Full/long title of the study

Improving the care of people with diabetes-related ketoacidosis (DKA): The DEKODE (Digital Evaluation of Ketosis and Other Diabetes Emergencies) study

Short study title/acronym

DEKODE DKA

Protocol version number and date

V 2.0 11.07.2025

Research reference numbers

IRAS Number	IRAS 344284
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This protocol has regard for the HRA guidance

Signature page

The undersigned confirms that the following protocol has been agreed upon and accepted and that the Chief Investigator agrees to adhere to the signed University of Birmingham's Sponsorship CWE declaration.

We agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

We also confirm that WE will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate, and transparent account of the study will be given, and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature:  Date: 29 January 2025

Name: Dr Punith Kempegowda

Sponsor statement:

The University of Birmingham, in conjunction with the National Institute for Health and Care Research (NIHR), is sponsoring this study.

Table of Contents

Glossary of Terms

Term	Abbreviation	Description
Quality Control Documents	QCD	Quality Control Documents can be instructions, forms, templates or checklists. They are developed to share best practices, promote standardisation to guarantee quality standards are maintained and reduce resources otherwise needed to develop similar documents. Unless indicated otherwise in the relevant SOP, QCDs are not mandatory and are designed to be an optional aid to UoB staff.
Quality Management System	QMS	A Quality Management System is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
Standard Operating Procedures	SOP	Standard Operating Procedures are detailed written instructions to achieve uniformity in the performance of a specific function. They define tasks, allocate responsibilities, detail processes, indicate documents and templates to be used and cross-reference to other work instructions and guidance or policy documents. They are standards to which the UoB may be audited or inspected.
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial, which does not necessarily have a causal relationship with the intervention, received.
Related Event		An event, which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: • Results in death • Is life-threatening • Requires hospitalisation or prolongation of existing hospitalisation* • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator *Hospitalisation for elective procedures (unless brought forward due to worsening symptoms), social reasons, or logistical reasons is not regarded as a SAE. (See Section 10).
Unexpected and Related Event		An event that meets the definition of both an Unexpected Event and a Related Event.
Unexpected Event		The type of event that is not listed in the protocol as an expected occurrence.
Source Data		All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

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Study summary

Diabetes-related ketoacidosis (DKA) is one of the most common causes of emergency hospital admissions for people with diabetes. When someone has DKA, their body doesn't have enough insulin, which causes high sugar and acid levels in their blood. Last year, there were more than 32,000 cases of DKA in the UK, and it cost a lot of money, over £90 million, to take care of it. DKA can make people feel very stressed, anxious, and uncomfortable. They may worry about it happening again or other problems it can cause. If DKA isn't treated properly, it can even be deadly.

In 2020, the DEKODE (Digital Evaluation of Ketosis and Other Diabetes-related Emergencies) project was started to improve DKA care in hospitals. The early results of DEKODE showed that people with DKA sometimes get different care, even in the same hospital. The model also helped us understand the common reasons that cause DKA. We can use this information to prevent future DKA. While this project was praised for its success, it also raised important questions. We don't know why there are such differences in DKA care, and we don't know what people who had DKA think about the care they received. Several people conduct audits to address this. However, it has not given any concrete answer due to many reasons. We want to find answers to these questions to improve the DEKODE program and use it in hospitals across the UK. Our ultimate goal is to give the best care possible to people admitted to hospitals because of this dangerous condition.

This research aims to improve the safety and management of DKA in people admitted to hospitals in the UK. We will achieve this through five work packages:

1: Description of the inequities in DKA care and outcomes in the UK

2: Lived experiences of people with DKA.

3: DEKODE- understanding the model, its implementation and effectiveness.

4: Investigating Recurrent DKA: A Retrospective Cohort Analysis Using DEKODE Background

5: Health economics evaluation of the DEKODE model

Funding and support in kind

FUNDER	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
NIHR Academy, 21 Queen Street, Leeds, LS1 2TW Tel: 0113 532 8422 Email:academy@nihr.ac.uk	NIHR Advanced Fellowship awarded to Dr Punith Kempegowda (ref: NIHR303671)

Role of study sponsor and funder

The funder of this research, the National Institute of Health and Care Research (NIHR), has no role in study design, collection, management, analysis or interpretation of data, writing of reports, or the decision to submit data for publication.

The NIHR requires that all publications arising from the research are published in open-access format, facilitating free, unhindered access to research results and outcomes at any time.

The chief investigator and his team are responsible for study design, collection, management, analysis or interpretation of data, report writing, and submitting data for publication.

Compliance Statement

The DEKODE DKA study will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the General Data Protection Regulation & Data Protection Act 2018, and the principles of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals before implementation.

Roles and responsibilities of study management committees/groups and individuals

Study Management Group

- **Roles & Responsibilities:**

The Study Management Group comprises the Chief Investigator, the study coordinator and other key individuals involved in the day-to-day management of the study. The Study Management Group will usually meet monthly to review progress and any issues arising; the agenda and minutes of the meetings will be filed in the Study Master File.

- **Membership:**

Dr Punith Kempegowda

Dr Parth Narendran

Prof Ketan Dhatariya

Prof Krishnarajah Nirantharakumar

Prof Sheila Greenfield

Prof Justin Warring

Dr Nevil Chackalaparambil Philip

Dr Martin Burrows

Patient & Public Involvement (PPI) Group

- **Roles & Responsibilities:**

Affected patients have provided input into the study design. In addition, a formally assembled PPWE group will give ongoing input into study documentation (in particular into the patient-facing documents), execution and analysis, as well as advice on study recruitment, publication of study findings and research-associated public engagement activities.

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KEYWORDS: Diabetes, Diabetic Ketoacidosis, quality improvement, implementation science

Study flow chart

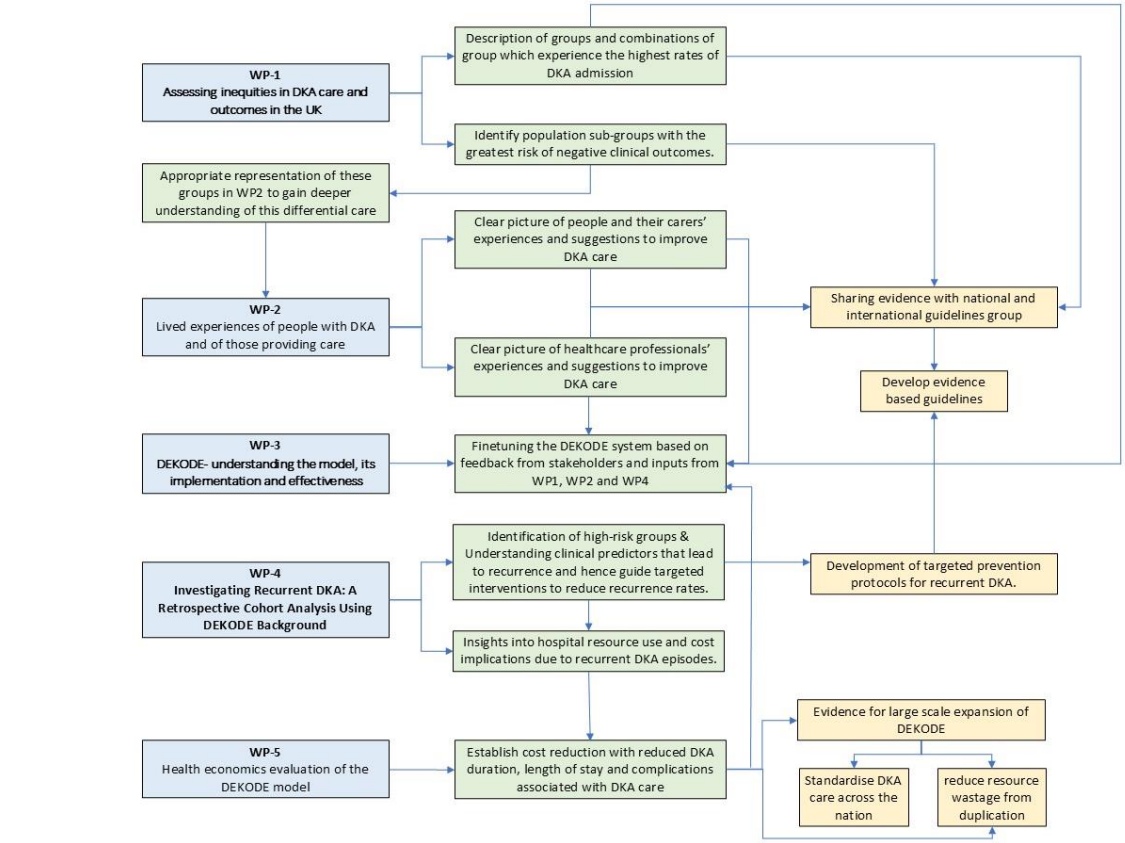

Figure 1: The blue boxes indicate the project work packages (WP), the green boxes indicate anticipated outcomes, and the yellow boxes indicate plans post-fellowship. WP-1 will identify populations most vulnerable to adverse clinical outcomes when admitted with DKA. WP-2 will capture the experiences of healthcare professionals, patients, and carers to improve DKA management. WP-3 will refine the DEKODE model based on feedback from WP-1, WP-2, and WP-4, facilitating its large-scale expansion and standardisation of DKA care across the UK. WP-4 will investigate recurrent DKA by identifying high-risk groups and clinical predictors, guiding targeted interventions and providing insights into the cost implications of recurrent DKA episodes. WP-5 will evaluate the health economics of the DEKODE model, establishing cost reductions through improved DKA management. Insights from WP-1 and WP-2 will shape and expand DEKODE to other hospitals within the UK.

Improving the care of people with diabetes-related ketoacidosis (DKA): The DEKODE (Digital Evaluation of Ketosis and Other Diabetes Emergencies) study

1. Background

The current gap in diabetes-related ketoacidosis (DKA) research lies in understanding the factors contributing to variations in care and outcomes between patients with DKA. There is a paucity of research on the influence of demographic factors such as age, sex, ethnicity, and region where the care was provided on patient experiences and outcomes. Identifying these crosslinks can provide crucial insights into developing targeted interventions, improving patient outcomes and promoting equitable DKA care among diverse populations.

DKA poses a grave threat to people with diabetes and is one of the most common reasons for emergency admission to hospitals in people with diabetes (1,2). A triad of hyperglycaemia, acidosis, and ketosis characterises it. Structured guidelines have transformed DKA from a certain fatality to a treatable complication (3). Although there has been an incremental reduction in mortality over the years (4,5), the condition is still associated with significant morbidity in people with diabetes (6,7).

Newer precipitating factors have increased the frequency of DKA in recent years. During the COVID-19 pandemic, an excess of diabetic ketoacidosis (DKA) in people with newly diagnosed diabetes was noted across all age groups (7). Checkpoint inhibitor-associated autoimmune diabetes mellitus (CIADM) is a distinct form of autoimmune diabetes that is a rare complication of immune checkpoint inhibitor therapy. A recent systematic review found that DKA occurred in 69.7% of CIADM (8). Another systematic review and meta-analysis of 42 studies, including 102 984 youths, found that incidence rates of type 1 diabetes (T1DM) and DKA at diabetes onset in children and adolescents were significantly higher after the start of the COVID-19 pandemic than before the pandemic (9). With these newer precipitating factors, DKA appears to be different from the classic DKA presentation. COVID-positive people with type 1 diabetes were more hyperglycaemic on admission than COVID-negative and pre-COVID people (10). People with type 2 diabetes (T2DM) presented unusually in DKA when infected with COVID-19, with greater ICU needs and higher mortality rates (10).

The financial burden from DKA on healthcare systems is substantial (11,12), and recent data shows an upward trend in the incidence of DKA and associated expenses. There were 32,920 DKA episodes from September 2021 to August 2022 in the UK, costing £90,771,230 to the NHS (13). These numbers and costs are much higher than similar periods in the previous years (September 2019 to August 2020: 29,490 episodes costing £72,595,060; September 2020 to August 2021: 31,825 episodes costing £80,395,750) (13). Therefore, addressing these escalating challenges is a priority.

2. Rationale

Previous studies shed light on comparable DKA durations between T1DM and T2DM (14), but a wider lens is needed to view the complete picture across the UK and beyond. Literature on variations in DKA care across regions, sex, ethnicity, or deprivation is scarce**.** This is crucial information required to guide the care process for our patients. Furthermore, no studies have assessed patient experience and satisfaction for people admitted with DKA. This information is crucial to ensure optimal and equitable DKA care.

The impact of clinical audits is limited, time-consuming, resource-intensive, limited scope, and potential for bias (15,16). These clinical audits may have a limited impact on clinical practice due to resistance from healthcare providers and limitations in audit design or methodology ((17). A significant chunk of the resources is drained for designing the audit and the data collection tool. When different hospitals spend valuable resources developing bespoke audits for their centres, it results in duplication and limits comparing findings and sharing best practices, which can improve patient outcomes. For example, studies have found that only a fraction of

recommendations made during an audit were implemented within six months, and some audits failed to address underlying problems (17).

Recently, a quality improvement project (QIP) has been employed to explore the trends in managing DKA care (18). While audits involve reviewing clinical practice against established standards, QIPs aim to implement changes for better patient outcomes. The latter can be more resource-intensive to facilitate collaboration, communication, and shared learning among healthcare professionals. When done locally, it still has the limitations of being unable to compare performances and share best practices. Therefore, there is a need to develop a standardised model which any interested hospital can adopt.

Our research has highlighted the potential of a QIP to revolutionise DKA care by reducing DKA duration from a median of 20.2 hours to 10 hours (19). This QIP helped us evaluate DKA management during the COVID-19 pandemic (10) and provided invaluable insights into the evolving landscape of DKA and its treatment (14). Inspired by the success of DKA QIP, we created DEKODE (Digital Evaluation of Ketosis and Other Diabetes Emergencies). This cloud-based model provides a ready-to-use data collection tool and eliminates the need for redundant design and pilot processes. The model identifies trends in DKA care using pseudonymised routine clinical data and provides feedback every three months. DEKODE empowers hospitals by providing quarterly feedback on critical parameters of DKA care, ranging from treatment appropriateness and complication rates to DKA duration and length of stay (20). DEKODE is now recognised as the national audit for DKA by the Association of British Diabetologists and recommended by National Health Service Get It Right First Time (NHS GIRFT) and the Diabetes Care Accreditation Program (DCAP) program by the Royal College of Physicians (RCP). Overall, **DEKODE is a win-win-win strategy**:

- Win for local hospitals- It streamlines local hospital efforts, saving precious time, money, and resources.
- Win at a national level- It fuels national progress by aggregating data from diverse centres, unravelling regional and temporal trends in DKA care.
- Win for patients- it champions patients by fostering continuous improvement and enabling hospitals to deliver superior DKA care.

We firmly believe expanding this model nationally, exploring the lived experiences of people admitted with DKA and understanding the motivations behind NHS participation in the DEKODE model can elevate the safety, efficiency, and consistency of DKA management and minimise inter-patient and inter-hospital variability by sharing best practices, ultimately transforming countless lives for the better.

3. Theoretical framework

The theoretical framework of the DEKODE study incorporates multiple disciplines to understand the complexities of DKA. This includes:

Epidemiology: Examining the distribution and determinants of DKA in different populations.

Sociology: Understanding the social determinants of health contributing to DKA incidence and outcomes.

Implementation Science: Developing and testing interventions to improve DKA management and prevent its occurrence

Health Economics: Assessing the economic impact of DKA on individuals and the healthcare system.

4. Research question/aims

- To determine the variations and inequalities in DKA care outcomes in the UK across age, sex, ethnicity, deprivation, region, and vulnerable population (e.g., people with mental health conditions/learning disabilities).
- To understand the experiences of people treated for and treating DKA.
- To identify the implementation principles for patient-centred care in people admitted with DKA and through DEKODE.
- To investigate the predictors, clinical outcomes, and healthcare impact of recurrent DKA episodes.
- To evaluate the cost-effectiveness of the DEKODE initiative.

5. Study Design

Our proposal has five work packages:

Work package 1: Assessing inequities in DKA care and outcomes in the UK.

Work package 2: Lived experiences of people treated for and treating DKA.

Work package 3: DEKODE- understanding the model's implementation and effectiveness.

Work package 4: Recurrent DKA

Work package 5: Health economics evaluation of the DEKODE model.

5.1. Work package 1: Assessing inequities in DKA care and outcomes in the UK.

Using linked health data, we will describe inequities in the following ways:

1) Incidence rate of DKA (objective 1.1), and

2) Clinical outcomes associated with DKA (objective 1.2)

We will examine how the incidence rate and outcomes vary over time by region, age, sex, ethnicity, deprivation status, presence of mental health conditions and region where the care was provided. Ethnicity will be defined by the list of ethnic groups from the UK Census (21). Deprivation status will be categorised based on the Townsend Deprivation Index quintile (22).

5.1.1. Objective 1.1: Incidence rate of DKA

Study design

We will undertake a population-based open retrospective cohort study between the 1st of January 2001 and the 31st of 2023 using data from the Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Practice Research Datalink (CPRD) primary care records linked to Hospital Episode Statistics (HES) (13,23). The data obtained from CPRD will be anonymized, and we will submit a separate ethics application specifically for this dataset in accordance with CPRD requirements.

Study setting

We will use CPRD Aurum (containing routinely collected data from practices using EMIS Web®) (24), CPRD GOLD (containing data from practices using Vision® software), and HES (contains details on admissions including International Classification of Diseases (ICD)-10 codes for diagnosis and Office of Population Censuses and Surveys (OPCS) codes for procedures) to achieve Our objectives.

Study population and exposure definition

The primary study population for incidence rates of DKA will be people living with T1DM and T2DM, while for the outcome study, this will consist of any patient with a record of DKA in the dataset. A record of DKA will be identified from HES using ICD-10 codes-(E10.0, E10.1, E11.0, E11.1, E12.0, E12.1, E13.0, E13.1, E14.0, E14.1).

Sample size calculation

The sample size was calculated, considering the desired types 1 and 2 error and estimated proportion. Based on the study by Holman et al. (25), WE calculated the mortality rates associated with DKA and coma (0.244 per 1000 person-years at risk) and mortality rates from all other causes in people living with diabetes (2.272 per 1000 person-years at risk). The sample size calculation was performed with an alpha error of 0.05, a beta error of 0.2 (power of 80%), and an estimated proportion of 0.1. Considering a two-tailed test, the ratio of sample size (unexposed/exposed) of 10 and drop rate of 0% (as this is a retrospective cohort study), a sample size with Fleiss' correction for continuity of 39358 participants (3578 with DKA and 35780 without DKA) was determined to be necessary to achieve the desired level of statistical power while maintaining a balance between accuracy and feasibility. This sample size was deemed adequate to provide sufficient statistical power to detect significant differences or associations within the study population.

Participant Recruitment

Inclusion criteria: Patients admitted with DKA from 1 January 2001 to 31 December 2023.

Exclusion criteria: Individuals with non-diabetic ketoacidosis or other metabolic disorders that could confound the study results.

Size of recruitment target: Approximately 3578 patients with DKA and 35780 matched controls

Recruitment Technique: Electronic Health Records (EHR): Utilizing the DExtER tool to identify and recruit patients from electronic health records. The data obtained from DExtER will be anonymized.

Objective 1 analysis plan

A series of yearly cohort studies will be performed to calculate DKA's crude incidence rate (IR) for each year from 2001 to 2022. The numerator will be the number of new cases (exposed patients with a DKA diagnosis) in that calendar year, divided by the total number of person-years at risk (denominator) for the given year for each type of diabetes (T1DM and T2DM) separately. The calculation for incidence will be based on the formula: (number of new cases/ person-years of included patients+α)x100,000.

Subgroup analyses

Stratified graphs describing crude incidence rates will be presented by age, sex, deprivation, ethnicity, mental health status and region (strategic health authority). Additionally, We will study populations by multiple factors through an intersectional lens (e.g., a combination of age, gender, ethnicity and deprivation), rather than treating a specific category (e.g., low deprivation). This can allow inequities to be defined with greater specificity and reduce the chances of minoritised populations being missed in analysis (26). The intersectional analysis may lead to unlimited permutations of groups (e.g., those aged 16-20, who are from a deprived group, who are female, etc). Therefore, We will also undertake an unsupervised clustering machine learning approach to identify and define clusters with the highest and statistically robust incidence rates.

5.1.2. Objective 1.2: Clinical outcomes associated with DKA (CPRD data).

Study design

We will undertake a matched retrospective cohort study to describe the long-term clinical outcomes of DKA. The control pool will be derived from patients with diabetes without a clinical code for DKA. Each DKA patient will be directly matched using the DExtER tool(27) by age (+/- 1 year), sex, type of diabetes and general practice (up to 4 controls).

Follow up.

In the exposed group, the index date will be the date of DKA diagnosis (incident patients). The same index date will be assigned to their respective control patients with diabetes to account for immortal time bias (28).

The exit date for all patients will be defined as the earliest of the following dates: date of death, date of transfer from the general practice (GP), last date of data collection from the GP, date of outcome of interest recorded, and study end date.

Covariates

We will account for key covariates that may influence the outcome of interest, including body mass index, smoking status, and comorbidity profile.

Outcomes

The primary outcome is the length of hospitalisation. The secondary outcomes include a 30-day all-cause re-admission rate, 30-day and 1-year all-cause mortality rates, 1-year cause-specific mortality, complications and within 30 days of admission with DKA complications such as renal impairment, large vessel thromboses (stroke, myocardial infarction), cardiomyopathy, pulmonary oedema, and gastrointestinal bleeding (29).

Analysis

Categorical baseline data will be described using proportions; continuous data will be described using means or median with standard deviations or interquartile range. Where there is missing data in our covariates, they will be treated as a separate missing category and included in the final analysis. Where appropriate, multiple imputation methods will be used.

Crude incidence rates per 100,000 person-years will be calculated for exposed and controlled patients with diabetes. For the outcome study, proportional hazard assumptions will be tested. If deemed suitable, Cox regression analysis will be performed to calculate the crude and adjusted hazard ratio (HR) of the outcomes in exposed versus control patients with diabetes. HRs will be presented with 95% confidence intervals, and statistical significance is assumed at $p<0.05$. Covariates known to affect the outcome of interest will be included in the adjusted analysis.

Subgroup analysis

We will describe the impact of being a member of different population subgroups by undertaking stratified analyses by sex, ethnicity, comorbid status and deprivation. Additionally, as informed by objective 1.1, where certain clusters appear to present more frequently, we will test the hypothesis to see if those groups have a higher risk of adverse outcomes than others who experience DKA.

Work package 1 output

Objective 1.1 will unravel the key groups of individuals most susceptible to DKA admissions and sub-groups at the highest risk of adverse clinical outcomes. These crucial findings will shape the design of Work Package 2, where we will delve into the experiences and perspectives of healthcare professionals, patients, and their carers to improve DKA care. We will ensure the representation of these adversely affected groups to explore why this may be. Objective 1.2 will shed light on the distinct clinical outcomes observed in DKA patients compared to those without the condition. The insights gained from Work Package 1 will drive the expansion and implementation of DEKODE across diverse NHS trusts, ensuring region-specific adaptations and optimal dissemination through the feedback system detailed in Work Package 3. Together, these objectives form a comprehensive approach to revolutionising DKA management and enhancing patient outcomes.

5.2. Work package 2: Lived experiences of people treated for DKA.

This work will delve into the unexplored lived experiences with DKA to complement and deepen the learning from WP1. We will employ rigorous methodologies such as surveys and interviews to unravel the intricacies of DKA care by hearing the narratives of those treated for and treating DKA in our collaborative NHS foundation Trusts This seminal study promises to revolutionise our understanding of DKA, illuminating the human aspect and guiding the development of patient-centred interventions.

Our collaborative centres currently include 40 hospitals within the UK. We are expanding this collaboration to include more hospitals to this project. For the purpose of this research project, we would be including only Univeristy Hospitals Birmingham NHS Foundation trust as a research site.. The objectives for this work package are:

- To understand the lived experiences of people admitted with DKA and their carers (objective 2.1)
- To understand the lived experiences of healthcare professionals providing DKA care (objective 2.2)

5.2.1. Objective 2.1: To understand the lived experiences of people admitted with DKA and their carers

Study design

To gather comprehensive data, we will invite all patients with DKA at University Hospitals Birmingham NHS Foundation Trust to complete the online Inpatient questionnaire via Microsoft forms (Appendix 1)for people with diabetes (30) and the EuroQol-5D (EQ-5D-Y) questionnaire(Appendix 2) (31). We estimate that approximately 500 patients admitted with DKA will complete the questionnaire during the study period. If we are unable to meet the required sample size, we will then expand the research sites to more hospitals part of the collaborative project and will apply for ethics approval To measure the long-term impact on health status after DKA, we will follow up with discharged patients and invite them to complete another EQ-5D-Y questionnaire at 3- and 6 months post-discharge. This will provide valuable insights into any changes in reported health status over time.

To delve deeper into the experiences and perspectives of these patients, we will invite a subset of people who completed the survey to participate in brief, semi-structured online interviews. The participation in the interview will be optional with no obligations. We will conduct these interviews on virtual platforms (Zoom® licensed through the University of Birmingham). (32). The interviews will last approximately 30 minutes. Only audio will be recorded on the zoom platform licensed through the University of Birmingham during the interview. Compared to an in-person meeting, this approach minimises exposure to viral illnesses such as COVID-19, influenza and respiratory syncytial virus. It also facilitates engaging with individuals of diverse backgrounds or those whose physical attendance requirements, such as disabilities, caregiving responsibilities, or financial constraints, may have otherwise been limited.

From those interested, we will aim to interview 20 to 30 participants about their experiences with DKA and its management to allow for data saturation (33). We will also invite one of their family members or a carer to participate in the interview. This is important as patients' family members or carers support the patient in their day-to-day activities. The carer can attend the interview immediately after the patient or on a different date at

their convenience. Within this sample, we will ensure the representation of those found to have the greatest differential impact on outcomes of DKA based on the findings of work package 1 through purposive sampling (34).

The semi-structured interview (Appendix 3A) will be guided by questions about the patient's experiences before, during, and after hospital admission for DKA. Additionally, we will probe and ask further questions based on emerging important topics, ensuring a thorough exploration of the participants' experiences (35). Following the patient interview, we will interview their carer separately with the same questions so that the patient can get their perspective. The absence of the patient will minimise any confirmation bias and help gain independent opinions of the carer. We will treat the patient and carer's responses separately to assess if there is any difference in their answers. We will aim for at least one carer per patient participant to attend this interview.

Previous studies have shown that most people admitted with DKA are of working age and have a good command of English (36), so all interviews will be conducted in English. However, in cases where language barriers arise, we will involve translators to facilitate translation of PIS and consent forms so participants can make informed decisions while consented they will continue to involve translator to conduct meaningful and accurate interviews.

By employing this rigorous and inclusive approach, we aim to shed light on the experiences of individuals affected by DKA and gain valuable insights into their perspectives on its management. Ultimately, this research will improve the care and support provided to DKA patients and their families.

5.2.2. Objective 2.2: To understand the lived experiences of healthcare professionals providing DKA care.

Study design

We will also conduct a similar online interview described in objective 2.1 for up to 30 other stakeholders involved in DKA management (junior doctors, nurses in acute and emergency care, diabetes inpatient specialist nurses and consultants in emergency medicine, acute medicine and diabetes who have regular involvement in DKA care). Within this sample, we will aim to reflect diversity in age, sex, ethnicity, deprivation and region across the UK. Similar to the interview with people admitted with DKA as described above, these interviews will also be guided by a set of questions, focussing on the time of DKA diagnosis, during management, after resolution and after discharge (Appendix 3b). Interviews will be conducted on Zoom and audio recorded through Zoom.

Participant Recruitment for Work Package 2

Inclusion criteria :

1. Patients
    a. Those admitted to the hospital with DKA.
    b. Have the capacity to provide consent.
    c. Age 16-99

2. Carers
    a. Those who are identified by patients as recruited above.
    b. Have the capacity to provide consent.
    c. Age 16-99

3. Healthcare workers
    a. Those involved in treating DKA for patients recruited above
    b. Have the capacity to provide consent.

Exclusion criteria:

1. Patients without DKA.
2. Providers not directly involved in DKA care.
3. Unable to provide consent

Size of recruitment target: Around 60 participants, including 20 patients and one caregiver per patient and 20 healthcare professionals, for qualitative interviews.

Recruitment Technique:

1. Patient - Healthcare professionals involved in the direct care of patients with DKA at hospitals participating in the DEKODE study will be invited to identify patients admitted with this condition. Once

confirmed with the DKA, the healthcare professionals will inform the patient about the study and provide a QR code which will provide a link to the survey with an inbuilt PIS. If the patients has agreed to participate in the interview, a member of the research team will contact them to arrange this.

2. Carer - At the end of the interview, a member of the research team will invite the patient to refer one of their carers for an interview to understand their perspective on DKA care. If the patient agrees, they will liaise with their carer to obtain their consent and then provide them with the contact details of our research team. The carer will then contact the research team who will then share the PIS with the carer and invite them for an interview after completing informed consent.
3. Healthcare professionals –Those involved in DKA in hospitals participating in DEKODE will be invited to take part in the study by healthcare professionals involved in DEKODE in our participating hospitals. Those interested will be given a QR code which has an inbuilt PIS, consent form and their contact details. Those who complete this will be contacted by a member of the research team for an interview.

Consent

The Chief Investigator is responsible for obtaining written informed consent from each recruited participant where appropriate. Consent can also be obtained from specific appropriately trained and delegated members of the study team (e.g., research nurse or clinical research fellow). The responsibility will be delegated on the Site Signature and Delegation Log.

The local team at the participant identifying centre will identify participants and offer an online questionnaire. This questionnaire comprises three key components: a link to the Participant Information Sheet (PIS), a consent form, and a section for providing contact details. Participants will first access the PIS, and if they are satisfied, they can proceed to complete the consent form. Once informed consent is provided, they will be directed to a section where they can submit their contact details, which will be used to arrange an interview. If a participant does not provide consent, they will be redirected to a submission page informing them that they cannot participate as they have not consented. Regardless of their decision, all participants will receive a copy of the PIS for their records. Participants will be presented with the exact nature of the study, the implications and constraints of the protocol and any risks involved in taking part. It will be stated that the participant is free to withdraw from the study without prejudice to future care and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as wished to consider the information and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study.

Investigators or their delegate(s) will ensure that they adequately explain the aim, study procedures and potential risks of participating in the study. They will also stress that participation is voluntary and that the participant is free to refuse to participate. They may withdraw from the study at any time without impacting their standard care. If the participant decides to withdraw from the study at a later time, we will delete any identifiable data collected for the study. However, any anonymised data already incorporated into the analysis will be retained according to current GDPR guidelines. If the participant continues to express interest in participating in the study, they will be asked to sign and date the latest approved version of the Informed Consent Form (ICF). The Investigators or their delegate(s) will then sign and date the ICF. A copy of the signed ICF will automatically be emailed to the participants once they submit the form. Once the participant is entered into the study, the participant's unique study identification number will be entered on the ICF maintained in the ISF.

It is anticipated that consent for participation in the DEKODE DKA study will usually be obtained on the day of the first study interaction. Throughout their study participation, the participants can ask questions about the study. Any new information relevant to the participant's continued participation will be provided.

Where new information becomes available that may affect the participants' decision to continue, they will be given time to consider and, if happy to continue, will be re-consented, which will be documented in the medical notes. The participant's right to withdraw from the study will also remain after re-consent.

The DEKODE DKA Study takes into account all ethical considerations of informed consent for research as per the guidance notes available on the HRA website: http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/

Analysis for Work Package 2

The interview data will be transcribed verbatim by the members of the research team and analysed thematically using open-analysis (37,38). Thematic inductive analysis is a qualitative research method that identifies patterns and themes in data without preconceived categories. It involves data familiarisation, coding, theme identification, refinement, and analysis. It captures participants' experiences and perspectives. It offers a systematic framework, allowing an open and exploratory approach. Deriving themes directly from data uncovers novel insights and generates knowledge grounded in participants' perspectives. Thematic inductive analysis is a flexible and comprehensive approach, providing deep insights and understanding of emerging themes in qualitative research. We will also analyse the data from carers to explore the similar and unique themes that emerge during the analysis. A second analysis will be carried out by applying the burden of treatment theory to the patient and carer data separately to help identify the work they must do when the patient is diagnosed with DKA (39). This second analysis will help us understand the 'burden' of coping with DKA for patients and their carers and what the condition imposes on them. This can aid in redesigning healthcare services to be better coordinated and more patient-centred in delivering DKA care.

Work package 2 outputs

Work Package 2 is a crucial part of our research, as it focuses on capturing the first-hand experiences and needs of individuals who have been treated for and have been treated for DKA. These findings will be integrated with those from Work Package 1. In the event of significant disparities between the results of the two work packages, we will elucidate the reasons for any differences. The combined results from these research efforts will be shared with all participating hospitals, along with feedback on the DEKODE system as described in work package 3. By sharing our findings and providing hospitals with the tools to identify and address disparities, we aim to create a more equitable and patient-centred healthcare system for individuals affected by DKA.

5.3. Work package 3: DEKODE- understanding the model's implementation and effectiveness.

The **DEKODE (Digital Evaluation of Ketosis and Other Diabetes Emergencies)** project was initiated to standardise and improve the care of patients with diabetes-related ketoacidosis (DKA) across hospitals in the UK. DEKODE is a digital platform that collects and analyses pseudonymized clinical data related to DKA care from participating NHS sites. The system provides regular feedback on key clinical parameters, such as treatment duration, complication rates, and outcomes, allowing hospitals to monitor and optimise DKA management. The system enables hospitals to identify trends, reduce variations in care, and share best practices, ultimately improving patient outcomes and resource utilisation

As the DEKODE initiative unfolds across 11 NHS organisations in the UK, it becomes vital to understand whether and why there is variation and the impact of participation on outcomes. By delving into these variations, We can gain insights into implementing and utilising treatment guidelines in different contexts. This knowledge will help us refine the DEKODE model for optimal support in DKA management and pave the way for its successful implementation in other hospitals nationwide, ensuring safe and effective care for individuals with DKA. The objectives for this work package are to:

- understand variation in implementing DEKODE different service contexts (objective 3.1)
- study how variations in implementation relate to the impact of DEKODE on participating hospitals (objective 3.2)

5.3.1. Objective 3.1- understanding variation in implementing DEKODE in different service contexts.

Study design

We will adopt a qualitative case study approach (40). This will involve a focused description and analysis of the implementation of DEKODE within different NHS organisations. The case study approach will allow us to conduct a detailed analysis of a given case and compare the findings between cases, facilitating further empirical and

propositional generalisation. The latter refers to a type of generalisation in research that involves making statements or claims about a broader population or context based on observations or findings from a specific sample or case. It is a way of concluding particular individuals or cases studied (41).

Study participants

We will use a purposive sampling strategy for this study (34). We will choose six NHS Trusts—three with an established DEKODE model (early adopters) and three where DEKODE is newly established. To facilitate the latter, we will expand the DEKODE programme nationally and invite one centre per region in the UK (maximum 10) to join DEKODE. This sites will be acting as participant identification sites for the research project and no research activity will be taking place here. The sample size is based on a study by Guest et al., who found that three focus groups were sufficient to identify the most prevalent themes within the data set (42). In the first instance, we will contact the lead for DEKODE at these NHS trusts and invite them to participate in the study. Upon accepting our invitation, we will request the lead to identify other people directly involved in implementing and sustaining the DEKODE model.

Participant Recruitment

Inclusion criteria: Healthcare professionals involved in providing DKA care in hospitals participating in DEKODE.

Exclusion criteria: Individuals who do not have sufficient interaction with the DKA care process.

Size of recruitment target: Approximately 20-30 participants for interviews.

Recruitment Technique: Information about DEKODE will be provided through national societies (Eg: https://abcd.care/audit/abcd-and-sanofi-dka-collaborative-working-project)

Consent

The Chief Investigator is responsible for obtaining online informed consent through a Microsoft forms from each recruited participant where appropriate. Consent can also be obtained from specific, appropriately trained, and delegated members of the study team (e.g., research nurse, or clinical research fellow). The responsibility will be delegated on the Site Signature and Delegation Log.

The local team at the participant identifying centre will identify participants and offer an online questionnaire. This questionnaire comprises three key components: a link to the Participant Information Sheet (PIS), a consent form, and a section for providing contact details. Participants will first access the PIS, and if they are satisfied, they can proceed to complete the consent form. Once informed consent is provided, they will be directed to a section where they can submit their contact details, which will be used to arrange an interview. If a participant does not provide consent, they will be redirected to a submission page informing them that they cannot participate as they have not consented. Regardless of their decision, all participants will receive a copy of the PIS for their records. Participants will be presented with the exact nature of the study, the implications and constraints of the protocol and any risks involved in taking part. It will be stated that the participant is free to withdraw from the study without prejudice to future care and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as wished to consider the information and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study.

Investigators or their delegate(s) will ensure that they adequately explain the aim, study procedures and potential risks of participating in the study. They will also stress that participation is voluntary and the participant is free to refuse participation. They may withdraw from the study without impacting their standard care. If the participant decides to withdraw from the study later, we will delete any identifiable data collected for the study. However, any anonymised data incorporated into the analysis will be retained according to current GDPR guidelines. If the participant continues to express interest in participating in the study, they will be asked to sign and date the latest approved version of the Informed Consent Form (ICF). The Investigators or their delegate(s) will then sign and date the ICF. A copy of the signed ICF will automatically be emailed to the participants once

they submit the form. Once the participant is entered into the study, the participant's unique study identification number will be entered on the ICF maintained in the ISF.

It is anticipated that consent for participation in the DEKODE DKA study will usually be obtained on the day of the first study interaction. Throughout their study participation, the participants can ask questions about the study. Any new information relevant to the participant's continued participation will be provided.

Where new information becomes available that may affect the participants' decision to continue, participants will be given time to consider and, if happy to continue, will be re-consented, and this will be documented in the medical notes. The participant's right to withdraw from the study will remain also after re-consent.

The DEKODE DKA Study takes into account all ethical considerations of informed consent for research as per the guidance notes available on the HRA website: http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/

Data collection

Those identified as stakeholders for implementing and sustaining DEKODE will be invited for a semi-structured online interview. The discussions in these meetings will revolve around local service factors (leadership, cultures, organisation structure) that shaped the adoption of DEKODE at the local level and how local services took account of social inequalities in care provision. The interview questions (Appendix 3c) will be on the following topics:

- Biographical information
- Understanding and Perceptions of DEKODE
- The values and benefits of DEKODE
- Adopting and putting DEKODE into practice
- Sustaining and improving DEKODE

We will conduct the interviews remotely using videoconferencing software and audio record them with the participants' consent. The interviews will be done through Zoom® licensed through the University of Birmingham. We anticipate these interviews will last approximately 60 minutes each. To minimise bias, we will employ an experienced qualitative researcher with a limited understanding of DEKODE to conduct the interviews.

Analysis

The data from focus group discussions will be transcribed verbatim and analysed thematically by a research team member as described in Work Package 2. Following analysis, we will establish themes separately for hospitals with established DEKODE and those where DEKODE is newly established. We will compare the two to identify similarities and unique themes. We will apply the NASSS (non-adoption, abandonment, scale-up, spread, sustainability) and CFIR (Consolidated Framework for Implementation Research) models to understand factors that influence the successful adoption of DEKODE and understand how centres are using the feedback from DEKODE to develop interventions to improve DKA Care. The CFIR and NASSS are both frameworks used in the field of implementation science, but they differ in their focus and scope. The CFIR primarily focuses on understanding and analysing the factors that influence the successful implementation of interventions or innovations in various settings. It provides a comprehensive framework that examines the intervention characteristics, outer and inner settings, individuals involved, and the implementation process. In contrast, NASSS addresses the challenges and complexities of implementing healthcare technologies. It encompasses the domains of non-adoption, abandonment, scale-up, spread, and sustainability. NASSS emphasises the unique issues related to healthcare technologies' adoption, discontinuation, and long-term viability.

5.3.2. **Objective 3.2: Study how variations in implementation relate to the impact of DEKODE on participating hospitals.**

Study design

The following data will be collected from all participating hospitals (routinely collected data as part of the national audit) :

- Patient demographics such as age, sex, ethnicity, type of diabetes (based on a clinical diagnosis, which may have been confirmed through islet autoantibody or C peptide testing if not done before hospitalisation) and weight based on self-identification or from medical records.
- date and time of admission for the index DKA episode,
- date and time of DKA diagnosis (defined as blood glucose >11 mmol/L or history of diabetes, pH ≤7.3 or bicarbonate ≤15 mmol/L and ketonemia ≥3 mmol/L (43),
- date and time of DKA resolution ((pH>7.3 and bicarbonate >15 mmol/L; and ketones <0.6 mmol/L), and
- date and time of discharge for DKA.
- Progression of treatment: total volume of insulin and fluids infused during DKA, total number of glucose and ketone measurements, number of episodes of hypoglycaemia (blood glucose <4.0 mmol/L), hypokalaemia (potassium <3.5 mmol/L) and hyperkalaemia (potassium >5.5 mmol/L).

All data obtained will be pseudonymised when entered into the DEKODE system as part of standard audit practice (DEKODE is now the nationally recommended audit for DKA). These hospitals are collecting this data as part of local audit process and are not as such involved directly with the research project and hence are not research sites.The key for re-identification is securely stored at the respective hospitals as part of the audit, separately from the pseudonymized data, ensuring that only authorized personnel at the local hospital with the appropriate permissions can access it.

The research team will have access to only de-identified data which will be securely stored at the University of Birmingham (UoB), adhering to strict data protection policies and regulations to ensure confidentiality and compliance with ethical standards.

Analysis

We will calculate the proportion of DKA episodes within 80-120% of JBDS-IP recommendations for DKA care for fixed-rate intravenous insulin infusion, fluids administered, hourly glucose and hourly ketone monitoring. During management, we will also measure the proportion of DKA episodes developing hypoglycaemia, hyperkalaemia and hypokalaemia. Finally, we will calculate DKA duration (time difference between DKA diagnosis and DKA resolution and length of stay (time difference between admission and discharge) for each DKA episode.

The data for these nine parameters will be shared quarterly with the leads of participating hospital teams. They will be encouraged to share the findings with all stakeholders to explore interventions needed to improve DKA care. Continuous data will be presented as median and interquartile range as our previous experiences have demonstrated that the data is not normally distributed. Categorical data are presented as frequency and proportions. We will then measure the differences in the nine parameters across six consecutive data cycles to explore the trends in each hospital and between hospitals using the Kruskal-Wallis test. Statistical significance will be accepted at a 95% confidence ($p<0.05$).

Work package 3 outputs

The findings of objective 1 will unveil the potential of DEKODE's implementation, considering each locality's unique needs and constraints. Combining these findings with the insights gained from Work Package 1 regarding social inequities, we can establish implementation principles that effectively tackle disparities in DKA care. The findings of objective 2 will establish the impact of various interventions driven by data from DEKODE. Identifying the interventions that successfully reduce variations between patients and hospitals will enable us to share these effective strategies with all participating healthcare facilities. By leveraging these compelling findings, we can pave the way for equitable and consistent DKA care that meets the diverse needs of patients while promoting positive outcomes throughout the participating hospitals and beyond.

5.4. Work package 4: Investigating Recurrent DKA: A Retrospective Cohort Analysis Using DEKODE

Background

Recurrent DKA is associated with increased morbidity, mortality, and healthcare costs. Identifying high-risk patient groups and understanding the factors contributing to recurrence is crucial for implementing targeted preventive interventions. This retrospective cohort study will analyse individuals with ≥2 DKA episodes using pseudonymised data from the DEKODE national audit, combined with clinical information maintained securely within participating NHS hospitals. The study will assess:

- The frequency of recurrent DKA episodes
- Key clinical determinants and risk factors, including glycaemic control, comorbidities, and socio-demographic characteristics
- Clinical outcomes, such as hospitalisation rates, length of stay, and mortality
- The study will be conducted in compliance with NHS Research Ethics Committee (REC) and Health Research Authority (HRA) guidance, ensuring strict governance and data security standards.

Study Design

Participants

- The study will include individuals who have experienced ≥2 DKA episodes, identified via the DEKODE national audit database.

Data Sources & Collection

- Data Extraction & Pseudonymisation:
  - Local NHS audit leads will extract patient-identifiable data from hospital records.
  - The research team will have access only to pseudonymised data. Identifiable patient information will not be shared beyond NHS centres.
  - Linkage keys will remain securely stored within NHS databases.
- Extracted Variables from the DEKODE Database:
  - Patient Demographics: Age, gender, ethnicity
  - Clinical History: Type and duration of diabetes, comorbidities, history of previous DKA episodes
  - Clinical Determinants:
    - Laboratory results at the time of DKA (e.g., glucose levels, ketone bodies, bicarbonate levels)
    - Insulin regimen and management strategies (e.g., fluid resuscitation, electrolyte management)
  - Healthcare Utilisation: Frequency of DKA-related hospitalisations, length of stay, and readmission rates
  - Interventions: Preventive measures such as educational programs, mental health support, and modifications in management plans
  - Outcomes: Mortality rates, complications arising from DKA, and quality-of-life measures post-recurrence

Data Governance & Ethical Considerations

- Consent & Legal Basis:

  Each NHS site has obtained local Information Governance (IG) approval to participate in the DEKODE audit. The research team will not have access to any patient identifiable data.

- Data Storage & Security:

  Identifiable patient data will be securely stored in NHS hospital databases, accessible only to authorised NHS personnel involved in data extraction. Pseudonymised data will be stored on the University of Birmingham (UoB) secure servers, ensuring compliance with UK GDPR, NHS Digital Data Security Standards and Institutional data protection policies. No identifiable data will be transferred outside the NHS or stored in non-secure environments.

Analysis

Descriptive statistics will summarise patient characteristics and DKA episode frequency. Logistic regression models will identify independent predictors of recurrent DKA, adjusting for potential confounders. Kaplan-Meier survival analysis will compare outcomes between patients with recurrent and non-recurrent DKA episodes. Cox regression models will adjust for multiple covariates to estimate hazard ratios for recurrent DKA. Sensitivity analyses will assess the robustness of findings, including the impact of missing data. The

study will evaluate the effectiveness of DEKODE implementation in reducing recurrence rates using logistic regression and time-to-event analysis.

Work Package 4 Outputs

By identifying high-risk patient groups and assessing the impact of DEKODE on reducing recurrent DKA, this research will provide valuable insights to guide Targeted clinical interventions, optimised diabetes management strategies, and Evidence-based policy recommendations to improve long-term patient outcomes.

5.5. Work package 5: Health economics evaluation of the DEKODE model

We will calculate the cost of managing DKA at the beginning, 12, 18 and 24 months after adopting DEKODE in participating institutions using the approach previously described by Dhatariya et al. (11). We will also calculate the length of stay for DKA at 6, 12, 18 and 24 months of the DEKODE model. This is important as we have previously shown the disconnect between DKA resolution and when the person gets discharged from the hospital. We aim to study the impact of DEKODE on changes to length of stay over time. The cost of managing a single episode of DKA will be estimated using NHS procurement data which is publicly available and hence a separate data sharing agreement is not required. This would then be extrapolated to participating hospitals by multiplying it by the total number of DKA episodes during the study period. No patient-identifiable data will be collected.

We will perform a cost consequence analysis on the following outcomes across time: total volume of insulin and fluids infused during DKA, total number of glucose and ketone measurements, number of episodes of hypoglycaemia (blood glucose <4.0 mmol/L), hypokalaemia (potassium <3.5 mmol/L) and hyperkalaemia (potassium >5.5 mmol/L). The analysis parameters will include:

- UK's NHS cost and incidents reports (for the reference case),
- Direct costs of treatment and ongoing management of the condition and any associated social care services collected through DEKODE,
- Indirect costs will be collected from literature NHS reports and other sources.
- Our approach to model development will be as follows:
- Identify data requirements for key parameters,
- Identify appropriate parameter estimates from a range of sources,
- Run the analysis and generate initial results,
- Discussion of the analysis outcomes,
- Report the outcomes for previously agreed scenario cases.

Apart from the calculation of the (early) deterministic results, we will implement a probabilistic sensitivity analysis (PSA) of all parameters as well as a one-way sensitivity analysis (OWSA) of key parameters to characterise the variance in the data. PSA is a technique used in economic modelling that allows the level of confidence in the output parameters of the analysis to be characterised regarding the uncertainty in the model inputs. In the probabilistic analysis, the parameters' value from clinical trials, observational studies, or expert opinion is represented as a distribution of their deterministic value. This is repeated, implementing 1,000 to 10,000 iterations of a Monte Carlo simulation, resulting in a distribution of outputs that can be graphed and analysed. We will also attend a short course to learn and apply a distributional cost-effectiveness analysis (DCEA) to incorporate health inequalities into the analysis. We will also study the change in reported health status over time by analysing the data from the quality-of-life surveys in Work Package 2.

6. Study setting

The study will be conducted across various hospitals in the UK that are participating in the DEKODE project.

7. Participant recruitment

Participant recruitment for the DEKODE study will be a comprehensive process aimed at ensuring the inclusion of a diverse and representative sample of patients with diabetic ketoacidosis (DKA), healthcare professionals

involved in DKA care, and other relevant stakeholders. The recruitment strategy will be tailored to each work package, utilising targeted and broad recruitment techniques.

7.1. Eligibility Criteria

7.1.1. Inclusion criteria

- **Work Package 1**: Patients admitted with DKA from 1 January 2001 to 31 December 2023.
- **Work Package 2**: Patients aged 16 to 99 admitted to the hospital with DKA, their carers, and healthcare workers (including healthcare assistants, nurses, and doctors) involved in the treatment of DKA.
- **Work Package 3**: Members from hospitals participating in DEKODE who are involved in providing care during the DKA Episode.

7.2. Recruitment target

7.2.1. Size of recruitment target

The recruitment targets will vary by work package, aiming to balance statistical power and feasibility:

- **Work Package 1**: Approximately 3578 patients with DKA and 35780 matched controls.
- **Work Package 2**: There will be around 60 participants, including 20 patients and one caregiver per patient and 20 healthcare professionals, for qualitative interviews and focus groups.
- **Work Package 3**: Approximately 20-30 participants for interviews.

8. Safety reporting

No interventions are involved in this study. Risks to participants are considered to be low.

Relevant UoB processes will be followed where applicable.

9. Ethical and regulatory considerations

9.1. Assessment and management of risk

The overall risk to the study participants is very low.

The only anticipated risk is the patient or their caregiver becoming emotionally upset while recollecting their experiences during the DKA episodes. In such a case they will be provided with information of Diabetes UK patient support groups to seek further help.

9.2. Research Ethics Committee (REC) and other Regulatory review & reports

9.2.1. Regulatory Review & Compliance

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996.
The study will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the General Data Protection Regulation and Data Protection Act 2018 and Human Tissue Act 2008) and the principles of Good Clinical Practice (GCP). The protocol will be submitted to and approved by the REC prior to implementation.

It is the responsibility of the Investigators to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interests of individual participants.

Substantial amendments that require review by the REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. The Chief Investigator or designee will work with R&D department as well as the study delivery team so they can put the necessary arrangements in place to implement the amendment and confirm their support for the study as amended.

All correspondence with the REC will be retained.

The Chief Investigator will notify the REC and sponsor of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC and sponsor including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC and sponsor.

9.2.2. Amendments

Any amendments (substantial or non-substantial) will be approved by the Investigators and sponsor and reported to the Health Research Authority/Research Ethics Committee using the appropriate processes. Amendment history will be tracked at the end of the protocol (section 13.3), reporting the amendment number, protocol version number, date amended, and approval issued, author(s) of changes and details of changes made.

9.3. Peer review

The Funder has reviewed and approved the study protocol. The funding decision made by the funder was informed by review through the NIHR Award Selection Panel, subsequent external peer review by four independent national and international expert reviewers, and review and recommendations from the NIHR Interview Committee, following the personal interview of the Chief Investigator. The Funder's Selection and Interview Panels comprise internationally leading clinical and scientific experts.

In addition to this extensive external peer review at the stage of funder approval, the protocol has also been reviewed by the principal investigators, and their feedback has been incorporated in this final protocol version.

9.4. Patient & Public Involvement

The Patient & Public Involvement (PPI) activities have been extensive, from proposal design to plans for dissemination. We worked with public members of the Joint British Diabetes Societies Patient Panel, Diabetes UK Communities in Action (CiA) group, and people with diabetes who were local to the West Midlands region. These groups are also involved with various national and international diabetes organisations, ensuring patient views are incorporated into relevant policies and guidelines. The purpose of this PPWE consultation was to elicit the views of people with diabetes about the value of the study and, more broadly, the safety and ethical issues associated with the proposed methods (particularly in work packages 2&3). Following the introduction, WE arranged a meeting. The meeting was over Zoom and lasted for 30 minutes. Two members of Diabetes UK Communities in Action attended the meeting. In this meeting, we presented the proposed fellowship, followed by a discussion to clarify queries. Following this meeting, we shared our fellowship application with the PPWE members, who shared it with several other group members. They emphasised the significant value of the study in shaping services for people admitted with DKA. Selected comments are as follows:

1. They appreciated the online nature of the interviews, which provided flexibility and safety.
2. They suggested asking about the quality of care alongside the satisfaction for people receiving DKA care in work package 2 to focus on diabetes inpatient specialist nurses rather than all nurses when gathering the experiences of managing DKA.
3. To be more specific in work package 3, explaining how and who will be involved and the methods for assessment.

Upon reviewing a revised proposal, a few further comments were suggested to ensure the number of hospitals included in the fellowship to be uniform and the application followed language matters principle throughout the application. The submitted version of Our proposal has all these suggestions incorporated. We have also invited these PPWE members to join the PPWE committee to oversee the delivery of the fellowship, the details of which are described in the section below.

9.5. Protocol compliance

Site set-up and initiation

All research team members must sign a Site Signature and Delegation Log. It is expected that all research team members will be GCP-trained. The research teams will attend a study initiation meeting that covers aspects of the protocol procedures, adverse event reporting, data collection and reporting, and record keeping.

Audit and inspection

All local Principal Investigators will permit study-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Chief Investigator will comply with these visits and any required follow-up.

Protocol deviations, non-compliance, and breaches

Accidental protocol deviations can happen at any time. The investigator will adequately document them on the relevant forms and report them immediately. Deviations from the protocol that frequently recur are not acceptable, will require immediate action, and could potentially be classified as a serious breach. Any major problems identified during monitoring may be reported to the sponsor. This includes reporting serious breaches of GCP and/or the study protocol.

9.6. Data protection and patient confidentiality

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and Data Protection Act 2018. Participants will always be identified using their unique study identification number. In the case of specific issues and/or queries from the regulatory authorities, access to the complete study records will be necessary, provided that participant confidentiality is protected.

The study team will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party. This is except for those directly involved in the participant's treatment and organisations for which the participant has given explicit consent for data to be shared.

Questionnaire data, data from Microsoft Forms and audio recordings from interviews of all work packages will be securely stored on the University of Birmingham servers. This will be password-secured and encrypted *in situ*. The audio recordings from Zoom will be securely transferred to the University of Birmingham (UoB) servers as soon as possible after the recording is completed. Once the transfer is confirmed, the recordings will be permanently deleted from Zoom. Audio recordings will be classified as personal data and will only be retained in compliance with data protection regulations and ethical standards. The recordings will be only stored until it is transcribed and will be deleted afterwards.

Patient-identifiable data will not be shared and will be stored separately from other data to ensure the protection of personal information and to comply with data protection regulations. The questionnaires, will only contain the study ID to maintain participant anonymity. No identifiable data will be included in the questionnaires. All participants will have a unique identifier created to track all information related to that participant. This will be securely stored on the University of Birmingham server.

Access to and use of the data will require authentication (password-based) and authorisation capabilities, respecting the data-sharing requirements of the partners involved. The default rule is that access is not granted to clinicians/researchers unless explicitly authorised by the study's Chief Investigator. All access to and use of the system will be audited through generated log files.

The security of the System is governed by the University of Birmingham (UoB) policies. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements for processing and storing sensitive data.. The Study Centre has arrangements in place for the secure storage and processing of the study data, which comply with UoB policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storage of backup tapes/disks stored in a fireproof safe.

- Logical measures for access control and privilege management, including restricted accessibility, access-controlled servers, separate controls used for non-identifiable data, etc.
- Network security measures include site firewalls, antivirus software, separate secure network-protected hosting, etc.
- System Design: The system will consist of a database and a data entry application with firewalls, restricted access, encryption, and role-based security controls.
- Operational Processes: the data will be processed and stored on secure servers governed by the University of Birmingham.
- Data processing: Study Statisticians will have access to anonymised data.
- System Audit: The system will benefit from the following internal/external audit arrangements:
  - Internal audit of the system
  - Periodic IT risk assessments

Data Protection Registration: UoB has a Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

9.7. Indemnity

The University has a Public Liability Policy and/or Clinical Trials policy in force, which provides coverage for claims for "negligent harm", and the activities here are included within that coverage.

9.8. End of study and archiving

This study is designed as a mixed-design study. It will end once all 5 work packages are completed. As per UoB policy, data will be retained for 10 years after the end of the study.

9.9. Access to the final study dataset

Access to data, including the final study dataset, will be limited to the Chief Investigator and named members of the research team.

10. Dissemination policy

All study outcomes will be published in peer-reviewed journals to share the findings with the wider medical and scientific community. No identifiable data will be published. We will also collaborate with various patient support groups such as Diabetes UK, patient representative groups in the Association of British Clinical Diabetologists (ABCD) and JBDS-IP to disseminate the findings of our studies to a wider population. In addition, the results of the qualitative work from Work Package 2 will be fed back to the participating hospitals to identify and address disparities; we aim to create a more equitable and patient-centred healthcare system for individuals affected by DKA. We will also share the findings of work packages 1 and 2 with the lead of the national and international DKA guidelines so they can be considered when developing the next iteration of DKA guidelines to incorporate patient views.

To reach audiences beyond traditional systems such as journal articles and newsletters, we will disseminate the findings of our studies via SIMBA (Simulation via Instant Messaging - Birmingham Advance) and CoMICs (Concise Medical Information Cines). SIMBA is an innovative teaching model conceptualised and developed to deliver simulation-based training through virtual sessions in various fields of medicine (45–48). Using SIMBA for diabetes-related ketoacidosis, we will develop various simulation-based learning modules based on real-life scenarios and inbuilt patient perspectives. Clinicians interested in diabetes-related emergencies will be invited to engage in these modules to improve their confidence in managing different scenarios.

CoMICs are short videos with illustrations and infographics to provide bite-sized information on various diseases and conditions. The current list of CoMICs can be accessed freely on: https://www.youtube.com/@simbasimulation8047. We will create various CoMICs based on the findings of my work packages. These CoMICs will be of two types: CoMICs for healthcare professionals and CoMICslite-aimed at people with diabetes and wider public. While the former will have a more detailed explanation of the methods and findings, the latter will be aimed at the population without medical expertise.

10.1. Authorship eligibility guidelines

Authorship will be determined based on the CRediT taxonomy. To be an author, individuals must substantially contribute to the research, participate in drafting or critically revising the manuscript, approve the final version, and agree to be accountable for the work. Contributions not meeting authorship criteria will be acknowledged.

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