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*Published in:*  
Diabetic Medicine

*DOI:*  
[10.1111/dme.14240](https://doi.org/10.1111/dme.14240)

*Publication date:*  
2020

*Document Version*  
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

### *Citation for published version (APA):*

de Galan, B. E., McCrimmon, R. J., Ibberson, M., Heller, S. R., Choudhary, P., Pouver, F. (2020). Reducing the burden of hypoglycaemia in people with diabetes through increased understanding: design of the Hypoglycaemia Redefining Solutions for Better Lives (Hypo-RESOLVE) project. *Diabetic Medicine*. <https://doi.org/10.1111/dme.14240>

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Article type : Trial Protocol

Title: Diabetic Medicine

Created by: Maria Davie

Email proofs to: bastiaan.degalan@radboudumc.nl

Article no.: DME-2019-00478

Accepted date: 14 January 2020

Article type: Trial Protocol

Short title/*Authors running head*: Understanding hypoglycaemia in diabetes • *B. E. de Galan et al.*

# **Reducing the burden of hypoglycaemia in people with diabetes through increased understanding: design of the Hypoglycaemia Redefining Solutions for Better Lives (Hypo-RESOLVE) project**

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## **Abstract**

**Background** Hypoglycaemia is the most frequent complication of treatment with insulin or insulin secretagogues in people with diabetes. Severe hypoglycaemia, i.e. event requiring external help because of cognitive dysfunction, is associated with a higher risk of adverse cardiovascular outcomes and all-cause mortality, but underlying mechanism(s) are poorly understood. There is also a gap in the understanding of the clinical, psychological and health economic impact of ‘non-severe’ hypoglycaemia and the glucose level below which hypoglycaemia causes harm.

**Aim** To increase understanding of hypoglycaemia by addressing the above issues over a 4-year period.

**Methods** Hypo-RESOLVE is structured across eight work packages, each with a distinct focus. We will construct a large, sustainable database including hypoglycaemia data from >100 clinical trials to examine predictors of hypoglycaemia and establish glucose threshold(s) below which hypoglycaemia constitutes a risk for adverse biomedical and psychological outcomes, and increases healthcare costs. We will also investigate the mechanism(s) underlying the antecedents and consequences of hypoglycaemia, the significance of glucose sensor-detected hypoglycaemia, the impact of hypoglycaemia in families, and the costs of hypoglycaemia for healthcare systems.

**Results** The outcomes of Hypo-RESOLVE will inform evidence-based definitions regarding the classification of hypoglycaemia in diabetes for use in daily clinical practice, future clinical trials and as a benchmark for comparing glucose-lowering interventions and strategies across trials. Stakeholders will be engaged to achieve broadly adopted agreement.

**Conclusion** Hypo-RESOLVE will advance our understanding and refine the classification of hypoglycaemia, with the ultimate aim being to alleviate the burden and consequences of hypoglycaemia in people with diabetes.

## **Background**

Diabetes is a major non-communicable threat to global health, affecting 10% of adults worldwide [1], and is among the most expensive chronic health conditions, imposing an increasing burden on healthcare resources [2]. Despite different underlying causes and approaches to treatment, both type 1 and type 2 diabetes can have devastating effects on physical and mental health and can continue to reduce both quality of life and life expectancy. Maintaining glucose at or close to recommended target levels has been shown to decrease risks of microvascular and macrovascular complications [3–7], and improves overall survival in people with recent-onset type 2 diabetes [6].

Insulin and insulin secretagogues (e.g. sulfonylureas) are effective in managing hyperglycaemia, but increase hypoglycaemia risk because their action is independent of glycaemic levels. Hypoglycaemia causes profound physiological and cellular stress, with marked stimulation of the autonomic nervous system and the hypothalamic–pituitary–adrenal axis, leading to symptoms ranging from feelings of unpleasantness to cognitive impairment, serious harm or death. In type 1 diabetes, 4–8% of premature deaths have been attributed to hypoglycaemia [8,9], not including the so-called ‘dead-in-bed’ syndrome, a mode of sudden death thought to result from hypoglycaemia-induced fatal arrhythmia

[10]. Severe hypoglycaemia, defined as an event causing sufficient cognitive dysfunction to require assistance from another person for recovery [11], is predictive of two- to threefold higher risks of cardiovascular morbidity and mortality in people with type 2 diabetes [12]. A recent analysis calculated that an unrealistically high prevalence of comorbid diseases would be needed to explain the association by frailty alone [13], yet the mechanisms underlying a causative relationship remain undiscovered.

On average, hypoglycaemia occurs at a rate of two events per week in those with type 1 and two per month in those with insulin-treated type 2 diabetes [14]. Reported rates of severe hypoglycaemia vary between 0.3 and 3 events per year in unselected cohorts of people with type 1 diabetes [15]. The distribution is highly skewed to those with impaired awareness of hypoglycaemia [16,17], a condition already recognized early following the discovery of insulin [18] and characterized by reduced ability to detect the onset of hypoglycaemia. Most estimates ignore ‘silent’ events that occur in these individuals or during sleep. Significant advances in diabetes management (e.g. insulin analogues, subcutaneous pumps, glucose sensor technology and structured education) appear to have had only a relatively modest impact on the incidence of hypoglycaemia [19].

The myriad of definitions for hypoglycaemia contribute to the variation in reported incidence rates of hypoglycaemia. The glucose cut-offs below which counter-regulatory responses to, and symptoms of, hypoglycaemia appear are not fixed and depend on both non-modifiable factors (e.g. age and duration) and modifiable factors (e.g. prior exposure to hyper- and hypoglycaemia) [20,21]. Despite agreement about the clinical relevance of any event of low plasma glucose that carries the potential to cause harm [22], uncertainty remains about where such harm starts and in whom, making it difficult to assign a single glucose threshold value to define hypoglycaemia. The International Hypoglycaemia Study Group (IHSG) has proposed a three-level classification: level 1: glucose  $\leq 3.9$  mmol/l (70 mg/dl), representing an alert value; level 2: glucose  $< 3.0$  mmol/l (54 mg/dl) to indicate ‘clinically important hypoglycaemia’, based on its association with cognitive dysfunction, reductions in hypoglycaemic awareness and mortality; and level 3: severe hypoglycaemia, as defined above [11].

This classification has been adopted by the American Diabetes Association, the European Association

for the Study of Diabetes, the International Society for Paediatric and Adolescent Diabetes [23] and the European Medicines Agency (EMA), and by an international expert panel on continuous glucose monitoring [24].

The evidence base supporting this classification remains relatively limited [25], particularly with respect to interstitial glucose measurements, which is relevant given the increasing use of glucose sensors, both clinically and in trials. Also, data on the health-economic consequences and on patient-reported outcomes related to ‘non-severe’ hypoglycaemia are largely lacking, but highly relevant in clinical practice, as hypoglycaemia affects virtually everyone using insulin. Thus, there is an urgent need to increase understanding of hypoglycaemia in diabetes and to provide more robust and comprehensive evidence to strengthen and/or refine the IHSG-proposed classification.

### **Project aim**

The Hypoglycaemia Redefining Solutions for Better Lives (Hypo-RESOLVE) project’s overall aim is to reduce the burden and consequences of hypoglycaemia in people with diabetes by increasing our understanding of hypoglycaemia, using a comprehensive multilevel approach that addresses unanswered questions and unmet needs [26]. In the present paper, we explain how clinicians and scientists with expertise in basic, clinical, psychological/behavioural and health-economic aspects of hypoglycaemia will work collaboratively with data science and biostatistics experts, industry partners, people with diabetes, healthcare organizations and other stakeholders to achieve this aim.

### **Project outline**

The work of Hypo-RESOLVE is structured across eight work packages (WPs), each of which has a distinct (scientific) focus, with strong interconnected linkages (Fig. 1). Central to the project is the further elucidation of the link between hypoglycaemia, whether measured by finger pricks or continuous glucose monitoring, and clinical (i.e. cardiovascular and mortality) consequences, its

underlying mechanism(s), and patient-reported and health-economic outcomes. We will also map definitions of hypoglycaemia as they are currently being used in national and international guidelines and maintain a close dialogue with regulators, including the EMA, and other stakeholders.

#### **Hypo-RESOLVE database: WP3 and WP4**

It is standard practice for hypoglycaemic events to be secondary or safety outcomes in clinical trials involving insulin treatment. A key objective of Hypo-RESOLVE is to collect these events alongside a range of clinical outcomes from over 100 clinical trials on insulin treatment and/or glucose monitoring in people with type 1 or type 2 diabetes, to construct a large, sustainable database, offering the statistical power needed to establish the glucose threshold(s) below which hypoglycaemia constitutes a risk. Entry criteria for these trials are: randomized trials initiated in 2001 or later; participants with type 1 or type 2 diabetes; insulin treatment alone or in combination with other drugs; and trial duration of at least 12 weeks. After a process of de-identification to ensure participant anonymity, original data from each trial will be extracted, reformatted and harmonized to the standard Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) format (<http://www.cdisc.org/>; Fig. 2). De-identified trial data will be uploaded to a secure server behind a firewall, inaccessible for downloads or changes, and subsequently harmonized and pooled into a single database, reachable for a variety of statistical analysis tools, implemented in the R statistical framework. After agreeing on categorization of hypoglycaemia, e.g. defined by presence (or absence) of symptoms, help from another person, certain glucose thresholds and duration, the associations with (un)known clinical and psychological consequences will be examined. A statistical analysis plan is being constructed and tested to perform analyses on the risk factors for, and consequences of, hypoglycaemia. Using data from the Scottish Diabetes Research Network Type 1 Bioresource [27], a Bayesian posterior distribution method was found to be a better fit to model the risk factors for the prediction of hypoglycaemia than the standard approach of negative binomial regression (manuscript in preparation).

## Mechanistic studies: WP2

The focus of basic research will be first on further elucidation of the pathogenesis of impaired awareness of hypoglycaemia. Animal studies with state-of-the-art transgenic approaches will also be used to discover novel pathways that contribute to the development of impaired awareness of hypoglycaemia as well as to identify therapeutic targets that may help to restore hypoglycaemia awareness.

A second crucial element of the project is to reveal the potential mechanism(s) underlying the association between (severe) hypoglycaemia and cardiovascular outcomes, which would complement analyses of the above-mentioned Hypo-RESOLVE clinical database. Recent research has shown hypoglycaemia to be a pro-inflammatory, potentially pro-atherogenic, stimulus [28], with the resulting response potentially modifiable by prior exposure to hypoglycaemia or the level of overall glucose control. We will characterize in detail the nature and time course of such inflammatory responses, including underlying processes, using hyperinsulinaemic hypoglycaemic glucose clamps. During and up to 1 week after the clamp, blood will be sampled and immune cells isolated for extensive phenotyping. The primary outcome is the effect of experimental hypoglycaemia on inflammatory responses; secondary outcomes include underlying molecular, metabolic and functional mechanisms, epigenetic profiles and oxidative stress, as well as cardiac function, assessed by echocardiography. The experiments will be conducted in people with: type 1 diabetes with intact awareness of hypoglycaemia; type 1 diabetes with impaired awareness of hypoglycaemia; type 1 diabetes with suboptimal glycaemia ( $\text{HbA}_{1c} > 64 \text{ mmol/mol}$  [8%]); and insulin-treated type 2 diabetes ( $n=16$  each). One group of volunteers without diabetes ( $n=16$ ), matched to those with type 2 diabetes, will undergo the same procedure. Another group ( $n=32$ ), matched to participants with type 1 diabetes, will be randomized to prior exposure to either two episodes of hypoglycaemia or normoglycaemia on the day before the clamp procedure. Sample sizes are based on a power calculation to meet the primary outcome for each subgroup separately, with comparisons between groups to be conducted in subsequent analyses. The broad inclusion criteria of this study, registered at [clinicaltrials.gov](https://clinicaltrials.gov) (NCT03976271), will enable us to assess the impact of awareness of hypoglycaemia,  $\text{HbA}_{1c}$ , prior



hypoglycaemia and duration of diabetes. Moreover, complimentary rodent studies will determine whether the effects in immune cells are replicated in specific organs (e.g. the heart) and tissues (e.g. adipose tissue), and to examine the impact of recurrent hypoglycaemia on end-organ histopathology and function.

### **Using continuous glucose monitoring to understand hypoglycaemia: WP5**

In the management of insulin-treated diabetes, self-monitoring of blood glucose, with its major limitations of (relatively) infrequent glucose measurements at (more or less) standard time points, is being superseded by (semi-)continuous glucose monitoring techniques. In the near future, these techniques will become increasingly important for monitoring glucose levels and patterns, assessing glycaemic targets and evaluating the effects of interventions, particularly in type 1 diabetes and in countries where individuals or the healthcare system can afford it. As continuous glucose monitoring starts to become used as an outcome measure to determine risk of hypoglycaemia, we also recognize that device metrics may be unstable over short durations. Glucose sensor data collected and harmonized in the constructed database (WP3) will enable analysis of the optimum duration of glucose sensor use and the relative contribution of sampling interval to determine an individual's risk of hypoglycaemia. We will use *in silico* modelling techniques to glucose sensor data to identify behavioural factors, including self-monitoring of blood glucose, carbohydrate counting and missed insulin administration, that modify the risk of hypoglycaemia.

Recent data show that, even in those with intact awareness of hypoglycaemia, up to 60% of episodes are asymptomatic and undetected by the individual [29]. This causes a clinical dilemma as to whether such events need to be treated or ignored, and raises issues about how people deal, psychologically, with visibility of the potentially overwhelming amount of (semi-)continuous data. We will therefore conduct a multinational observational study aiming to understand the impact of both symptomatic and asymptomatic episodes of low glucose sensor readings. Participants will be asked to wear blinded glucose sensors for 10 weeks, in addition to their usual means of glucose monitoring. They will also use an app to register all self-treated episodes of hypoglycaemia and answer questions in real-time

relevant to various domains of life that may be affected by hypoglycaemia. The primary objective is to determine the optimal definition of sensor hypoglycaemia in terms of threshold and duration by elucidating the optimum value of these variables that provides the best sensitivity and specificity for patient-reported hypoglycaemia. Secondary outcomes include the impact of symptomatic as well as asymptomatic hypoglycaemia and low interstitial glucose values on clinical, psychosocial and health-economic variables, such as activity, sleep quality, energy levels, well-being, quality of life and productivity. A sample size calculation based on the number of expected episodes of patient-reported hypoglycaemia and sensor-detected hypoglycaemia taken from a series of large observational datasets, calculated that 180 adults with type 1 and 325 with type 2 diabetes are required to meet our primary objective. Allowing for withdrawals and to be able to evaluate outcomes in those with impaired awareness, we aim to recruit 250 participants with type 1 diabetes, 50 of whom have impaired awareness, and 350 with type 2 diabetes ( $n=600$  in total). We will investigate differences in the impact of hypoglycaemia between type 1 and type 2 diabetes, and the impact of other aspects such as sleep and baseline hypoglycaemia rate on these factors.

### **Psychological burden and health-economic impact: WP6 and WP7**

The potential of hypoglycaemia to cause cognitive decline, social embarrassment, loss of consciousness, accidents and physical injury is a well-known cause of fear of hypoglycaemia [30] among individuals with diabetes, as well as partners, parents and other family members [31,32].

Substantial fear of hypoglycaemia often results in a coping strategy of maintaining glucose levels in the higher range, thus accepting increased exposure to hyperglycaemia and greater risks of associated vascular complications [33]. Indisputably, hypoglycaemia (and the fear of it) remains a major barrier to people with diabetes achieving and maintaining the glucose levels necessary to avoid the long-term complications associated with chronic hyperglycaemia [34].

To achieve better insight into the overall burden of hypoglycaemia for people with diabetes and their families, extensive systematic literature reviews will be performed to collate and critique all quantitative and qualitative studies investigating the impact of hypoglycaemia on quality of life and associated psychological outcomes among adults or children with diabetes and family members.

Findings will be summarized and, where possible, subjected to meta-analyses. Existing patient-reported outcome instruments relevant to assessing the burden of hypoglycaemia will be identified, and their psychometric characteristics will be summarized and critiqued. This knowledge will be used to develop new or refine existing patient-reported outcome instruments that can be used in various populations for health-economic evaluation purposes. In addition, these instruments will be developed into a preference-based measure, such that it can be used to generate quality-adjusted life-years for use in cost–utility analyses. As such, Hypo-RESOLVE will be able to precisely map the health-economic consequences of hypoglycaemia, including the costs of hypoglycaemia for healthcare systems in Europe and elsewhere.

In parallel, a qualitative multi-country online survey will be conducted to explore the unmet psychological needs of people with diabetes and their families in relation to the prevention, experience and management of hypoglycaemia. We plan to include 800–1000 participants from Denmark, Germany, the Netherlands and the UK, stratified into groups of adults with type 1 or type 2 diabetes, children and adolescents with diabetes, and family members. The findings will subsequently be used to design a multinational quantitative online survey to further address knowledge gaps, including the impact of (severe and self-treated) hypoglycaemia in adults and adolescents and on relationships, unmet care needs and barriers to talking about hypoglycaemia.

#### **Integration of the results of Hypo-RESOLVE: WP8**

The findings from Hypo-RESOLVE will be collated into a comprehensive summary for high-level communication with stakeholders and development of a consensus guideline with uniformly agreed definitions and data collection methods for the standardization of clinical investigations with regard to hypoglycaemia. A dialogue has thus been established with key European and American regulators, HTA body representatives, professional and diabetes organizations and other stakeholders.

#### **Project organization: WP1**

The Hypo-RESOLVE consortium comprises 23 partner organizations from academic centres across Europe, industry and biotech partners owning the vast majority of global insulin producing capacity

and the manufacturing of glucose monitoring devices, respectively, organizations representing people with diabetes, and a project management office. A multi-layered governance model has been agreed to ensure suitable levels of cooperation, scientific exchange and project management, as well as a decision-making process, in order to achieve the project's objectives. An international Patient Advisory Committee has been formed that interacts closely with each of the WPs to ensure that the voice of people with diabetes resonates in the direction, goals and strategy of the project. Finally, multi-disciplinary Strategic Advisory and Ethics Boards have been appointed to provide reflection and feedback from scientific and ethical perspectives, respectively.

### **Expected impact**

Using detailed and varied statistical analyses, Hypo-RESOLVE will provide robust evidence about risk factors and clinical, psychological and health-economic consequences of asymptomatic (i.e. sensor-detected), non-severe and severe hypoglycaemia in people with diabetes. Integration of these data offers the unique opportunity to refine and solidify an evidence-based classification of hypoglycaemia, whether measured in (capillary) blood or the interstitium, for its use in clinical practice, trials design and research, and for the development of clinical guidelines. The results of Hypo-RESOLVE are expected to be of considerable interest to a broad range of stakeholders, including people with diabetes, healthcare professionals, the scientific community, health technology assessment bodies, regulators, industry and payers (Table 1). The project's progress will be reported through scientific publications, the Hypo-RESOLVE website ([hypo-resolve.eu](http://hypo-resolve.eu)), social media (@HypoResolve), and stakeholder meetings, to ensure widespread dissemination to, and engagement with, all those potentially interested in the project's progress and outcomes and to endorse the ramifications of its analyses for classifying hypoglycaemia.

## **Hypo-RESOLVE limitations**

Although comprehensive, Hypo-RESOLVE will not provide answers to all questions relating to hypoglycaemia in people with diabetes. In particular, the Hypo-RESOLVE database may be (too) limited for directly examining harm of sensor-detected hypoglycaemia and investigating hypoglycaemia in certain populations. Children, the elderly, pregnant women, ethnic subgroups and people at highest risk of (severe) hypoglycaemia, including those with impaired awareness of hypoglycaemia, chronic kidney disease or other chronic comorbidities are usually excluded from most clinical trials. However, the harm of sensor-detected hypoglycaemia may be derived indirectly from the observational clinical study on continuous glucose monitoring. Also, examining the impact of hypoglycaemia on children, and in particular their carers, is a specific objective of the ‘psychology’ WP, whereas elderly populations will be included in the health-economic work. Finally, people with impaired awareness of hypoglycaemia will be recruited to the experimental, psychological and clinical studies, and animal studies will include models of this condition.

## **Conclusion**

Despite almost 100 years of experience with insulin as a treatment for diabetes and major advances in its management, hypoglycaemia remains a continuous threat to people with diabetes who require treatment with insulin or secretagogues. The clinical, psychological and health-economic consequences of hypoglycaemia and, in particular, the glucose threshold identifying increased risk for harm, remain to be fully established. Hypo-RESOLVE will apply a comprehensive multi-level, multi-disciplinary scientific approach to examine the links between hypoglycaemia (at various levels) and potentially harmful outcomes and its underlying mechanism(s), where applicable. Thus, Hypo-RESOLVE will advance our understanding of hypoglycaemia, so as to alleviate its burden and improve the lives of all people affected by diabetes.

## **Funding sources**

Hypo-RESOLVE has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 777460. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and T1D Exchange, JDRF, International Diabetes Federation (IDF) and The Leona M. and Harry B. Helmsley Charitable Trust. The industry partners supporting the JU include Abbott Diabetes Care, Eli Lilly, Medtronic, Novo Nordisk and Sanofi-Aventis. The funder had no role in the design of the project or its WPs, the collection or analysis of data, the writing of the manuscript or the decision to submit for publication.

## **Competing interests**

B.D.G. has served on scientific advisory boards for Novo Nordisk and received research grant support from AstraZeneca and Sanofi. S.R.H. has served on advisory boards for Eli Lilly, Novo Nordisk, Sanofi Aventis and Zealand Pharma and been a member of speaker panels for Novo Nordisk. R.J.M. has served on advisory boards for Eli Lilly, Novo Nordisk, Sanofi Aventis and been a member of speaker panels for Novo Nordisk. J.S. has served on the advisory boards of Janssen, Medtronic, Roche Diabetes Care and Sanofi Diabetes. Her research group (ACBRD) has received honoraria in respect of these activities, and she has also received unrestricted educational grants and in-kind support from Abbott Diabetes Care, AstraZeneca, Medtronic, Roche Diabetes Care and Sanofi Diabetes, sponsorship to attend educational meetings from Medtronic, Roche Diabetes Care and Sanofi Diabetes, and consultancy income and/or speaker fees from Abbott Diabetes Care, AstraZeneca, Medtronic, Novo Nordisk, Roche Diabetes Care and Sanofi Diabetes. M.R. is an employee of Eli Lilly and company. C.T. has served on scientific advisory boards for Merck and Novo Nordisk and received research grant support from AstraZeneca. M.M. is employee of Novo Nordisk A/S. All other authors declare no conflicts of interest.

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**Table 1** Expected impact of Hypo-RESOLVE for stakeholders

Stakeholder	Expected impact
People with diabetes	<ul style="list-style-type: none"><li>• Facilitating patient–clinician interaction when discussing glucose-lowering interventions that affect risk of hypoglycaemia</li><li>• Assessment of risk of hypoglycaemia at the individual level</li><li>• More support in relationships with partners, family members, co-workers and friends</li><li>• Better appreciation of indirect costs of (non-severe) hypoglycaemia, such as overall functioning, sleep, well-being, quality of life, productivity and work-related absenteeism and presenteeism</li><li>• Advancement of personalised glucose management</li></ul>
Healthcare professionals	<ul style="list-style-type: none"><li>• Improved knowledge of clinical and psychological impact of hypoglycaemia (at various levels)</li><li>• Better appreciation of trial outcomes</li><li>• More insight into the pathways underlying hypoglycaemia-sensing and impaired awareness of hypoglycaemia</li><li>• Equipped healthcare professionals better to discuss treatment choices with people with diabetes and their family members</li></ul>
Payers	<ul style="list-style-type: none"><li>• Calculation of the overall costs of the hypoglycaemic burden</li><li>• Enabling more accurate cost-effectiveness of interventions aimed at improving glucose control</li><li>• Help with directing resources to where they can be used the most efficiently</li></ul>
Regulatory authorities	<ul style="list-style-type: none"><li>• Better understanding of the clinical, psychological and health-economic impact of hypoglycaemia, and of valid assessment tools</li><li>• Facilitating the conduct and use of meta-analyses to compare both efficacy and (hypoglycaemic) safety of glucose-lowering interventions</li><li>• Providing strong evidence base for development of guidelines and its adoption by other stakeholders, including payers</li></ul>

Scientific community	<ul style="list-style-type: none"> <li>• Further delineation of mechanisms underlying the link between hypoglycaemia and cardiovascular risks</li> <li>• Setting the standard for glucose levels to be used in experimental hypoglycaemia research (e.g. clamps)</li> <li>• Invitation to scientists to use the constructed Hypo-RESOLVE database to answer new research questions</li> </ul>
Industry	<ul style="list-style-type: none"> <li>• Enabling better comparisons of glucose-lowering interventions and strategies across trials and benchmarking industry's products against those of competitors</li> <li>• Harmonization of hypoglycaemia measures by SMBG or CGM will inform the industry how to best apply CGM in future clinical trials</li> <li>• Discovering new targets for intervention will open avenues for the development of novel hypoglycaemic risk reducing pharmaceutical agents and technological solutions</li> <li>• Helping to better define populations most in need of hypoglycaemia risk reducing interventions in clinical trials</li> </ul>

CGM, continuous glucose monitoring; SMBG, self-monitoring of blood glucose.

FIGURE 1 Organizational structure and interaction of the work in Hypo-RESOLVE: project management [work package (WP)1], animal and human pre-clinical experiments (WP2), construction of the sustainable Hypo-RESOLVE database (WP3), analysis of the Hypo-RESOLVE database to refine and solidify the classification of hypoglycaemia (WP4), glucose monitoring studies (WP5), psychological burden of hypoglycaemia (WP6), health-economic impact of hypoglycaemia (WP7) and interaction with stakeholders and engagement with people affected by or living with diabetes (WP8).

FIGURE 2 Workflow for the construction of the Hypo-RESOLVE database. API, application programming interface; WP, work package.

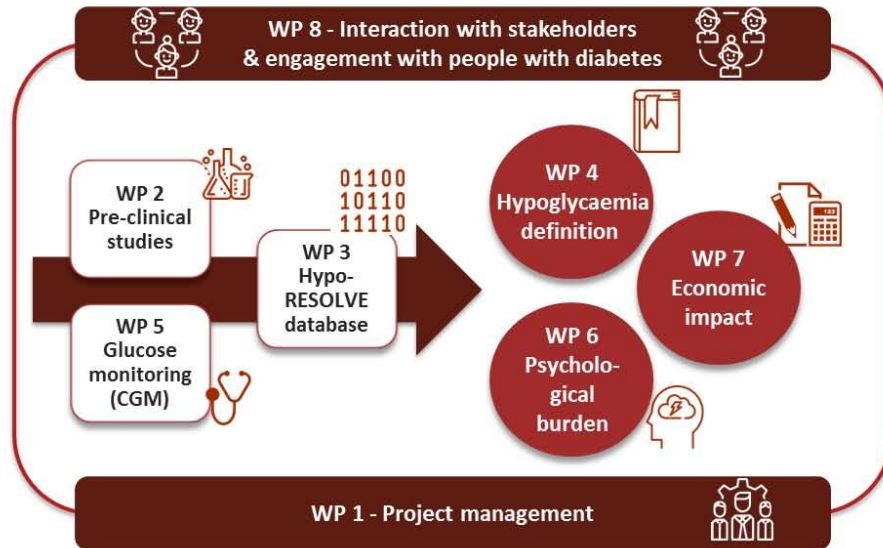


Figure 1: Organisational structure and interaction of the work in Hypo-RESOLVE: project management (WP 1), animal and human pre-clinical experiments (WP 2), construction of the sustainable Hypo-RESOLVE database (WP 3), analysis of the Hypo-RESOLVE database to refine and solidify the classification of hypoglycaemia (WP 4), glucose monitoring studies (WP 5), psychological burden of hypoglycaemia (WP 6), health-economic impact of hypoglycaemia (WP 7) and interaction with stakeholders and engagement with people affected by or living with diabetes (WP 8). WP denotes work package.

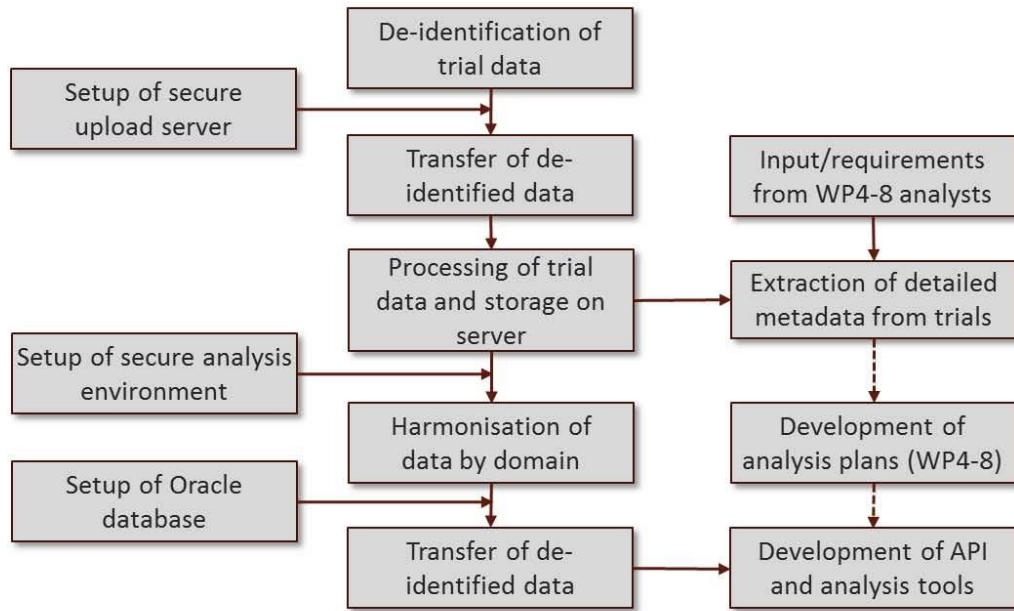


Figure 2. Workflow for the construction of the Hypo-RESOLVE database. API denotes application programming interface.