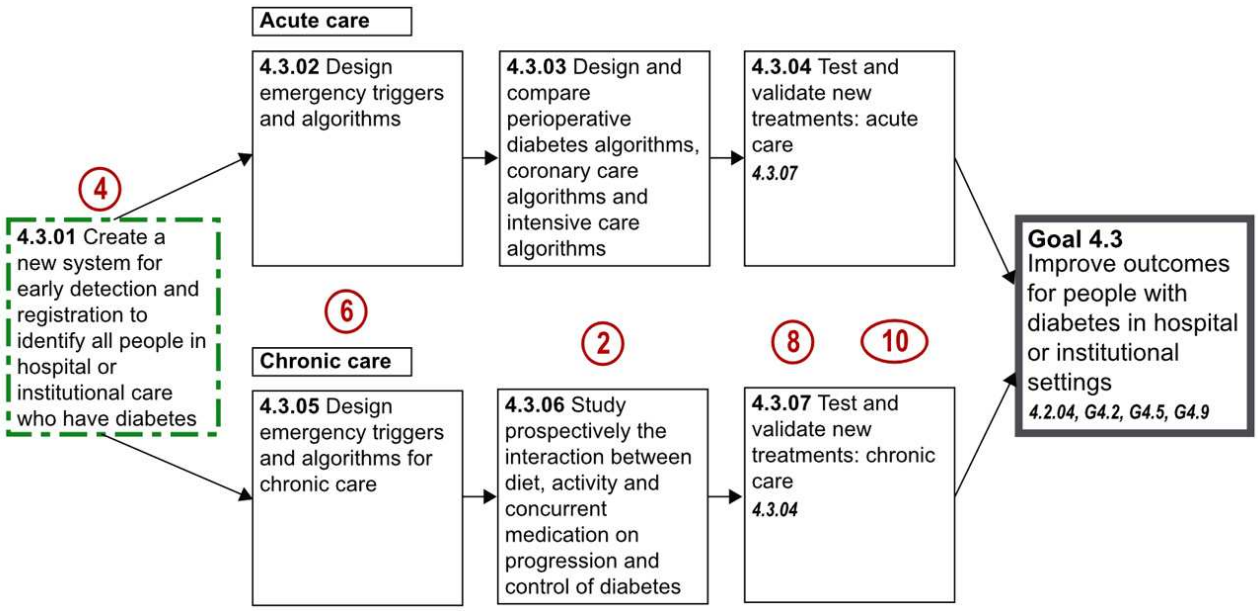
Track 2. Training and education of health professionals working with hard-to-reach groups

Research into staff education and training is urgently needed. Education and training has been mentioned (*track 1*) but it is of such paramount importance that it has been given an individual track with regards to health inequities.

Milestone 4.2.05. Develop educational programmes for professionals on health inequalities

To achieve comparable outcomes for all people with diabetes regardless of ethnicity, age and socio-economic status, research must address the development of an education process for all health professionals that draws attention to current inequities and how they should be treated. There is a current need to evaluate present health professional education and develop training that will embrace both a multicultural approach and also a life-course approach (*see also* Milestone 4.4.03). Such training and educational packages will need to be tested and validated before being endorsed. Experiences can be shared particularly when considering diverse cultures and languages; the use of telehealth tools and techniques within a Europe-wide platform would be most useful here.

Goal 4.3 Improve outcomes for people with diabetes in hospital or institutional settings



Roadblock 2. Variation, lack of standardisation or international consensus across Europe in laboratory conditions, measurement techniques, sample handling and clinical diagnoses and practice
Roadblock 4. Lack of birth cohorts and registries with repeated examinations for long-term follow-up studies over the life-course
Roadblock 6. Fragmented electronic medical records, even within a single institution
Roadblock 8. Gap in professional skills
Roadblock 10. Resistance to implementation of large-scale clinical research in the setting of usual care and fragmentation of usual clinical care from the tradition of clinical research

Introduction and background

This road map focusses on patients with diabetes who are in hospital or in institutional settings, including long-term care for the elderly, psychiatric hospitals, prisons and other chronic care facilities (*see also* Goals 4.2, 4.5, 4.9). Taken together, this group of patients constitutes a particularly vulnerable population, whose outcomes are worse, often since diabetes can be lost or ignored because of the effects of other co-morbidities or complexities. If diabetes is neglected or hidden behind another illness, metabolic outcomes are likely to be sub-optimal, and costs and complications likely to increase.

There are two tracks to this road map: 1. acute care of short-term illness and emergency situations; 2. chronic institutional care of long-term illness. The overall goal of this map is to harness research to improve the outcomes for these vulnerable patients, including morbidity, mortality, length of stay, costs, and quality of life (*see also* Milestone 4.2.04 and Goals 4.2, 4.5, 4.9).

Track 1. Acute care

Milestone 4.3.01. Create a new system for early detection and registration to identify all people in hospital or institutional care who have diabetes

The first step to support this research, and to improve patient care, is to be able to identify those patients who have diabetes. Currently, diabetes is often missed or ignored in these settings, because another illness or procedure takes precedence. However, it is long known that patients with diabetes have worse outcomes, longer hospital stays and have higher costs than other patients, matched for other clinical variables. Various approaches could be taken to solve this problem. Accurate diabetes registries on a regional, national or even international basis could solve the problem for patients already diagnosed with diabetes. However, diabetes is often diagnosed for the first time while patients are in hospital or institutional care. Thus what is also needed is greater awareness among carers together with screening and integration of laboratory and electronic record systems to trigger the diagnosis of diabetes where it is already clearly evident, if looked for.

Milestone 4.3.02. Design emergency triggers and algorithms
The acute hyper- and hypoglycaemic emergencies related to diabetes are much more common in hospital or care settings. Morbidity and costs are high, and there is potential for mortality, particularly in elderly patients. These emergencies are much better treated by algorithms that are standardised across regions, countries and continents and with specialist input in consultation.

Milestone 4.3.03. Design and compare perioperative diabetes algorithms, coronary care algorithms, and intensive care algorithms
The past decade has seen active debate and controversy around the management of diabetes (and glycaemic control in particular) in the settings of acute major illness, such as post myocardial infarction and the intensive care unit. The zeal for intensive glycaemic management that initially held promise has been followed by more recent scepticism and awareness of the potential for harm in such approaches. There is a requirement for further research across a large number of centres, with sufficient statistical power and with appropriately matched patient groups in terms of other clinical variables. These studies are crucially important for the short- and long-term health of hospitalised patients with diabetes, both in terms of morbidity, mortality and cost of care.

Milestone 4.3.04. Test and validate new treatments: acute care
Up to now, most of the major clinical trials of new diabetes treatments have been conducted in moderate numbers in an outpatient setting. Results from these studies cannot be generalised to the very different and more complex population of people in hospital with diabetes. Given the high prevalence of diabetes in patients in hospital or long-term institutional care (track 2), there is an opportunity to design a whole range of new trials in these populations. Such a strategy raises several roadblocks, mostly around the traditional separation between clinical research and usual clinical care, particularly in hospitals. This approach promises to reduce both morbidity and mortality in the vulnerable population of those in hospital with diabetes (*see also* Milestone 4.3.07).

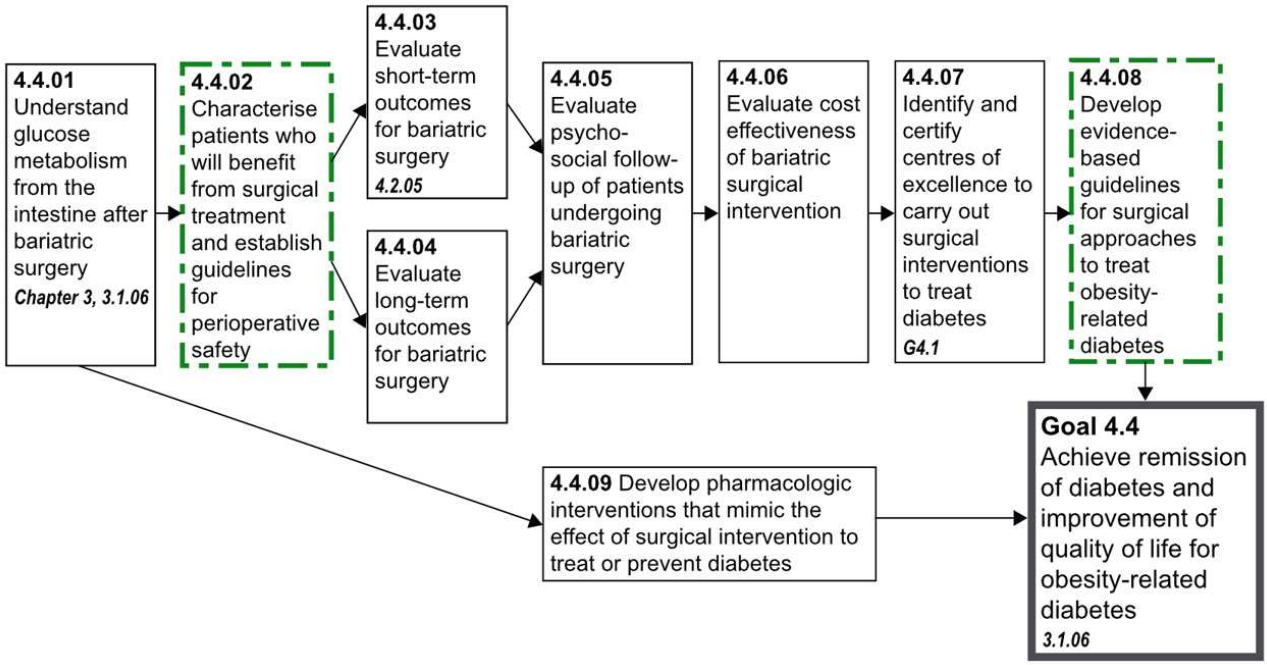
Track 2. Chronic care

Milestone 4.3.05. Design emergency triggers and algorithms for chronic care
The acute hyper- and hypoglycaemic emergencies related to diabetes are much more common in hospital or care settings. As for Milestone 4.3.02 the morbidity and costs are high, and there is potential for mortality, particularly in elderly patients. These emergencies are similarly much better treated by standardised algorithms (across regions, countries and continents) and with specialist input in consultation. Designing, agreeing and implementing these algorithms on a wider scale is a research challenge, particularly for the neglected areas of chronic care outside the acute hospital setting.

Milestone 4.3.06. Study prospectively the interaction between diet, activity and concurrent medication on progression and control of diabetes. This Milestone is concerned with studying the evolution of and progression to diabetes in patients in chronic institutional care, where the risk is higher and factors contributing need greater study. The issues in chronic care are somewhat different to those in the acute setting and it is essential that they are not neglected.

Milestone 4.3.07. Test and validate new treatments: chronic care
Given the high prevalence of diabetes in patients in hospital or long-term institutional care, there is an opportunity to design a whole range of new trials in these populations (*see also* Milestone 4.3.04).

Goal. 4.4. Achieve remission of diabetes and improvement of quality of life for obesity-related diabetes



Roadblock 3. Practical and ethical challenges of locating research participants among diverse groups
Roadblock 7. Lack of specific bioinformatic software to analyse and integrate multiple data on biological (genetic), psychological, lifestyle and social factors
Roadblock 9. Lack of appropriate professional training and education

Introduction and background

Bariatric surgery is the most effective treatment for obesity resulting in long-term weight loss and amelioration of obesity-associated co-morbidities, particularly type 2 diabetes. Surgical therapies, apart from offering morbidly obese patients the best hope for substantial and sustainable weight loss, may lead to a reduction in morbidity and mortality. Metabolic benefits of bariatric surgery occur rapidly and independently of the weight loss and are correlated with the particular anatomical restructuring of the surgery.

Understanding the mechanisms mediating the beneficial outcomes of bariatric surgery could result in new non-surgical treatment strategies for obesity and type 2 diabetes. The physiological issues associated with bariatric surgery and diabetes remission have yet to be clarified, and insight gained from such research would be useful for the development of new pharmacotherapy for the treatment of obesity and diabetes (*see also* Milestone 3.1.06).

The number of morbidly obese patients (BMI ≥ 40) requesting surgical treatment is increasing. While new surgical procedures are being developed there is the need to ensure a low post-operative mortality rate, that quality of life is enhanced and that the treatment is cost-effective. Bariatric surgery needs to be developed as a cost-effective and sustainable treatment that can be supported by national health services especially as obesity is more prevalent in underdeveloped countries and affects more people at lower socioeconomic levels.

Types of bariatric surgery

The field of bariatric surgical procedures consists of three major approaches. The first surgical approach, called *restrictive*, is aimed at decreasing the patient's caloric intake. Examples of restrictive surgery are the vertical banded gastroplasty and laparoscopic adjustable gastric band procedures, which only restrict stomach size. The second approach, called *malabsorptive*, is aimed at decreasing the absorption of nutrients. Jejunoileal bypass, which is rarely used today, and biliopancreatic diversion, with or without duodenal switch procedures belong to the malabsorptive category. More complicated surgeries combine both restrictive and malabsorptive principles and fall under the third category, *combination* surgery; Roux-en-Y gastric bypass, or simply gastric bypass, is the most common type of combination bariatric surgery performed and the one demonstrating the most robust metabolic effects.

Milestone 4.4.01. Understand glucose metabolism from the intestine after bariatric surgery

During bariatric surgery, bowel segments are re-routed and a substantial portion of the stomach is removed. Nutrients from the stomach are diverted from the proximal portion of the intestine to a more distal portion; thus, digestive physiology is altered significantly by excluding ingested nutrients from the upper intestine.

Key enzymes for gluconeogenesis are expressed in the small intestine where they are induced in states of energy deficit. The resulting intestinal glucose production apparently activates portal-vein glucose sensors to engage a neurocircuit that increases hepatic insulin sensitivity and decreases hepatic glucose output. Furthermore, sensors in the liver may detect the elevated glucose and send an appetite-suppressing signal to the brain, which contributes to the satiety and weight loss seen with gastric bypass. Research is required both in animals and particularly in human subjects to understand better the effects of these surgical procedures on glucose and fat metabolism (*see also* Milestone 3.1.06).

The gut is now known to act as a large endocrine organ, producing hormones that have important sensing and signalling roles in the regulation of appetite and energy homeostasis. Potential mechanisms underlying the direct antidiabetic impact of bariatric surgery may include modulated nutrient stimulation of lower intestinal hormones (e.g. glucagon-like peptide 1), compromised ghrelin secretion and other hormones apart from the aforementioned such as peptide YY, oxyntomodulin, glucose-dependent insulinotropic polypeptide, cholecystokinin and pancreatic polypeptide, modulations of intestinal nutrient sensing and regulation of insulin sensitivity, and other changes yet to be fully characterised.

These changes cause corresponding alterations in brain centres, such as the hypothalamus, which is responsible for energy homeostasis, and through these higher centres, hormones regulate long-term changes in energy stores. Apart from the hormones, variations in nutrient content may influence such interactions. So far, reports of the effect of different surgical procedures on these hormones have been controversial. Differences in surgical technique, research methodologies, blood collection time points and sample assays as well as sample processing could account for discrepancies in the literature. The use of standardised protocols would limit such pitfalls and further clarify the effect of surgery itself on the circulating levels of gut hormones.

Questions remain regarding the lipid-carbohydrate based neurocircuits that influence hepatic glucose production, the response to intestinal nutrient sensing and metabolism as well as the way in which these pathways are affected by intestinal bypass. Research aimed at determining the relative importance of the physiology of brain-liver-intestine crosstalk and at identifying additional mechanisms promises not only to improve surgical design but also to identify novel targets for the treatment of diabetes (*see also* basic research proposed in Chapter 3).

Milestone 4.4.02. Characterise patients who will benefit from surgical treatment and establish guidelines for perioperative safety

According to the 1991 National Institutes of Health (NIH) consensus conference on gastrointestinal surgery for severe obesity, patients are candidates for surgery if they are morbidly obese (BMI>40 kg/m^2 or >35 kg/m^2 with co-morbidities), have failed attempts at diet and exercise, are motivated and well informed, and are free of significant psychological disease.

Current evidence suggests that surgical therapies offer the morbidly obese the best hope for substantial and sustainable weight loss. Minimally invasive methods currently available have increased the demand for bariatric procedures. Comparative data indicate that procedures with more dramatic clinical benefits carry greater risks, with those offering greater safety and flexibility being associated with less reliable efficacy. However, no evidence-based clinical reviews so far exist to guide patients and surgeons in selecting the bariatric surgical technique most applicable to a given patient in a given situation. For this reason existing techniques must be reviewed and graded as to their level of evidence before they can be recommended.

Patient selection algorithms should favour individual risk:benefit and quality-of-life considerations over traditional anthropometric and demographic figures. Bariatric care should be delivered within credentialed multidisciplinary environments. All bariatric surgical techniques including laparoscopic Roux-en-Y gastric bypass, adjustable gastric banding, biliopancreatic diversion with duodenal switch, and primary laparoscopic sleeve gastrectomy, have been proven effective. Currently, the choice of operation is driven by patient and surgeon preferences.

Obesity has also a significant adverse impact on reproductive outcome. It influences not only the possibility of conception but also the response to fertility treatment, and increases the risk of miscarriage, congenital anomalies and pregnancy complications in addition to potential adverse effects on long-term health of both mother and infant (*see also* Milestone 4.7.03). Women should aim for a BMI in the normal range before starting any form of fertility treatment, and a weight reduction to a BMI of less than 30 kg/m^2 is preferable before pregnancy. The effect of bariatric surgery in achieving a weight reduction that will affect fertility has not been evaluated and guidelines are needed for the follow-up of fertility after bariatric surgery. Moreover studies are needed on the outcome of pregnancies following bariatric surgery weight loss. Recommendations for surgical intervention in morbidly obese women are lacking.

Obesity rates are increasing among children and adolescents. However, ethical issues for bariatric surgery in these age groups remain to be resolved, and more studies are needed to investigate the efficacy and safety of bariatric surgery in younger ages. The concept of major obesity surgery for very young patients is hugely controversial, and there have been no studies to date to provide a basis on which intermediate and long-term risks can be assessed. The effects of bariatric surgery on growth and fertility need to be investigated further.

Bariatric surgery is not benign, and patients experience the same risks as anyone undergoing major surgery; however, it has to be proven relatively safe for patients who would normally be considered high-risk, and the low mortality rate should be reassuring. These parameters (surgical morbidity and mortality as well as efficacy) require formal prospective study in people of older age who are more likely to have additional cardiometabolic risk factors.

Milestone 4.4.03. Evaluate short-term outcomes for bariatric surgery

Major adverse events following surgery, some necessitating reoperation, include anastomosis leakage, pneumonia, pulmonary embolism, band slippage and band erosion. Improvement of surgical procedures, mastering of the techniques and close collaboration of the relevant specialists should be aimed for.

Postoperative support groups are an important part of a bariatric programme and may help to improve postoperative results and limit relapse. Thus one important research topic is the study of the effect of patient support groups and education on postoperative results.

The institutional needs of a bariatric programme extend across outpatient and inpatient environments, and the entire environment and facilities should be appropriate and comfortable for patients with morbid and supermorbid obesity; such design should be evidence-based to achieve the best results. Healthcare providers and staff who work with bariatric patients should undergo training to specialise in this area and meet the needs of this particular group of patients (*see also* Milestone 4.2.05).

Milestone 4.4.04. Evaluate long-term outcomes for bariatric surgery

Despite a large increase in bariatric surgery, the number of operations performed is still far less than the number of morbidly obese patients. Many factors, such as patient and provider attitudes towards obesity and bariatric surgery, cost, and health insurance coverage, contribute to the low uptake of surgery as a method for weight reduction and even more for diabetes remission. In turn, these issues will likely lead to disparity across the European region.

Mixed attitudes toward bariatric surgery are found in the literature with patient perception that it is a dangerous and extreme measure. The overall attitude of patients and providers toward bariatric surgery is inconsistent and more prospective research is required to provide evidence of the efficacy and safety of these procedures. Key factors in patient safety include comprehensive preoperative evaluation, use of appropriate and reliable evaluation instruments, and the development of short- and long-term treatment plans.

Standardised, randomised studies need to be designed and implemented to include analysis of postoperative mortality and morbidity, change in obesity-related co-morbidities (type 2 diabetes, hypertension, lipid disorders, cardiovascular risk) and other adverse events.

Milestone 4.4.05. Evaluate psychosocial follow-up of patients undergoing bariatric surgery

Success following bariatric surgery should not only include weight loss and improvement or cure of co-morbid conditions but also improve eating behaviour, quality of life and a range of psychosocial variables. Unfortunately, bariatric surgery does not lead to identical results in each patient. Patients who fail to adjust their eating behaviour and lifestyle after surgery may experience adverse reactions. Compliance and adjustment may be attributed largely to psychological factors, implying that the operation on its own represents only one element in the treatment of severe or morbid obesity.

Considering the role of psychosocial factors on the outcomes of the surgery and the impact of the operation on the psychological and social situation, mental health professionals should participate in the process of evaluation and treatment. Psychological evaluation of the patient before weight loss surgery is essential because of the prevalence of psychiatric co-morbidities in people with severe obesity and the behavioural adaptations required for successful surgical outcomes. Although there is currently no international standard for the specific components of these evaluations, there is general agreement in the literature about the objectives and the kinds of assessment methods that are most useful. Further research is needed to evaluate the appropriate methodology to be applied in such patients. It may be that it is more important to focus on improving postoperative support instead of searching for only technical surgical outcome predictors.

Uncontrolled eating and grazing have been identified as two high-risk eating patterns after surgery. Clearer characterisation of favourable and unfavourable postsurgical eating behaviours, reliable methods to assess their presence, and empirically tested postsurgical intervention strategies are required to optimise weight loss outcomes and facilitate psychological well-being in at-risk groups.

Reconstructive surgery following weight loss after bariatric surgery results in a significant improvement in overall quality of life. Reconstructive surgery should be incorporated in the multidisciplinary care programme following weight loss surgery in the morbidly obese patient in order to improve the psychosocial outcome of bariatric surgery and must be included in costing. However, increased costs may exacerbate further differences between countries across Europe, including the 27 European Union Member States.

Milestone 4.4.06. Evaluate cost-effectiveness of bariatric surgical intervention
Although bariatric surgery has been shown to be effective in reducing body weight in most morbidly obese patients, it remains to be proven that it also results in greater quality of life and decreased healthcare costs for patients and for the healthcare system.

All bariatric surgical techniques, both open and laparoscopic, in widespread current use must be studied and be compared with each other and with non-surgical interventions. All age groups and BMI measures of weight change, quality of life, perioperative and postoperative mortality and morbidity, change in obesity-related co-morbidities and adverse events should be studied. Full cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses and cost-consequence analyses have to be evaluated and economic modelling needs to be developed.

Uncertainties remain and further research is required to provide detailed data on patient quality of life; impact of surgeon experience on outcome; late complications leading to reoperation; duration of co-morbidity remission, and resource use. Randomised controlled trials are appropriate to provide evidence on bariatric surgery for young people and for adults with Class I (BMI 30-34.9 kg/m^2), Class II (BMI 35-39.9 kg/m^2) and Class III (BMI 40 kg/m^2 and above) obesity. New research must report on the resolution and/or development of co-morbidities such as type 2 diabetes and hypertension so that the potential benefits of early intervention can be assessed.

Studies that prove the benefits and cost-effectiveness of bariatric surgery should influence national healthcare systems for the financial coverage of people in most need. Age- and BMI-based candidacy guidelines should not limit access for patients experiencing progressive or poorly controlled obesity-related co-morbidities if the risk: benefit analysis favours surgery. A multi-track approach to treatment across Europe should be established for people who have undergone surgery as well as for poorer patients in those countries where people cannot afford this treatment.

Milestone 4.4.07. Identify and certify centres of excellence to carry out surgical interventions to treat diabetes
The issue of 'health tourism' should be addressed by ensuring that all centres, regardless of location, are identified and validated as being approved to carry out surgery for obesity. Such data could be collected and monitored by the EPCRD (*see also* Goal 4.1). This would reduce possibilities of incorrect treatment and lack of follow-up on the patient's return to their country of residence if the surgery is carried out abroad.

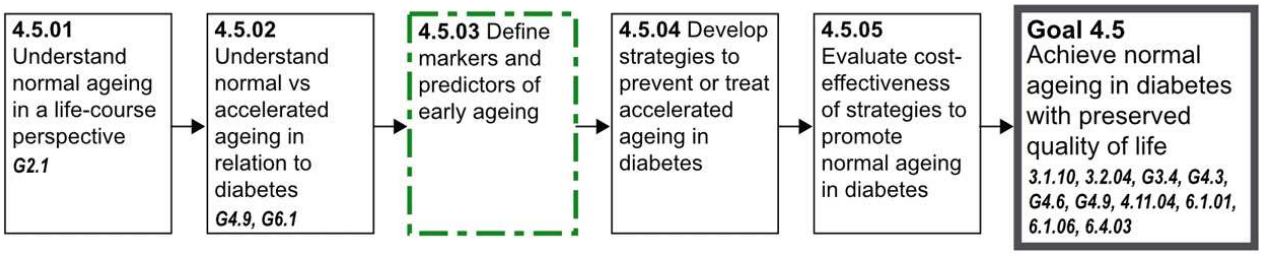
Milestone 4.4.08. Develop evidence-based guidelines for surgical approaches to treat obesity-related diabetes
Gastrointestinal operations are now being used worldwide to treat diabetes in association with obesity, and increasingly, for diabetes alone. However, the role for surgery in diabetes treatment is not clearly defined and there are neither clear guidelines for these practices nor sufficient plans for clinical trials to evaluate the risks and benefits of such 'diabetes surgery', and the duration of remission of diabetes is not yet known. Clinical trials to investigate the exact role of surgery in patients

with less severe obesity and diabetes are a priority before bariatric surgery is considered a therapeutic tool for diabetes. Before prospectively collected comparative data among the different bariatric operations are available it remains impossible to make definitive recommendations for one procedure over another. Randomised controlled comparative clinical trials need to be performed in order to evaluate long-term effects of the bariatric surgery, before its use in younger ages and specifically in children.

Milestone 4.4.09. Develop pharmacologic interventions that mimic the effect of surgical intervention to treat or prevent diabetes

Research to elucidate mechanisms through which diabetes remission is achieved with bariatric surgery should facilitate the design of new drugs to treat and prevent diabetes. Mounting evidence indicates that certain operations involving intestinal diversions improve glucose homeostasis through varied mechanisms beyond reduced food intake and body weight, for example by modulating gut hormones. Surgery-specific, weight-loss-independent effects of bariatric surgery on fast remission of type 2 diabetes and glucose homeostasis also include altered physiology from excluding ingested nutrients from the upper intestine and enhanced nutrient stimulation of the lower intestine hormones. These processes modulate intestinal nutrient sensing and regulation of insulin secretion and insulin sensitivity along with other changes yet to be fully characterised.

Goal 4.5. Achieve normal ageing in diabetes with preserved quality of life



Roadblock 3. Practical and ethical challenges of locating research participants among diverse groups
Roadblock 4. Lack of birth cohorts and registries with repeated examinations for long-term follow-up studies over the life-course
Roadblock 7. Lack of specific bioinformatic software to analyse and integrate multiple data on biological (genetic), psychological, lifestyle and social factors

Introduction and background

Europe has a rapidly growing ageing population with increased mean life expectancy. These older individuals become much more prone to a range of chronic diseases, including diabetes, especially type 2 diabetes. There is a well-documented gap in life expectancy between people who develop diabetes and healthy people of similar age. Diabetes itself can be considered a disease of premature ageing, specifically of the cardiovascular system and also of other tissue and organ systems, at least in a substantial proportion of patients. However, some patients appear to be protected against this accelerated ageing process, and the underlying mechanisms of these protective processes remain unclear.

A European research strategy for ageing and diabetes is likely to include: experimental studies in animals to investigate biomedical aspects of the normal ageing process, as well as in diabetes; studies in people without diabetes; studies in people with diabetes of short-, intermediate- and long-duration to investigate the process of ageing in different organs. The impact of diabetes treatments specifically on these ageing processes is also a research priority. Thus, specific studies of biological and molecular ageing in patients treated with the traditional oral hypoglycaemic agents, insulins, as well as the wide range of newer agents, are required. The risk of cancer (an age-related phenomenon in general) in relation to diabetes is an area of growing interest as diabetes itself as well as some drugs used for the treatment of diabetes may also impact on the cancer risk and the modification of this risk (*see also* Milestones 3.1.10, 3.2.04, 4.11.04, 6.1.01, 6.1.06, 6.4.03 and Goals 3.4, 4.3, 4.6, 4.9).

Milestone 4.5.01. Understand normal ageing in a life-course perspective

The biological process of ageing starts early in life, at the time of conception since genetic factors are important in shaping organ development and rate of ageing. One measure of this is telomere length, which is determined *in utero* and shortens with every cell division. Therefore the telomere length is a marker of biological ageing that can be determined in adult life, preferably at several time points. Subjects with a faster telomere attrition rate are supposed to have a more rapid biological ageing. In addition, a number of studies have shown the programming effect of fetal growth patterns resulting for some children in a state of small for gestational age at birth. If this condition is combined with a rapid catch-up growth in postnatal life the risk of age-related diseases in adult life is increased, for example cardiovascular disease and type 2 diabetes. If however, fetal and early post-natal life development is normal, conditions favour normal biological development and ageing (*see also* Goal 2.1).

Recently, new evidence has shown that cognitive function in early life is a factor of importance to influence the life-course and patterns of ageing. Cognitive function is shaped not only by genetics and early life growth, but also by socio-cultural factors during childhood and adolescence. Normal ageing is thought to be facilitated by normal cognitive function, good nutrition and lack of adverse psychosocial factors. The latter could be evaluated repeatedly during the life-course, thus contributing to a better understanding of how the social and psychosocial environment interacts with genetic and early life factors for shaping the biological ageing (such as gene-environmental interactions, epigenetics).

Milestone 4.5.02. Understand normal vs accelerated ageing in relation to diabetes
The process of ageing in humans is shaped by evolutionary selection, but many aspects of ageing are still poorly understood, especially in a chronic disease state such as diabetes. The first Goal is therefore to understand the ageing process in general (Milestone 4.5.01), but also specifically in diabetes (Milestone 4.5.02). There are examples of ageing in different organs that can be used as a focus for research in diabetes; these include the brain and the risk of age-dependent cognitive decline and development of dementia, both of the vascular type and Alzheimer´s dementia (*see also* Goal 4.9). Another example is the ageing of the vessel wall, as it applies to arteries (arterial stiffening, arteriosclerosis, and atherosclerosis, or the venous vessels increasing the risk of thrombo-embolism, *see also* Goal 6.1).

As many people with diabetes face a decreased lifespan and an increased burden of disease and co-morbidities, it is important to delineate the consequence of accelerated normal ageing in these patients and what is added to that in the form of diabetes-specific influences on the ageing process. This could be measured by the way hyperglycaemia-related molecules [glycated proteins, advanced glycated end-products (AGES) etc] interact with different biological tissues, e.g. in the lungs or in the arterial wall, or by the way telomere length is shortened in patients with diabetes (both type 1 and type 2) with or without cardiovascular disease, such as myocardial infarction.

Milestone 4.5.03. Define markers and predictors of early ageing
Ageing is ultimately based on the interaction between genes and the environment (e.g. hyperglycaemia). One of the consequences of diabetes is a process of early (accelerated) ageing of organs that is different from healthy ageing and is also a measurable process.

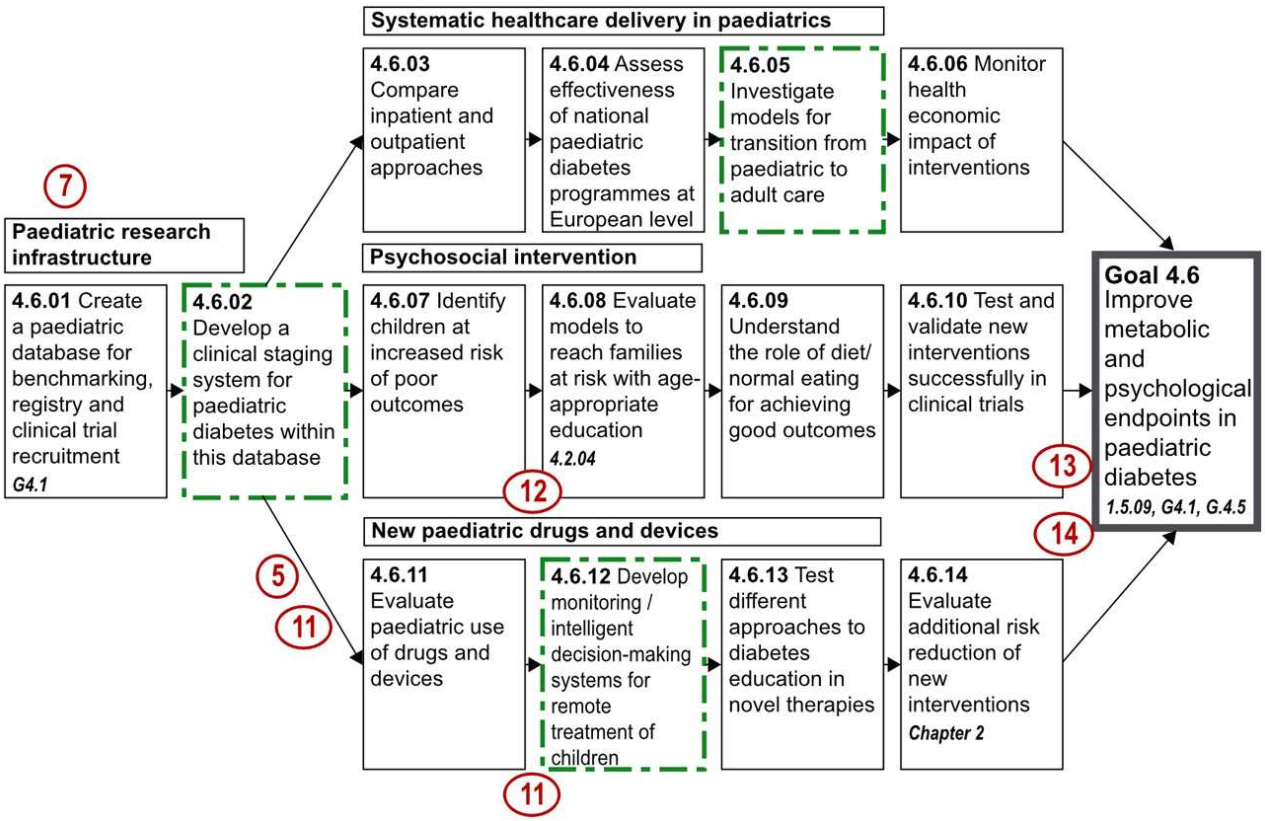
Longstanding hyperglycaemia causes glycation of tissues. This process resembles ageing due to oxidative stress and chronic inflammation. The principal complications of diabetes occur in vascular tissues and diabetes can be considered as a disease of early vascular ageing. It is equally important to understand why certain patients can withstand many years of diabetes with no vascular complications. Some cohort studies of this phenomenon have been initiated and are a high priority for the elucidation of factors protective against the ageing process.

It has been shown that subjects with type 2 diabetes have shorter telomeres than people without diabetes and that even shorter telomeres could be found when diabetes is combined with myocardial infarction. Telomeres form the cap of the DNA helix and are shortened with every cell division and represent a molecular marker of ageing. Research in telomere biology in patients with diabetes is therefore needed to better understand these aspects of the ageing process.

Milestone 4.5.04. Develop strategies to prevent or treat accelerated ageing in diabetes
Research on progression of ageing in diabetes will require specific studies of the effects of a range of interventions on markers of ageing (*see also* Goal 3.1): lifestyle interventions (diet, exercise, smoking cessation); functional foods (food constituents that may decrease postprandial hyperglycaemia or protect from oxidative stress); drug treatments (for glycaemia but also for other aspects of the vascular ageing process such as endothelial dysfunction and AGE-breakers, to stop the glycation of proteins in various organs); technology applications (e.g. for counteracting vascular changes before complications occur); analysis of compliance with the above treatments and the impact of self-care strategies on the ageing process.

Milestone 4.5.05. Evaluate cost-effectiveness of strategies to promote normal ageing in diabetes
New methods for modelling the cost of diabetes and its complications should be further developed, preferably based on large cohorts or national or even international registers of treated patients with diabetes (*see also* Goal 4.1).

Goal 4.6. Improve metabolic and psychological endpoints in paediatric diabetes



Roadblock 5. Lack of large European diabetes networks
Roadblock 7. Lack of specific bioinformatic software to analyse and integrate multiple data on biological (genetic), psychological, lifestyle and social factors
Roadblock 11. Drug regulatory issues: paediatric drug approvals lag behind adult decision-making
Roadblock 12. Partnerships between academia and industry (both pharmaceutical and other industry) are needed
Roadblock 13. Huge differences in structure, process, quality and delivery of diabetes care between European countries
Roadblock 14. Advances in diabetes treatment or new drugs or new devices can only be implemented if society is able to support such treatments

Introduction and background

Adolescents with type 1 and type 2 diabetes are particularly prone to poor metabolic and psychosocial outcomes due to the potentially long diabetes duration they will face. At the same time the study of the effect of diabetes in this age group provides an opportunity to study early vascular ageing without other concomitant diseases. Successful ageing with diabetes starts in childhood as many processes leading to debilitating complications later in life have their onset in childhood. This offers a unique opportunity to identify potential factors that are important to delay accelerated biological ageing in diabetes. Also, preventive strategies that prove effective in childhood and adolescence are likely to be particularly cost-effective as most of the healthcare cost is incurred for the treatment of late complications.

There is a predicted 70 percent increase in prevalence of diabetes by 2020 with more and more young children being affected. These children show a more rapid decrease in beta cell function and have less residual insulin production than adolescents or adults. The average metabolic outcomes of children with diabetes as judged by international cohort studies of HbA1c were found to be significantly worse than in the adult population, with those of adolescents being the worst. Also, studies with new technologies such as continuous glucose monitoring have shown a less favourable effect in youth compared to adults.

Implementation of new technologies has to be seen in the context of family and peer group influence and the absence of complex decision-making by the patients themselves. In addition, lifestyles of

young children who have a long overnight sleep as well as unpredictable activity and eating behaviour have to be considered. The age-dependent changes of insulin sensitivity (being highest in young children and lowest during puberty) or the influence of frequent infectious diseases are further challenges to achieve outcomes comparable to adults.

Normal psychosocial development of children requires that diabetes management allows flexibility with informed self-management. However with current therapies, children are often forced onto restrictive treatment regimens and face discrimination in school and among peers. Studies in the UK and Scandinavia confirm higher mortality rates in all paediatric age groups with diabetes compared to healthy children. Children and young people with diabetes are at risk of developing serious disabling complications similar to adults. In addition, long-term research shows that poor control during the early years of the disease has a major impact on the long-term prognosis despite better control thereafter (so-called 'metabolic memory'); this makes it imperative to improve outcomes in this age group.

Unfortunately there are still many differences in access to diabetes care and treatment across Europe. Studies involving 18 paediatric diabetes centres from 12 European Union Member States plus Switzerland and Norway revealed significant outcome differences among these centres indicating the need to find a way to share best practices.

Special emphasis has to be put on the transition from paediatric to adult care. Organisation of paediatric and adult care is not continuous in many European Union states. Models ensuring an effective transfer into adult care are needed for a long-term preservation of the potential benefits from improved paediatric diabetes care.

Successful implementation of this road map would improve the situation for children with diabetes in Europe and ensure that all children have the right to participate fully in all the experiences of childhood and adolescence, regardless of whether they have diabetes and wherever they live. Also it will reduce the effects of accelerated vascular ageing imposed by the diabetic state and provide the basis for a long-term participation in professional and family life without, or with delayed debilitating long-term diabetes complications (*see also* Milestone 1.5.09 and Goals 4.1, 4.5).

Due to the comparatively small patient numbers in paediatric diabetes (both type 1 and type 2 diabetes) appropriately powered clinical studies require a multi-centre framework. Thus, independent funding for collaborative research infrastructure and continuity is urgently needed.

Track 1: Paediatric research infrastructure

Milestone 4.6.01. Create a paediatric database for benchmarking, registry and clinical trial recruitment

A prerequisite for clinical research is a good database. To identify patients eligible for trials or to compare outcomes between different centres, a common data set needs to be developed. The World Health Organization (WHO) paediatric data set was developed nearly 20 years ago as part of the St. Vincent declaration initiative. On a European level much progress has been made regarding health indicators and diabetes epidemiology (for example EUBIROD, European Best Information through Regional Outcomes in Diabetes, supported by the European Commission DG SANCO), so that this WHO data set is now outdated. An improved universal dataset is required as well as an information technology infrastructure to exchange such data between centres (*see also* Goal 4.1).

Milestone 4.6.02. Develop a clinical staging system for paediatric diabetes within this database

Both type 1 and type 2 diabetes in children develops in different phases from the initial genetic predisposition, with subclinical metabolic changes (and immunological processes such as antibody development, particularly in type 1 diabetes) preceding overt clinical diabetes (during which typically the diagnosis is made in the majority of the cases), often followed by a partial remission phase when some of the residual beta cell function is temporarily restored after the onset of treatment. After complete beta cell failure (not all paediatric patients actually reach this stage) insulin substitution is necessary leading to a more unstable metabolic state.

The rate of progression from one stage to another is age-dependent. In type 1 diabetes, diabetes-associated antibodies are often already found within the first two years of life, while clinical diabetes is diagnosed on average at 11 years. Children with diabetes onset in the preschool age, i.e. more rapid progressive disease, have less residual beta cell function than those diagnosed in adolescence.

Not all interventions and therapeutic procedures will be similarly effective in different phases of diabetes. Procedures aiming at restoration or preservation of beta cell function need staging by genetic,

biochemical and clinical parameters. Such assessment should replace what we now call 'remission phase' (Honeymoon phase) or prediabetes in children. This staging system would allow development of strategies aimed at primary prevention (for those at increased genetic risk), secondary prevention (for those with subclinical abnormalities) and tertiary prevention of late complications in full-blown disease.

The development of large clinical databases including data on genetic background, immunological features and clinical course of the disease (for example changes in residual beta cell function over time) is a prerequisite for developing and testing such a clinical staging system. Ideally it could be combined with a biobank to link clinical data with biomarkers. Subsequently, it would be used to monitor the interventions described in the other tracks.

Track 2. Systematic healthcare delivery in paediatrics

Milestone 4.6.03. Compare in-patient and out-patient approaches
Differences between leading paediatric diabetes centres are present during both the early and later stages of the disease. There is increasing evidence that the early course of diabetes during the first year of clinical diabetes has a huge impact on the later metabolic results (metabolic memory) and psychosocial coping with the chronic disease.

One major difference between the initial approaches to paediatric diabetes is that some health systems prefer an initial in-patient training phase compared to a system of outpatient education at onset. The limited study data have focussed only on short-term outcomes and have not aimed at more ambitious metabolic targets that are currently recommended also for the young age group. This initial phase of diabetes care requires further prospective study on a large scale.

Milestone 4.6.04. Assess effectiveness of national paediatric diabetes programmes at a European level
The status report of children with diabetes in Europe identifies several shortcomings in epidemiological and health outcomes research in Europe. For example epidemiological data are collected often only for younger children. Thus, only five of the 27 European Union Member States have data for the 15-18-year age group. Also, only 13 out of 25 countries have reported a national paediatric diabetes register. Presently, only seven countries have a national plan or special provisions addressing children with diabetes and 16 out of 25 countries have recognised paediatric diabetes centres. Exchange of information between centres of reference for paediatric diabetes is crucial to implementing advances of paediatric diabetes therapy. Health technology assessments as well as comparisons of cross-border healthcare would allow the effects of varying national strategies of healthcare delivery to be evaluated. This line of research could be the basis for exchanging best practices and identifying cost-effective interventions in different health policy frameworks.

Milestone 4.6.05. Investigate models for transition from paediatric to adult care
There is a large heterogeneity of models for the transition from paediatric to adult care. The time point of such a transition ranges from school age to young adult (i.e. 21 years or older). Such different models need to be investigated for their effectiveness. As the transition period constitutes the period during which first complications can be detected and early intervention for micro- and macroangiopathy is likely to be more effective than later in life, this period deserves particular attention. Outcomes both in terms of clinical diabetes (such as glycaemic control, complications) as well as psychosocial goals (such as educational level, professional status, home making) have to be compared regarding structured and unstructured transition models and earlier and later transition in different healthcare delivery systems. Transition care for diabetes will thus require formal prospective study.

Milestone 4.6.06. Monitor health economic impact of interventions
A reporting system needs to be developed that allows the assessment of different health care interventions both at national and international levels. Currently health economics data are lacking in paediatric diabetology and need to be coupled with clinical outcomes. The status report of paediatric diabetes within the SWEET project identified significant differences between countries with respect to access to specialised healthcare teams and modern therapies (insulin analogues, insulin pumps, glucose sensors). To finance the advances of translational research for the most vulnerable population such data need to be generated and updated regularly. Combining the clinical paediatric data set (*see also* Milestone 4.6.01) with health economics data will make it possible to evaluate the cost-effectiveness of trends in risk factor control, equity and the quality of paediatric diabetes healthcare services.

Track 2. Psychosocial intervention

Milestone 4.6.07. Identify children at increased risk of poor outcomes
Family structures are rapidly changing across Europe. Comparative research of good and poor outcomes in paediatric diabetes has identified family function as extremely important for achieving good outcomes. When the basic methods for following up patients with paediatric diabetes are established in a multi-centre international fashion, sub-groups of children with certain genetic markers, biomarkers, psychosocial factors or influences of early childhood can be studied. Currently little is known as to how to tailor diabetes healthcare delivery to different family structures (such as single parent and 'patchwork' families) or parenting strategies, in terms of their influence on the long-term metabolic and psychosocial outcomes. Different therapeutic, educational, psycho-interventional strategies have to be tested in proper controlled trials once such children at increased risk of poor longitudinal outcomes have been identified.

Milestone 4.6.08. Evaluate models to reach families at risk with age-appropriate education
Diabetes education of children and families is essential for achieving better outcomes. However, little research is available to compare different strategies for delivering age-appropriate education. Furthermore, these educational interventions need to be tested within different social and cultural backgrounds (*see also* Milestone 4.2.04). Particularly with new technological advances, it will be necessary to identify approaches in the paediatric age group that are as effective as in adults.

Milestone 4.6.09. Understand the role of diet/normal eating for achieving good outcomes
A prerequisite for successful diabetes therapy is to adjust it to food. For example, the insulin dose and action profile needs to be balanced against the expected carbohydrate intake. There are several areas of controversy: the quantification of carbohydrate (e.g. grams, exchanges, portions/servings) or the influence of other nutrients on glycaemic control and long-term prognosis (e.g. fat, fibre, sucrose). In addition, so far no structured research has addressed the impact and psychological effect of dietary counselling methods. It is well known that adult eating behaviour is developed during childhood. Therefore, a better evidence base for such strategies could have a long-term effect on patient-oriented outcomes, both in paediatric and adult care.

Milestone 4.6.10. Test and validate new interventions successfully in clinical trials
Paediatric trials of new interventions need to look at patient-oriented outcomes that are relevant to age. For example, endpoints such as debilitating complications are not appropriate for the paediatric age group. Meaningful endpoints may include psychosocial variables such as maintaining a family structure, coping of parents or achieving positive school outcomes. Such innovative trial designs need to be evaluated to test new interventions in paediatric trials.

Track 3: New paediatric drugs and devices

Milestone 4.6.11. Evaluate paediatric use of drugs and devices
Several new drugs i.e. new insulins and drugs for treatment of type 2 diabetes have become available, with more expected in the near future. These may become of special value for younger patients. For example, incretins may not only offer novel approaches for adult type 2 diabetes but may even be effective in the prediabetic stage often encountered in obese adolescents. In type 1 diabetes more rapid-acting insulins may allow an even better treatment of the rapid blood glucose swings regularly encountered in the young age group, particularly with the closed-loop or semi-closed-loop delivery systems currently under development. Randomised controlled trials of continuous glucose monitoring have shown that patients in the paediatric age group are less likely to wear such devices continuously than adults and show poorer metabolic outcomes. This indicates that the current arsenal of insulins and devices is inadequate to tailor satisfactory insulin regimens. Also drugs to restore or preserve residual beta cell function need to be evaluated depending on the clinical stage of the disease. Randomised controlled trials looking at the effects on both metabolic outcomes as well as on the psychosocial development and quality of life of children and family are necessary to make the appropriate decisions for the allocation of healthcare resources. At present most paediatric studies are limited to paediatric investigational plans needed for regulatory submission for drug approval by the European Medicines Agency (EMA). Disparities across Europe are likely regarding the achieved quality of life with diabetes and the potential effect that such new treatments and devices may have. Provisions for comparative research in this area are lacking.

Milestone 4.6.12. Develop monitoring/intelligent decision-making systems for remote treatment of children

Recent study results with continuous glucose monitoring systems indicate less favourable outcomes for paediatric patients than adult patients. This suggests that such advanced technologies need to be coupled with parental or diabetologist supervision as many of the associated tasks interfere with normal life. As the self-motivation found in adults cannot be expected from children, special provisions for remote monitoring and treatment have to be put in place. Children tend to spend more and more time away from the core family in modern European societies. Therefore, systems for supervised diabetes care need to be developed for this age group. Different approaches need to be investigated into how parental supervision or adult decision-making can be provided to make these new technologies as effective in paediatric care as in adult life.

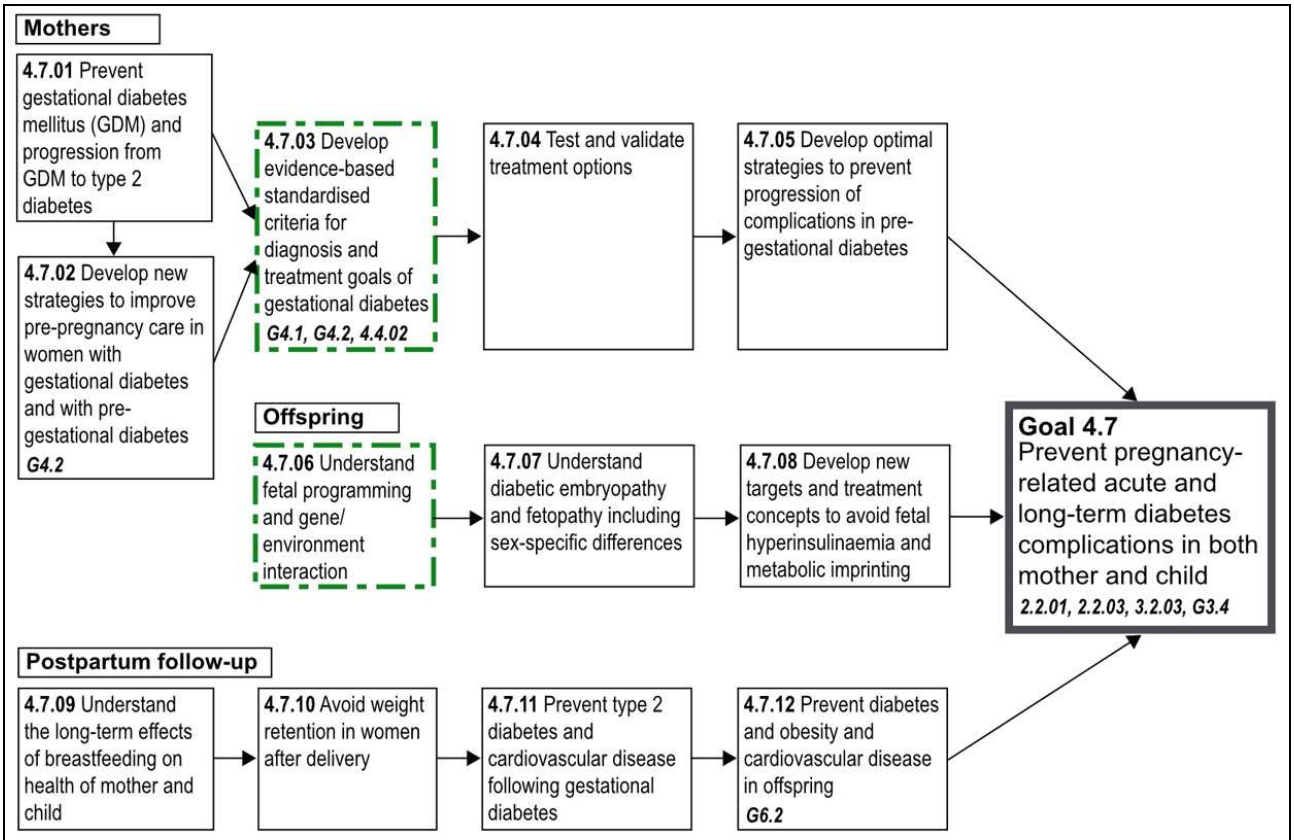
Milestone 4.6.13. Test different approaches to diabetes education in novel therapies

As with standard diabetes therapy, any new treatment strategy needs to be accompanied by an educational strategy. Although it is generally agreed that education in the paediatric age group needs to be tailored to age and cultural background, little comparative research evidence or data on cost-effectiveness are available. Paediatric diabetes education needs to take into account not only the person with diabetes but also family members and other caregivers involved in the provision of care. Educational materials and programmes need to be tested for efficacy and cost-effectiveness. For example, individual teaching approaches have to be compared to group education or interactive Internet-based learning programmes. Also, the necessary time intervals for follow-up education have to be determined.

Milestone 4.6.14. Evaluate additional risk reduction of new interventions

Even if restoration of residual beta cell function is one day achievable even before onset of clinical symptoms of diabetes (*see also* Chapter 2), or technological advances on the road to the artificial pancreas (closed-loop system) become available also for paediatric patients, it is likely that such treatments will not be available to or successful in all patients. Despite the availability of novel strategies, certain sub-groups at risk for poor outcomes will remain. These patients who cannot be treated successfully with modern therapies need to be identified at a very early stage and treated with traditional approaches such as conventional insulin therapy.

Goal 4.7. Prevent pregnancy-related acute and long-term diabetes complications in both mother and child



Roadblock 2. Variation, lack of standardisation or international consensus across Europe in laboratory conditions, measurement techniques, sample handling and clinical diagnoses and practice (including GDM)
Roadblock 3. Practical and ethical challenges of locating research participants among diverse groups
Roadblock 4. Lack of birth cohorts and registries with repeated examinations for long-term follow-up studies over the life-course
Roadblock 13. Huge differences in structure, process, quality and delivery of diabetes care between European countries
Roadblock 15. Lack of appropriate animal models to study fetal programming, fetopathy and embryopathy

Introduction and background

Gestational diabetes mellitus (GDM) occurs in 5-15 percent of pregnancies and is increasing in prevalence. Women with a history of GDM have a very high risk of developing type 2 diabetes (80 percent within 5-10 years following pregnancy) and are also at increased risk for cardiovascular disease. However, prevention trials have shown that diet and exercise as well as pharmacological intervention can diminish the risk substantially (by 50 percent). In addition to acute pregnancy-associated complications (diabetic fetopathy) the offspring also have increased risk of obesity and metabolic syndrome in childhood and adolescence. Genetic predisposition, but also fetal programming and metabolic imprinting may contribute to these long-term risks in offspring. Genes and other factors contributing to fetal programming and metabolic imprinting, predisposing the offspring to obesity and diabetes in adulthood, are currently unknown as are factors underlying the different vulnerability of male and female offspring.

Criteria for diagnosis of GDM differ across the world and optimal treatment strategies and blood glucose targets during pregnancy to avoid maternal and fetal complications are still not known. The efficacy of conventional and new oral antidiabetic drugs and that of glucagon-like peptide 1 analogues or receptor agonists during pregnancy and breastfeeding have not yet been studied. Folic acid dosage during pregnancy in diabetes, as well as the impact of iron supplementation, vitamin D and antioxidants, is controversial.

The mechanisms of diabetic embryopathy and fetopathy are unclear and thus better understanding of the underlying pathophysiology and the generation of the best evidence-based therapeutic strategies are required. The ultimate Goals are to: prevent gestational diabetes; achieve normal pregnancy outcomes in diabetic pregnancies; prevent progression to type 2 diabetes in women with gestational diabetes and their offspring; prevent long-term cardiovascular disease in mothers with diabetes and their offspring and encourage an appreciation of the importance of sex- and gender-specific approaches to diabetes care (*see also* Milestones 2.2.01, 2.2.03, 3.2.03 and Goal 3.4).

Track 1. Mothers

Milestone 4.7.01. Prevent gestational diabetes (GDM) and progression from GDM to type 2 diabetes
The genes, epigenetic mechanisms and the effect of environment (including lifestyle) in determining predisposition to impaired glucose tolerance/diabetes during pregnancy should be identified. Sub-groups of patients with predominantly beta cell dysfunction and those with predominantly insulin resistance should be distinguished and targeted therapy should be implemented in randomised controlled trials.

Milestone 4.7.02. Develop new strategies to improve pre-pregnancy care in women with gestational diabetes and with pre-gestational diabetes
Many women with hyperglycaemia are first detected early during pregnancy and are therefore at increased risk of diabetic embryopathy. Improved methods to detect prediabetes/unknown type 2 diabetes prior to conception should be tested and validated also to target reduced fertility.

Women with pre-gestational impaired glucose metabolism and diabetes should be identified and treated accordingly. Pre-pregnancy care programmes have to be optimised and validated for all women with pre-gestational diabetes. Investigation of educational programmes with better adherence and acceptance and new motivational strategies should be undertaken to develop programmes to improve preparation for pregnancy. In addition, special programmes should be developed and validated for ethnic minorities at particular risk for type 2 diabetes (*see also* Goal 4.2).

Milestone 4.7.03. Develop evidence-based standardised criteria for diagnosis and treatment goals of gestational diabetes
The existence of different criteria for the diagnosis of GDM greatly limits comparison between regions and countries. The incidence of GDM in Europe is unclear as the diagnosis varies according to the test, diagnostic criteria, the ethnic group and the follow-up period. Therefore, it is essential that standardised criteria are developed and validated. This would allow clinical care delivery to be compared across Europe and ensure that Europe-wide research studies can be compared and validated to improve treatment (*see also* Goal 4.1 and Goal 4.2).

The achievement of normoglycaemia during pregnancy is currently limited by increased risk of hypoglycaemia, in particular in the first half of pregnancy, and is the most common cause of maternal death. It is unclear if recurrent hypoglycaemia is harmful to the developing fetus. It is important to develop and validate new concepts/methods to achieve normoglycaemia, without hypoglycaemia before and during pregnancy.

Currently the recommendations for weight gain during normal and diabetic pregnancy are inadequate. New studies are required to test and validate the optimal weight gain for pre-conception body mass index (BMI) categories (*see also* Milestone 4.4.02).

Milestone 4.7.04. Test and validate treatment options
Despite improvements in metabolic control, pregnancy outcomes for women with diabetes are still worse compared to those without diabetes. In addition to glucose control the impact of additional metabolic parameters such as lipids should be evaluated. Parameters of oxidative stress related to glucose peaks may play a role during pregnancy and use of antioxidants or vitamins could be useful in future therapy.

Continuous glucose monitoring (CGM) should be explored and validated in diabetic pregnancies to improve the possibilities for metabolic control. These aspects of monitoring and treatment require prospective clinical trials.

Milestone 4.7.05. Develop optimal strategies to prevent progression of complications in pre-gestational diabetes
Deterioration of diabetes complications, in particular retinopathy and nephropathy, is still a concern in diabetic pregnancies and is related to higher perinatal complication rates. Furthermore, pre-

existing cardiovascular disease will increase due to the rapidly growing number of obese women with type 2 diabetes before pregnancy.

Strategies should be developed and validated to identify risk factors and early biomarkers associated with progression of diabetes complications during pregnancy. With this knowledge, intervention programmes can be designed to prevent the progression of complications during and after pregnancy in women with pre-gestational diabetes. Educational programmes, prevention programmes and programmes for behaviour modification should be developed and validated to improve awareness in those individuals at risk.

Track 2. Offspring

Milestone 4.7.06. Understand fetal programming and gene/environment interaction
Intrauterine milieu and fetal programming play important roles in the development of chronic diseases such as obesity, diabetes, vascular disease and hypertension in adult life. GDM, hypertension, overfeeding as well as famine are associated with increased long-term risks to the fetus. In addition, epigenetic mechanisms and gene/environment interactions affect the health of the offspring. Substrates and environmental factors may affect male and female offspring in different ways. These sex differences require further detailed investigation, as does the relationship between sex hormones, sex hormone-binding globulin and glucose/insulin metabolism and the risk of diabetes and diabetes complications in both sexes.

Milestone 4.7.07. Understand diabetic embryopathy and fetopathy including sex-specific differences
Embryopathy (abortions, malformations) is the main cause of increased fetal and perinatal mortality and still a major concern in diabetic pregnancy. Fetopathy (macrosomia, fetal hyperinsulinism) is associated with life-long changes of neuroendocrine pathways related to obesity. The underlying mechanisms remain unclear. The pathophysiologic mechanisms and life-long sequelae of fetal growth abnormalities such as growth retardation and overgrowth require further study. Both are more common in diabetic pregnancies and are themselves linked to an increased risk of diabetes in the offspring.

Milestone 4.7.08. Develop new targets and treatment concepts to avoid fetal hyperinsulinaemia and metabolic imprinting
Understanding the causes of fetal hyperinsulinaemia would help to identify new therapies. No reliable treatment option is available at present to prevent fetal hyperinsulinaemia or metabolic imprinting. Therefore, new treatment options have to be tested first in animal models. The optimal therapy should then be tested and validated together with best surveillance of metabolic control in large randomised controlled trials with evaluation of both acute effects on fetal growth and perinatal outcome and long-term follow-up of the offspring. New and more effective treatment options with no or minimal side effects, in particular without hypoglycaemia, and exclusion of potential harm to the fetus have to be developed, tested and validated.

Track 3. Postpartum follow-up

Milestone 4.7.09. Understand the long-term effects of breastfeeding on health of mother and child
Breastfeeding is recommended for women with diabetes and thought to reduce the risk of obesity in their offspring. However, research in this area is limited and data controversial. This area requires much more detailed prospective study in relation to long-term effects on health and body weight of both the mother and child.

Milestone 4.7.10. Avoiding weight retention in women after delivery
Parity is an important contributor to overweight and obesity in women. This is likely to relate to hormonal changes, changes of adipokines and the increase in fat mass during pregnancy. Weight retention during the first year after delivery predicts further weight gain at follow-up. Weight reduction and behaviour modification programmes are needed and should be validated to prevent weight retention in particular after delivery in women with GDM and those with pre-gestational diabetes. Intervention should reduce progression to overt diabetes in women with prior GDM and prevent recurrence of GDM and its associated risks for the offspring in the subsequent pregnancy.

Milestone 4.7.11. Prevent type 2 diabetes and cardiovascular disease following gestational diabetes
Women with GDM have a seven-fold higher risk of frank diabetes compared to women with normal glucose tolerance. Biomarkers that identify those women at particular risk of gestational diabetes, diabetes and vascular disease have to be identified and validated.

Although there are several diabetes prevention studies that included women with prior GDM, analysis of the results of this important sub-group at particular risk is missing in most studies or only performed retrospectively (post-hoc sub-group

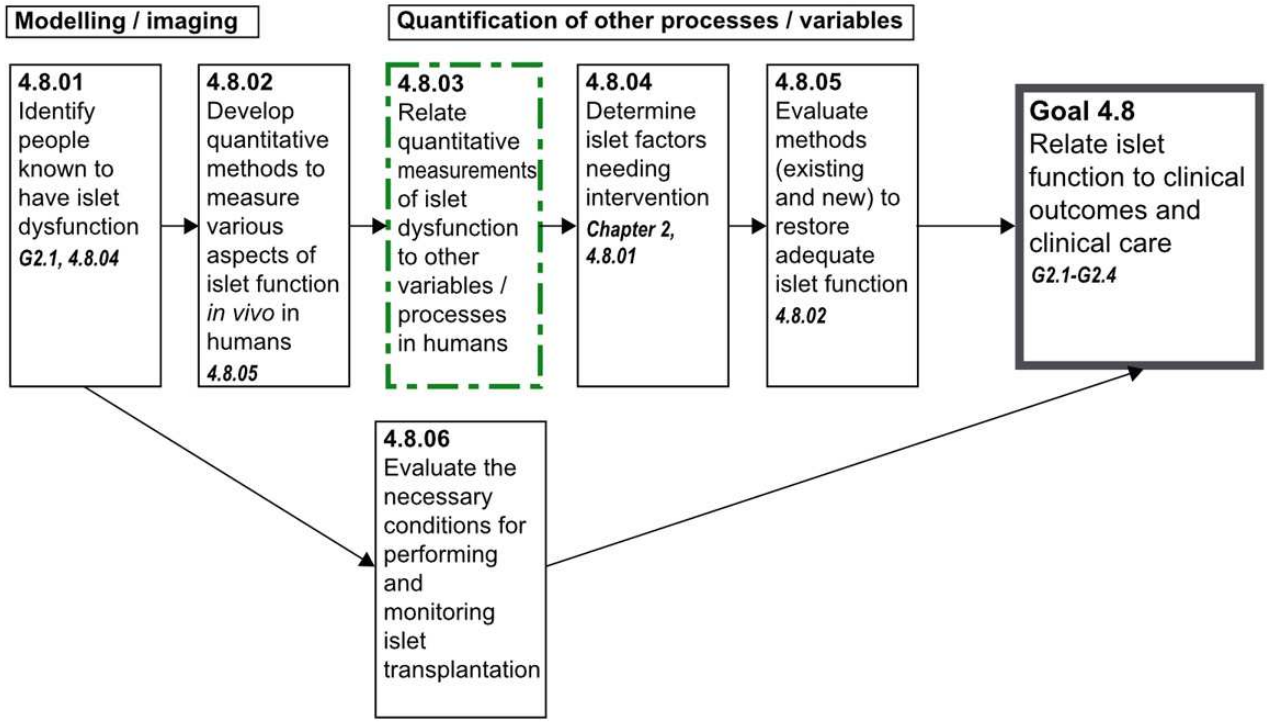
analysis). Therefore, large prospective studies in well-characterised women with prior GDM with different phenotypes and genotypes have to be undertaken and intervention strategies designed and validated to prevent type 2 diabetes and cardiovascular disease after GDM as well as recurrence of GDM.

Milestone 4.7.12. Prevent diabetes and obesity and cardiovascular disease in offspring

Recent studies show an increased risk of obesity, prediabetes and even diabetes in the offspring of women with GDM and pre-gestational diabetes. In particular newborns with growth abnormalities (small for gestational age, large for gestational age) are at risk of development of the metabolic syndrome and an increase in cardiovascular risk factors early in life. Biomarkers that identify those children at particular risk of diabetes and vascular disease have to be identified and validated (*see also* Goal 6.2).

Gender-sensitive risk scores for the offspring need to be defined. Large follow-up studies in offspring and prevention strategies will be necessary as part of the overall Goal to reduce and limit the epidemic of diabetes.

Goal 4.8. Relate islet function to clinical outcomes and clinical care



Roadblock 1. Ethical guidelines: in particular regarding data sharing and transfer, collection and use of biological materials, including DNA
Roadblock 2. Variation, lack of standardisation or international consensus across Europe in laboratory conditions, measurement techniques, sample handling
Roadblock 4. Lack of birth cohorts and registries with repeated examinations for long-term follow-up studies over the life-course
Roadblock 12. Partnerships between academia and industry (both pharmaceutical and other industry) are needed

Introduction and background

Islet dysfunction is an early event in the cascade of metabolic defects leading to diabetes. Longitudinal studies have shown that insulin secretory defects and insulin sensitivity defects confer equal relative risks of developing diabetes in persons with apparently normal glucose tolerance. Temporal progression of the metabolic disorder is manifested by inadequate islet cell responsiveness to all secretagogues (a *global* defect) and to glucose in particular, by the time a susceptible individual has attained impaired glucose tolerance. Preventing islet deterioration is a major goal for the prevention of diabetes and for the prevention of progression of preexisting diabetes. Understanding the causes of islet impairment, developing simple methods to measure impaired islet function, and developing improved strategies for intervention are critical to helping the person with diabetes better manage their own condition and live a healthier life. This area of research is of great interest to the biotechnology and pharmaceutical industry as it directly applies to the development of therapies.

The road maps for islet biology research (*see also* Goals 2.1-2.4) describe research directions focussed on the islet/beta cell itself (mostly *in vitro* studies to understand biochemical cascades, metabolic pathways, mitochondrial functions). In a complementary fashion, this clinical road map focusses on research with the 'intact' individual person in order to design more effective, simpler tests of islet function performed in the whole body and, ultimately, to develop interventions to restore islet function. Techniques of bioengineering and mathematical modelling are incorporated to better understand complex multi-organ pathophysiologic processes. An example would be the progression of beta cell failure as a function of changes in insulin sensitivity over the course of a diabetes prevention trial, or an intervention with incretin, or even in the years following stem cell transplantation (in the future). The aim is to yield an adequate restoration, and then maintenance, of the islet function, through pharmaceutical intervention, stem cells, transplantation, cell regeneration or growth, reduced apoptosis and other strategies.

Milestone 4.8.01. Identify people known to have islet dysfunction
People with characteristics known to indicate islet dysfunction (e.g. diabetes itself, pancreatitis and other secondary forms of diabetes, but particularly the range of prediabetic conditions such as impaired fasting glucose, impaired glucose tolerance, former gestational diabetes) are needed to provide data to allow the development of methods to quantify specific indices that reflect islet function *in vivo*. Identification of such subjects can be made with simple typical criteria used routinely in clinical research, such as measurements of glucose, insulin, C-peptide, proinsulin, amylin at fasting and/or during oral or intravenous glucose tolerance testing (*see also* Milestone 4.8.04 and Goal 2.1).

Milestone 4.8.02. Develop quantitative methods to measure various aspects of islet function *in vivo* in humans
New, less demanding methods for characterising islet processes are needed in order to reduce the burden on patients and clinical researchers. Thus, simple, easy to perform tests with mathematical modelling in all its different forms, relatively non-invasive, and able to be carried out at the subject's bedside would facilitate research in large cohorts of subjects. Such methods would improve the precision and accuracy of the outcomes of large clinical research studies for diabetes. Other more sophisticated techniques, such as non-invasive imaging of the pancreas and islets, also need to be developed to provide further insight on specific parameters of islet function that cannot be measured directly including the poorly understood relative contribution of decreased beta cell mass and function to impaired islet function.

Evaluation of islet function can be achieved by quantifying parameters related to insulin-mediated glucose control. The quantification can be attained through different approaches ranging from simple tests that, by perturbing the steady-state (usual) condition, clarify the different behaviour of the pancreas and peripheral insulin target tissues, to complex imaging analysis that provides information on a whole organ. For example, an intravenous injection of glucose that does not induce the 'proper' insulin response is a marker of secretion impairment; similarly, the arginine infusion test can be used to evaluate the insulin reserve in the cell. Imaging is a fast-developing field with new techniques and approaches introduced continuously. Research to apply innovative methods, such as magnetic resonance imaging and positron emission tomography, to imaging of the pancreas should allow assessment of the concentration of molecules *in vivo* with high sensitivity. In addition, islets can be inspected in order to evaluate their mass, vascularity, apoptosis, infiltration and other parameters that might be important in diabetes patients.

Eventually, the development of more 'user friendly' tests of islet function could provide detailed, useful information on a person's health status and may be used by general practitioners (family doctors) or by people with diabetes to stage and manage their own condition (*see also* Milestones 4.08.04, 4.8.05).

Milestone 4.8.03. Relate quantitative measurements of islet dysfunction to other variables/processes in humans. The aim here will be to quantify the role of islet impairment in the general diabetes picture and determine islet factors needing intervention. Diabetes is a multifaceted disease, but the role of islet dysfunction is fundamental. Quantifying islet dysfunction in diabetes would allow researchers to better characterise the processes through which islet dysfunction leads to eventual islet failure. Since islet function is related to processes occurring outside of the pancreas, other variables and physiologic mechanisms must be quantified to find possible relationships between measurements of islet dysfunction and measurements of these other variables (e.g. insulin resistance, glucagon, lipids, HbA1c, incretins, liver function, renal function). For instance, understanding the relationship between insulin sensitivity in liver, skeletal muscle and adipose tissue, and beta cell sensitivity to glucose could clarify the role of insulin release in insulin-resistant states. Physicians could therefore intervene in a more focussed way, knowing whether the main defect in an individual patient is at the level of insulin action or insulin secretion. In the first case, just restoring islet function may not be enough to effectively treat a person with diabetes.

Milestone 4.8.04. Determine islet factors needing intervention
Once it has been assessed that islet function is compromised according to specific criteria arising from the observation of known dysfunctions (*see* Milestone 4.8.01), assessing the relative contribution of the various components of the islet dysfunction (*see also* Chapter 2) would allow for more sharply targeted and hopefully more effective intervention.

Milestone 4.8.05. Evaluate methods (existing and new) to restore adequate islet function
Data from previously conducted clinical trials in selected groups of subjects should be (re-) evaluated to assess the outcomes of the interventions. At the same time, new trials must be

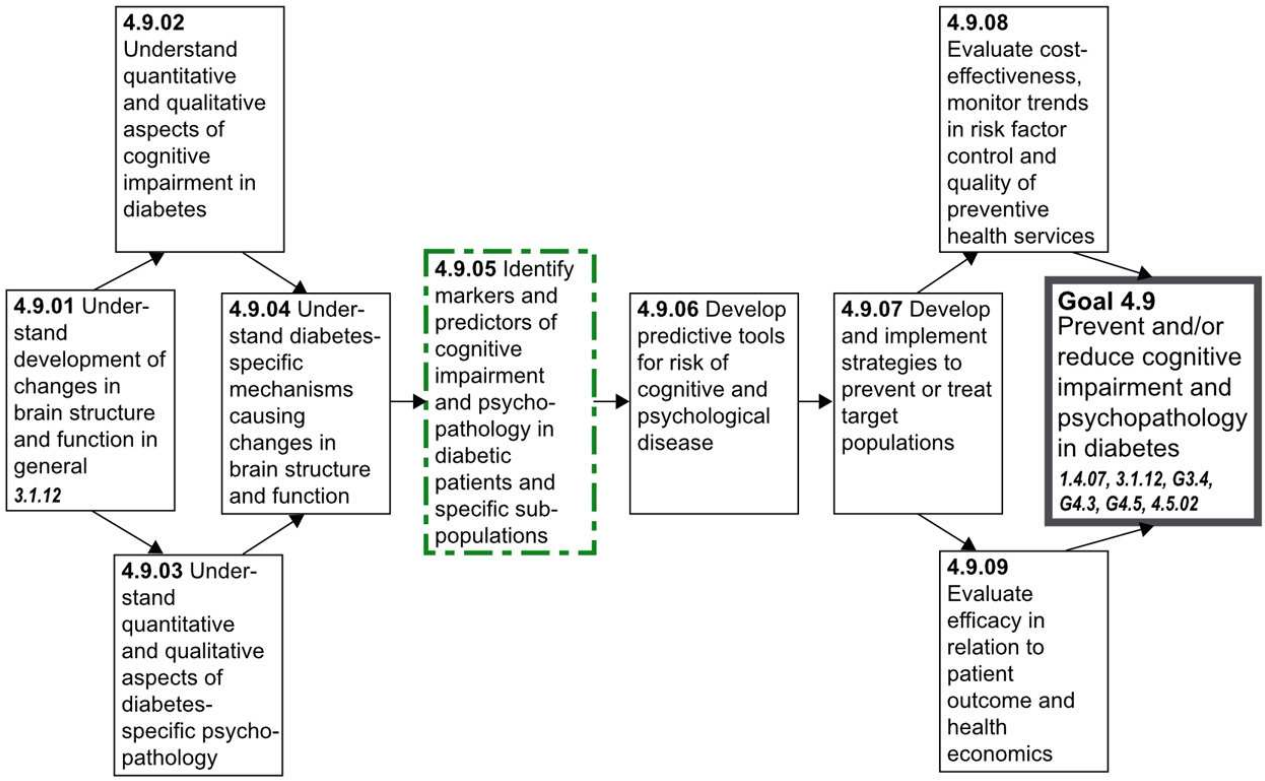
designed and promoted to validate new methods (*see also* Milestone 4.8.02) aimed to restore adequate islet function. Methods to be explored would be genetic manipulation, stem cells, pharmaceutical interventions, monitoring and artificial delivery systems. In the case of pharmaceutical interventions, a major emphasis must be placed on distinguishing between true (sustained) restoration of islet function and the acute effects of the drug.

This Milestone will require the design, development and implementation of specific software (bioinformatics) for (user friendly) data analysis with mathematical modelling, microarrays, and other advanced techniques. Simulation/modelling may also be used, but only after a thorough validation against real data both arising from the prior experiments and from new specifically designed tests.

Milestone 4.8.06. Evaluate the necessary conditions for performing and monitoring islet transplantation

For any type of surgery it is necessary to evaluate whether the intervention is feasible (the condition of the patient), but also all the steps mentioned above are essential in monitoring the progress of islet cell transplantation, because they help to indicate the success (or not) of the intervention itself.

Goal 4.9. Prevent and/or reduce cognitive impairment and psychopathology in diabetes



Roadblock 3. Practical and ethical challenges of locating research participants among diverse groups
Roadblock 16. Barriers in the multidisciplinary approach to guiding people with diabetes through health care structures (e.g. referral from primary to hospital care and back)

Introduction and background

Cognitive impairment and psychopathologies including depression, anxiety and eating disorders, occur more frequently in people with diabetes relative to those without the disease. Cognitive impairment and psychopathology reduce quality of life and affect long-term outcomes. Barriers to research in this field have included uncertainty regarding the causal relationships between diabetes and cognitive impairment/ psychopathology; lack of knowledge regarding the diabetes-specific effects on these conditions; lack of information about prevalence; methodological issues in diagnosis, measurement and classification.

Cognitive impairment and psychopathology can worsen glycaemic control and outcomes, thus it is important that novel research approaches are addressed to the above areas of uncertainty. The overarching Goal of this road map therefore is to prevent and/or reduce cognitive impairment and psychopathology in diabetes, by stimulating research activities that will study specific (molecular) mechanisms that lead to the development of cognitive impairment and psychopathology, specifically in people with diabetes. Be able to identify people at the highest risk of developing these conditions and develop and validate interventions for prevention and cure of these conditions. (*See also* Milestones 1.4.07, 3.1.12, 4.5.02 and Goals 3.4, 4.3, 4.5).

Milestone 4.9.01. Understand development of changes in brain structure and function in general

Normal ageing is associated with changes in brain structure and function. Changes in the brain may be different in men and women, as sex hormones influence brain function and behaviour. Prospective studies are required to investigate these processes in patients with diabetes. Such research would include serial measurements of parameters of brain function and structure, and the correlation between these changes and the sequential evolution of diabetes itself and its complications (*see also* Milestone 3.1.12).

Milestone 4.9.02. Understand quantitative and qualitative aspects of cognitive impairment in diabetes
Prospective animal and human studies are required to investigate the effects of diabetes on cognitive function. This line of research would include autopsy studies in patients where appropriate pre-mortem clinical histories are available.

Milestone 4.9.03. Understand quantitative and qualitative aspects of diabetes-specific psychopathology
Diabetes itself may be a risk factor for the development of cognitive impairment and psychopathology, and the occurrence of some of these conditions has been ascribed to the risk of complications. Research is required to understand the cause-consequence relationship between these common chronic diseases. Large cohort studies are clearly required to achieve the necessary statistical power. Early (prevention, pathophysiology) as well as long-term (to understand the progression and development of the disease entities) monitoring and the use of various methods [validated questionnaires and tests; non-invasive imaging (*see also* Milestone 3.1.12)] will be required.

Milestone 4.9.04. Understand diabetes-specific mechanisms causing changes in brain structure and function
Recent data indicate that diabetes adversely affects brain structure and function by directly affecting neurons and associated cells or via its effects on the vasculature. It will be important to distinguish between direct metabolic effects and those possibly driven by altered insulin action in the brain in diabetes. However, in humans these data are unavailable because of limited access to brain tissue for the necessary investigations. Progress will not be made in this area until it becomes possible to study human brain tissue more directly either *in vivo* (with novel less invasive probes) or post-mortem, with the appropriate consent and clinical history and collateral information.

Milestone 4.9.05. Identify markers and predictors of cognitive impairment and psychopathology in diabetic patients and specific subpopulations
In order to map the progress to cognitive changes and psychological diseases in patients with diabetes, prospective studies are required with a multidisciplinary approach incorporating basic research and clinical science. The aim of this research strategy is to describe markers of risk and progression to cognitive impairment and psychopathology in patients who are healthy at baseline.

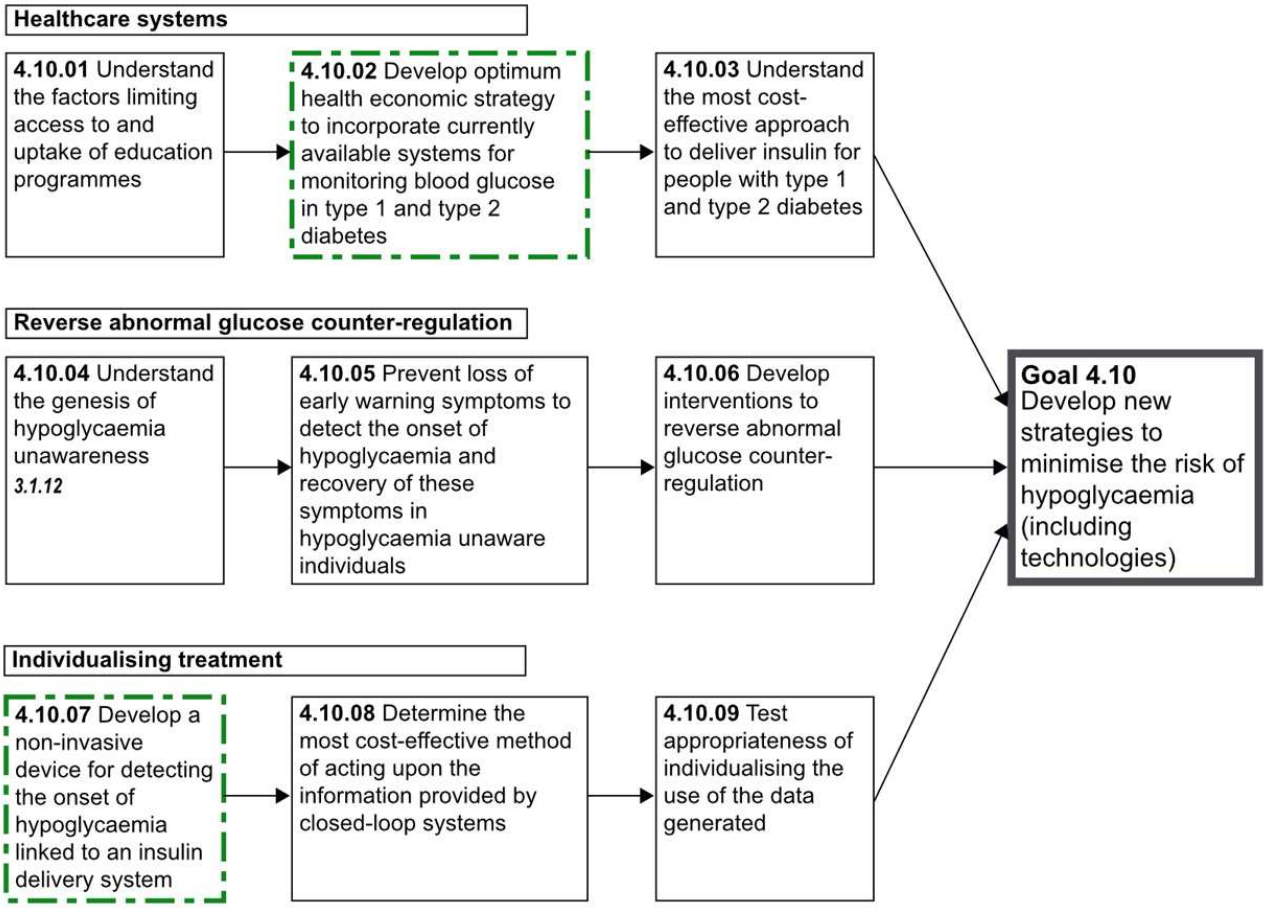
Milestone 4.9.06. Develop predictive tools for risk of cognitive and psychological disease
Simple tests that reliably predict future cognitive impairment and psychopathology in people with diabetes and specifically allow early detection of high-risk groups are an important research Goal. These types of prospective studies are required in diabetes patients in general, but there are specific vulnerable sub-groups in whom such research could be prioritised, including children who develop diabetes at a very young age, adolescents, and adult patients with diabetes-related complications [to investigate the *primary* development of the central nervous system (CNS) complications]. Equally important are those patients with pre-existing cognitive impairment and psychopathology, who have then developed diabetes (i.e. to investigate the effect of diabetes on the rate of secondary progression of the already existing CNS diseases).

Milestone 4.9.07. Develop and implement strategies to prevent or treat target populations
Treatments for cognitive decline and psychopathology in individuals with diabetes should be compared and evaluated in randomised prospective clinical trials.

Milestone 4.9.08. Evaluate cost-effectiveness, monitor trends in risk factor control and quality of preventive healthcare services
The costs of long-term care of those with cognitive impairment or serious psychological illness are enormous. Evaluation of the cost-effectiveness of the development and application of all interventions in patients with diabetes, both preventive and therapeutic, is therefore a high priority. Thus, specific allocation of budgets or shifting them to prevent and treat cognitive impairment/ psychopathology in diabetes will require an evidence base.

Milestone 4.9.09. Evaluate efficacy in relation to patient outcome and health economics
In addition to the above research strategies, an ultimate one is the measurement and evaluation of these interventions on patient outcome and on overall health economics.

Goal 4.10. Develop new strategies to minimise the risk of hypoglycaemia (including technologies)



Roadblock 1. Ethical guidelines: in particular regarding data sharing and transfer, collection and use of biological materials, including DNA
Roadblock 7. Lack of specific bioinformatic software to analyse and integrate multiple data
Roadblock 10. Resistance to implementation of large-scale clinical research in the setting of usual clinical care
Roadblock 12. Partnerships between academia and industry (both pharmaceutical and other industry)
Roadblock 13. Huge differences in structure, process, quality and delivery of diabetes care between European countries
Roadblock 14. Advances in diabetes treatment or new drugs or new devices can only be implemented if society is able to support such treatments

Introduction and background

Despite advances in the technology of insulin delivery, self-monitoring of interstitial and blood glucose and structured patient education, hypoglycaemia (low blood glucose) remains an important consideration for people with diabetes and healthcare professionals. The consequences of even a single episode of hypoglycaemia can range from a minor nuisance to major disruption in daily life for people living with diabetes. Consequently, some individuals resist attempts by the diabetes team to intensify insulin therapy leading to poor control and diabetes complications. Regular episodes of hypoglycaemia can limit employment, driving and educational attainment, and shorten life. There is also decreased awareness of hypoglycaemia with increasing number of episodes. The socioeconomic costs of dealing with severe hypoglycaemia are considerable. The Goal is therefore to minimise the risk of hypoglycaemia in people with diabetes. This will be reached by three convergent research tracks.

Track 1. Healthcare systems (to provide universal access to quality assured structured education, modern insulin-delivery systems and glucose monitoring technologies according to clinical need)

Research suggests that severe hypoglycaemia can be reduced by participation in structured education and by technology, including continuous subcutaneous insulin infusion (CSII-insulin pump therapy), continuous interstitial glucose monitoring (CGM) as well as traditional finger-stick blood glucose monitoring. Access to technology is limited with significant geographic variation across Europe. Even when patients can access technology, hypoglycaemia and the threat of very low glucose levels remains a major limitation in day-to-day life with diabetes.

Milestone 4.10.01. Understand the factors limiting access to and uptake of education programmes
Both for type 2 as well as type 1 diabetes, specific qualitative research is needed to investigate the barriers to comprehensive education in self-management. Telehealth is already used in some locations as a means to provide education, and to monitor from the home and provide intervention and feedback as necessary. This could be extended to investigate barriers to update of education and to develop new educational services.

Milestone 4.10.02. Develop optimum health-economic strategy to incorporate currently available systems for monitoring blood glucose in type 1 and type 2 diabetes
Optimisation of blood glucose monitoring systems including better understanding of factors influencing performance such as accuracy (e.g. drug interactions) and comparisons between systems are required particularly for the early detection of hypoglycaemic events. More research needs to be done to develop the most cost-effective approach to glucose monitoring for different classes of therapies tailored to individuals.

Milestone 4.10.03. Understand the most cost-effective approach to deliver insulin for people with type 1 and type 2 diabetes
This will require study of the use of insulin-delivery systems, including collaboration with industry to reduce the cost and improve the convenience of these devices. Such studies require research into training and education as well as psychosocial influences, and numeracy and literacy.

Track 2. Reverse abnormal glucose counter-regulation

The brain depends on a continuous supply of glucose from the peripheral circulation. Patients treated with insulin and oral sulphonylureas are at risk of hypoglycaemia. As blood glucose starts to fall, this is 'sensed' predominantly by the hypothalamus area of the brain, which switches on a complex hierarchy of physiological responses consequent upon activation of the autonomic nervous system. These include development of early warning symptoms to alert the individual to take appropriate action such as ingesting carbohydrate. Release of hormones (glucagon, adrenaline, noradrenaline, cortisol and growth hormone) all have the opposite effect to insulin i.e. they increase glucose production by the liver and reduce glucose use by muscle.

In order to reverse abnormalities in the central nervous system (CNS) response to hypoglycaemia, both clinical and basic investigations are required. At the level of clinical research these will include non-invasive and invasive approaches with the measurement of biochemical and other markers along with imaging, including functional magnetic resonance imaging and other novel imaging technologies.

Milestone 4.10.04. Understand the genesis of hypoglycaemia unawareness
A proportion of patients lose hypoglycaemia awareness, usually after longstanding diabetes. The research strategy would include the recruitment of cohorts of patients who do and do not have these features and dissecting the causes of differences in hypoglycaemia awareness in otherwise comparable subjects. This research would include the development of predictive markers and models for this serious complication (*see also* Milestone 3.1.12).

Milestone 4.10.05. Prevent loss of early warning symptoms to detect the onset of hypoglycaemia and recovery of these symptoms in hypoglycaemia unaware individuals
Hypoglycaemia unawareness can be transient, such as during pregnancy, or more permanent after many years of diabetes and is invariably associated with defective glucose counter-regulation. It is also associated with recurrent episodes of low blood glucose, i.e. hypoglycaemia begets hypoglycaemia. Three clinical categories are recognised: a complete failure to develop early warning symptoms; generation of early warning symptoms but failure to relate them to a low blood glucose because of cognitive impairment (due to neuroglycopoenia); generation of early warning

symptoms with an understanding that they are caused by low blood glucose but an inability to take appropriate action. Research should address patient cohorts in each of the above distinct categories. Studies would include the testing of novel strategies for prevention as well as reversal of hypoglycaemia unawareness. Different approaches are required in sub-groups of patients including children, adults and the elderly.

Milestone 4.10.06. Develop interventions to reverse abnormal glucose counter-regulation
Complex physiological mechanisms defend against severe hypoglycaemia. These include activation of the autonomic nervous system and release of counter-regulatory hormones. For people with type 1 diabetes, release of glucagon in response to falling glucose is lost after 5 years of diabetes. After 10 years many patients also have attenuated adrenaline responses, increasing the risk of severe hypoglycaemic events. Prospective human studies are required to understand the temporal sequence of these alterations in defensive physiology in patients with various forms of diabetes. Further to this, specific interventional approaches require formal study and comparison in these cohorts to test and validate novel treatment approaches such as the meticulous avoidance of hypoglycaemic episodes, nutritional interventions and technological devices.

Track 3. Individualising treatment

Milestone 4.10.07. Develop a non-invasive device for detecting the onset of hypoglycaemia linked to an insulin-delivery system
A highly desirable component of diabetes management is a non-invasive glucose monitoring system. Any closed-loop insulin-delivery system requires accurate glucose measurement (sensing) coupled with a reliable algorithm for determining insulin dose, timing and delivery with minimal user/patient input. The connection of CGM with CSII by a mathematical algorithm to form an 'artificial pancreas' is a major milestone along this research track.

Novel research approaches to closed-loop systems for insulin delivery are a high priority. Specific approaches will require collaboration between clinicians, engineers, mathematical modellers, and industry in order to design studies and specific intervention programmes to test novel device systems and combinations in various cohorts of patients at different stages of diabetes.

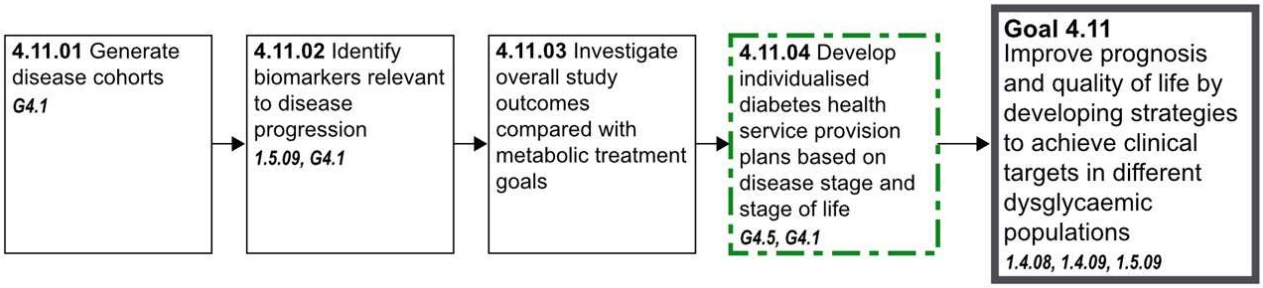
Milestone 4.10.08. Determine the most cost-effective method of acting upon the information provided by closed-loop systems
Further to the research outlined above, a broad qualitative and quantitative research approach is required to study the:

- cost of the closed-loop system
- size: anecdotally the most common reason for declining a technological approach remains a reluctance to be 'attached to a machine'
- requirement for finger-stick glucose monitoring for calibration
- acceptability and effectiveness of intermittent/episodic use of the system
- confounding effect of concomitant medications and electronic devices and physical conditions (altitude, temperature etc)
- role of literacy and numeracy of the user.

Milestone 4.10.09. Test appropriateness of individualising the use of the data generated
Individualisation of treatment includes consideration of age group, stage of disease, travel, shift work and inter-current illness. Technology developments can assist this process of individual customisation: these include bolus calculators, multiple bolus options and alterations in basal infusion rates in insulin pumps. Furthermore, new systems are likely to have the facility for add-on applications to aid in diabetes management beyond simply the recording of a single blood glucose value. These will include data management systems, personalised diet histories to examine the previous glycaemic fluctuations with certain meals and the impact of exercise, alcohol and travel, and perhaps for weight management. The next generation are also likely to incorporate telehealth functions and be smaller infusion devices, perhaps with the hand-held component having the facilities for social networking and sending SMS messages.

Significant barriers will need to be overcome but they are not in the true sense immovable roadblocks to research in that they could be resolved with appropriate collaboration and funding. These include the lack of a rapid-acting insulin with consistent and reproducible insulin absorption and action Currently available real-time monitoring systems are not non-invasive and require calibration. The physiological lag between interstitial and blood glucose measurements would need to be overcome. There is no fail-safe algorithm for relating insulin delivery to glucose measurements. There is interference with some glucose measurement techniques by other medications such as maltose and paracetamol. The cost of the system.

Goal 4.11. Improve prognosis and quality of life by developing strategies to achieve clinical targets in different dysglycaemic populations



Roadblock 1. Ethical guidelines: in particular regarding data sharing and transfer, collection and use of biological Materials including DNA

Roadblock 2. Variation, lack of standardisation or international consensus across Europe in laboratory conditions, measurement techniques, sample handling and clinical diagnoses and practice

Introduction and background

There is increasing recognition that general guidelines and treatment algorithms for diabetes are difficult to fit into clinical practice. Furthermore, treatment algorithms have come under criticism recently for their lack of foundation on an evidence base. Particularly for type 2 diabetes, the heterogeneity between patients is so wide that it is difficult and unscientific to generalise treatment recommendations. The long natural history of type 2 diabetes and its gradual progression run in parallel with the life-course of the patient, and with other co-morbidities. All of these components of temporal evolution of diabetes in the setting of the life of the individual call for a greater focus on personalised treatment – and a lesser reliance on general guidelines that may not 'fit' the needs of the individual.

Recent evidence shows that certain groups of patients may face *increased* risks (for example, for cardiovascular events) at HbA1c below 7.5 percent. Thus there is a need for better staging of patients according to diabetes phenotype, duration of disease, stage of life and the presence or absence of complications. Glucose targets (and other treatment targets) probably need to be different for these different sub-groups. Thus, early diagnosis and early treatment to near-normal glucose target in newly diagnosed patients (prior to the onset of complications) is likely to yield excellent long-term outcomes, as has been shown by analysis of the United Kingdom Prospective Diabetes Study (UKPDS). However, aggressive treatment to target in older patients with longer-duration disease (and cardiovascular complications, whether diagnosed or silent) may increase cardiovascular risk and risk of mortality. Studies in new large population cohorts will be necessary to support this research strategy, and prospective studies are now needed to address these questions.

The overall Goal of this map is to improve prognosis and quality of life in specific target populations of patients with diabetes (*see also* Milestones 1.4.08, 1.4.09, 1.5.09).

Milestone 4.11.01. Generate disease cohorts

Large collaborative networks will be required to generate study populations sufficiently powered to address these complex questions. One way to achieve this in Europe is the European Platform for Clinical Research in Diabetes (EPCRD). The first step is therefore to create large registries of diabetes patients, who will have consented to be studied in this way, classified initially according to age (life-phase), sex, date of diagnosis of diabetes and disease phase (*see also* Goal 4.1). This approach could then incorporate many cohorts with different characteristics, particularly age, but also gender, duration of diabetes, urban or rural setting, region within Europe etc.

Milestone 4.11.02. Identify biomarkers relevant to disease progression

When the large disease cohorts have been identified from Milestone 4.11.01 the next stage will be to undertake large-scale phenotyping in order to study a wide range of biomarkers relevant to disease progression and the risk of complications, including a search for novel markers and predictors of later outcomes. These would include: C-peptide, immune and inflammatory markers, HbA1c, lipid profiles, genetic markers, other novel markers (*see also* Milestone 1.5.09). A large-scale international diabetes clinical biobanking project is envisaged here. This approach would be greatly strengthened if established in the framework of the EPCRD, as has been outlined previously (Goal 4.1). Such an

integrated framework would allow the study of phases of disease progression and the onset of relevant complications and clinical endpoints (in specifically defined sub-populations) on a scale never previously possible.

Milestone 4.11.03. Investigate overall study outcomes compared with metabolic treatment goals

The questions raised by recent outcome studies require further investigation in large-scale prospective randomised controlled clinical trials. Thus, the central question of overall outcome compared with metabolic treatment goal (HbA1c) in early- compared with late-phase patients requires prospective study. A Europe-wide trial network could deliver such studies, which require very large scale and power to address and answer these complex questions. Many clinical outcomes could be similarly studied by this approach.

Milestone 4.11.04. Develop individualised diabetes health service provision plans based on disease stage and stage of life

The approach outlined in this map can form the basis for health service planning for diabetes, taking a more streamlined approach to care based on the stage of disease and stage of life of the individual patient (*see also* Goal 4.5).

Large-scale prospective randomised trials as described above allow the estimation and comparison of costs of care along different 'tracks', for example the cost of prevention of complications compared with the costs of more intensive treatments, regional comparisons, comparisons by age group to evaluate cost-effectiveness. The true costs of diabetes-related late complications have already been quantified in various studies in Europe, and amount in total to up to 10 percent of national health budgets. What has not been studied sufficiently are the costs of preventive care, and in particular those at specific stages of life and stages of disease evolution. This type of analysis will be facilitated by the EPCRD, (*see also* Goal 4.1). The overall goal of this research approach is to be in a position to target investment and clinical resources in the best way to improve the overall prognosis of people with diabetes, and to improve their quality of life, regardless of where they live, their age and their stage of disease evolution.

Roadblocks Chapter 4

Roadblock 1. Ethical guidelines: in particular regarding data sharing and transfer, collection and use of biological materials including DNA
Guidelines on data privacy are extremely complex and many are highly restrictive. Individual countries are likely to have different approaches to data handling and patient confidentiality.

Roadblock 2. Variation, lack of standardisation or international consensus across Europe in laboratory conditions, measurement techniques, sample handling and clinical diagnoses and practice
Lack of standardisation in laboratory assays (such as HbA1c, insulin and lipids) and in clinical practice means the same clinical picture can be managed differently in both quantitative (because of laboratory variability) and qualitative terms thus impacting on validation of clinical research in different settings. In diabetic pregnancy there is also no international consensus for the diagnosis of gestational diabetes mellitus or a standardised oral glucose tolerance test for such cases.

Roadblock 3. Practical and ethical challenges of locating research participants among diverse groups
Locating research participants is challenging among socially diverse groups (including: ethnicity, older age or early ageing, low socio-economic status, psychopathology and cognitive dysfunction, overweight and obesity). Barriers exist at several levels: limited literacy means potential participants are unaware of projects or of the research implications of those studies. Individuals in such groups often have sub-optimal health care service delivery. Unintentional labelling and stigmatisation caused by participation could impose negative attitudes towards changing behaviour. New strategies should be developed in order to increase participation, especially if barriers exist related to social background,

Roadblock 4. Lack of birth cohorts and registries with repeated examinations for long-term follow-up studies over the life-course
For research in pregnancy, childhood, normal ageing and ageing in diabetes there is a lack of diabetes registries (national and international). With diabetes of long duration (50-60 years) this also means that people already diagnosed with diabetes can 'lose' this diagnosis when admitted to hospital or long-term care, resulting in confusion and inappropriate treatment. Research on cost -effectiveness and its application to health care policy require such long-term data. For example morbidity from gestational diabetes mellitus is often mild and treatment expensive. The long-term benefits to mother and child are difficult to calculate and need follow-up of up to 20 years.

Roadblock 5. Lack of large European diabetes networks
There is a lack of networks focussing on clinical aspects of diabetes treatment those that do exist are mainly supported by pharmaceutical companies. This means there is a lack of reference centres, and experts in specialities such as paediatrics.

Roadblock 6. Fragmented electronic medical records, even within a single institution
Alongside the fragmented electronic records system is the lack of integration of the laboratory record (which may prove the presence of undiagnosed diabetes) with the main clinical record.

Roadblock 7. Lack of specific bioinformatic software to analyse and integrate multiple data. This applies to data on biological (genetic), psychological, lifestyle and social factors. New bioinformatic approaches (e.g. Google Health) have the potential to revolutionise the way that medical data are stored and transferred; however, they are not available to benefit specific sub-groups (e.g. children) with a chronic disease such as diabetes.

Roadblock 8. Gap in professional skills
The different skills between generalists, who provide most of the care to patients with diabetes in hospitals and institutional settings, and diabetes specialists, who work mostly in ambulatory care is a research roadblock.

Roadblock 9. Lack of appropriate specific professional training and education
This lack pertains to physicians and health care professionals providing treatment and care in specialised treatment centres, and referring patients from general health care settings.

Roadblock 10. Resistance to implementation of large-scale clinical research in the setting of usual clinical care and fragmentation of usual clinical care from the tradition of clinical research
This includes difficulties with ethics approval, intellectual property, language, culture and simple logistics. These barriers result in fragmentation of usual clinical care from the tradition of clinical research with a lack of awareness of research issues.

Roadblock 11. Drug regulatory issues: paediatric drug approvals lag behind adult decision-making in the regulatory pathway
The EMA needs to have sufficient paediatric scientific input to put promising drugs and technological advances on an accelerated pathway without compromising safety to make them available also for the young age group and pregnant women at the earliest possible stage.

Roadblock 12. Partnerships between academia and industry (both pharmaceutical and other industry) are needed
Such partnerships (that might also include SMEs) are necessary for the development and bringing to market of new drugs and devices, especially in the area of paediatrics where they are still limited. Additional incentives and support are needed.

Roadblock 13. Huge differences in structure, process, quality and delivery of diabetes care between European countries
Such differences are especially apparent in specialties such as paediatrics and obstetrics and in particular sub-groups. They must be taken into account when researching and testing interventions in the clinical setting.

Roadblock 14. Advances in diabetes treatment or new drugs or new devices can only be implemented if society is able to support such treatments
In particular, discrimination against children with diabetes and lack of support in school and the peer-group environment make it very difficult for families to implement advanced therapy. Also, national differences can lead to inequality of access to new therapy across Europe.

Roadblock 15. Lack of appropriate animal models to study fetal programming, fetopathy and embryopathy
There are ethical issues in studying these processes in pregnant women because of the risk of harm to the developing fetus, and thus only observational studies can be undertaken.

Roadblock 16. Barriers in the multidisciplinary approach to guiding people with diabetes through health care structures (e.g. referral from primary to hospital care and back)
Collaboration is required for joint studies of diabetes and cognitive/psychological diseases and is particularly challenging for inter-disciplinary research that will require major commitment of resources and joint structures.