

RESEARCH ARTICLE

Ambulance clinician use of capillary blood ketone meters to improve emergency hyperglycaemia care: A stepped-wedged controlled, mixed-methods feasibility study

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Abstract

Aim: To determine whether it was feasible, safe and acceptable for ambulance clinicians to use capillary blood ketone meters for 'high-risk' diabetic ketoacidosis (DKA) recognition and fluid initiation, to inform the need for a full-powered, multi-centre trial.

Methods: Adopting a stepped-wedge controlled design, participants with hyperglycaemia (capillary blood glucose >11.0 mmol/L) or diabetes and unwell were recruited. 'High-risk' DKA intervention participants (capillary blood ketones ≥3.0 mmol/L) received paramedic-led fluid therapy. Participant demographic and clinical data were collated from ambulance and hospital care records. Twenty ambulance and Emergency Department clinicians were interviewed to understand their hyperglycaemia and DKA care experiences.

Results: In this study, 388 participants were recruited (Control: $n=203$; Intervention: $n=185$). Most presented with hyperglycaemia, and incidence of type 1 and type 2 diabetes was 18.5% and 74.3%, respectively. Ketone meter use facilitated 'high-risk' DKA identification (control: 2.5%, $n=5$; intervention: 6.5%, $n=12$) and was associated with improved hospital pre-alerting. Ambulance clinicians appeared to have a high index of suspicion for hospital-diagnosed DKA participants. One third (33.3%; $n=3$) of Control and almost half (45.5%; $n=5$) of Intervention DKA participants received pre-hospital fluid therapy.

Key interview themes included clinical assessment, ambulance DKA fluid therapy, clinical handovers; decision support tool; hospital DKA management; barriers to hospital DKA care.

Conclusions: Ambulance capillary blood ketone meter use was deemed feasible, safe and acceptable. Opportunities for improved clinical decision making, support and safety-netting, as well as in-hospital DKA care, were recognised. As participant recruitment was below progression threshold, it is recommended that future-related research considers alternative trial designs. [Clinicaltrials.gov: NCT04940897](https://clinicaltrials.gov/ct2/show/NCT04940897).

KEY WORDS

ambulances, diabetes, diabetic ketoacidosis, fluid therapy, hyperglycaemia, ketones

1 | INTRODUCTION

Diabetic ketoacidosis (DKA) is a potentially life-threatening condition and usually associated with type 1 diabetes; however, it is now also associated with type 2 diabetes, particularly with sodium-glucose cotransporter (SGLT) inhibitor use.^{1,2} Reported incidence rates and prevalence of DKA in adults with diabetes have been found to be variable; current estimates vary from 8 to 263 cases per 1000 patient years.^{3–5}

There is limited literature regarding ambulance-based hyperglycaemic and DKA care, however, it has been recognised that there is scope for care improvement.^{6–8} Unlike in other clinical settings, ambulance capillary blood ketone testing is not standard practice, although paramedic-led intravenous fluid (0.9% sodium chloride) therapy in DKA is recommended when there are signs of clinical shock or dehydration.⁹ In the absence of blood ketone meters, ambulance DKA recognition and clinical management strategies are based on an individual's medical history information and non-specific clinical signs and symptoms, which can be susceptible to error.^{7,10} Given the increasing prevalence of diabetes,¹¹ ambulance clinicians having the scope to identify and positively impact DKA care could offer significant health benefits for people with diabetes and reduce healthcare costs.

The aims of this feasibility study were to determine whether ambulance clinicians could reliably and safely identify DKA using capillary blood ketone meters; to initiate protocolised fluid therapy; and gather feasibility data to inform a full-scale stepped-wedge controlled trial to evaluate the clinical and cost-effectiveness of these devices in the emergency ambulance setting.

2 | METHODS

2.1 | Study design

KARMA2 was a multi-centre, stepped-wedge controlled feasibility study delivered across one UK county (Cambridgeshire) served by the East of England Ambulance Service NHS Trust (EEAST) and three study partner hospital sites (Addenbrookes, Cambridge; Hinchingbrooke, Huntingdon; Peterborough City, Peterborough). Study participants were recruited during November 2020 to August 2021 (Control: 5 months; subsequent Intervention: 5 months).

NOVELTY STATEMENT

What is already known?

- Ambulance blood ketone assessments are not routine clinical practice; non-specific clinical signs and symptoms are used for hyperglycaemic care strategies.

What has this study found?

- Capillary blood ketone meter use for 'high-risk' DKA recognition and fluid initiation is deemed feasible, safe, acceptable and useful by ambulance and Emergency Department. Ambulance clinicians associate meter use with improved clinical decision making, participant care and safety-netting.

What are the implications of the study?

- Capillary blood ketone meter use is encouraged in ambulance care delivery.

2.2 | Participants

Study-trained ambulance clinicians (control: $n=113$; intervention: $n=48$) recruited patient participants during the study. Only ambulance clinicians participating in the control phase were eligible to receive study training for the subsequent intervention phase. Participant inclusion criteria were attended by study-trained clinician; 18 years or more; consented to participation (by informed person, personal or nominated consultee); person without diabetes: blood glucose $>11.0\text{ mmol/L}$; person with diabetes: unwell; if conveyed, destination: participating hospital. Exclusion criteria were previously recruited into KARMA2 and conveyance to non-study hospital. To minimise any potential recruitment bias, approaches used for clinician training and support were similar during both study phases.

During the intervention phase, 20 clinician participants—10 study ambulance clinicians (paramedics and non-paramedics) and 10 Emergency Department (ED) clinicians (doctors and nurses)—provided informed consent to participate in a semi-structured, study interview.

2.3 | Participant care

2.3.1 | Control

Following written consent, participants received usual ambulance care, in accordance with Joint Royal Colleges Ambulance Liaison Committee (JRCALC) and EEAST Clinical Guidelines, as determined by their presenting clinical condition and need for ongoing care. While no study clinical interventions were associated with this phase, if clinically indicated participants could receive treatments (such as fluid therapy) in accordance with practice guidelines. All participants not conveyed to hospital were referred to their general practitioner (GP) via the EEAST referral service for review and clinical referral as appropriate.

2.3.2 | Intervention

Consented participants, in addition to receiving usual ambulance care, received an additional ambulance capillary blood ketone (CBKa) assessment, in accordance with ketone meter manufacturer guidance (CareSens Dual; Spirit Healthcare, Leicester, UK). Decision to convey to hospital was determined by the study clinician, based on the participant's presenting clinical condition, blood ketone level and need for ongoing care. Those with a CBKa value ≥ 3.0 mmol/L were considered to be at 'high-risk' of DKA and in a life-threatening condition. They were conveyed directly to the ED, with a pre-alert message including the term 'high-risk DKA' and CBKa value obtained.

'High-risk' DKA participants attended to by KARMA2 paramedics received fluid therapy: those presenting with a systolic blood pressure of < 90 mmHg, with evidence of circulatory failure or dehydration, received intravenous fluids, that is, 250 mL bolus of 0.9% sodium chloride. In the absence of apparent physiological changes on clinical reassessment, these participants received a further 250 mL fluid bolus, to a maximum of 2000 mL. Normotensive (systolic blood pressure > 90 mmHg) participants received 250 mL 0.9% sodium chloride, repeated once if no apparent physiological changes were observed. In the absence of a KARMA2 paramedic, study non-paramedics were advised to request a paramedic to provide fluid therapy, however, not to delay participant conveyance to hospital.

Participants with a CBKa value < 3.0 mmol/L were managed with reference to Joint British Diabetes Societies (JBDS) guidelines, where such individuals are not considered to be in a high-risk DKA state. These participants received care in line with their medical complaint and current JRCALC and EEAST Clinical Guidelines: if not conveyed to hospital, participants were referred to their

General Practitioner (GP) via the EEAST referral service for review and clinical referral as appropriate.

2.4 | Study outcomes

As a feasibility study, main outcomes were to evaluate ambulance clinicians' acceptance of a research protocol, routine use of blood ketone meters in the ambulance setting, and collection of necessary study research data from both ambulance and hospital sites.

Study progression criteria were at least 70% of eligible patient consented to participate; demographic, clinical and research data were collected for at least 70% of participants; adverse event rate (e.g. complications arising from fluid administration) was less than 1%; and no significant barriers to ketone meter use were identified during clinician interviews.

2.5 | Data collection

Participant demographic, diabetes history and clinical assessment data were collated from ambulance and hospital participant care records, using a purpose-designed, electronic, secure Microsoft Forms-based clinical report form. Clinician interviews were conducted using Microsoft Teams, with separate digital audio recordings produced for subsequent analysis.

2.6 | Statistical methods

Quantitative data: given the feasibility nature of this study, differences in outcomes between control and intervention participants were not formally tested; however, their characteristics were summarised using descriptive statistics (e.g. mean, range, proportions). The selected total sample size indicated 20–30 'high-risk' DKA study participants would be recruited. Qualitative data: interviews were analysed using an inductive thematic approach, identifying emerging patterns within the data.

3 | RESULTS

3.1 | Participants

In total, 400 participants were consented during the study phases (see Figure 1), with 12 participants being subsequently excluded (control: $n=5$; intervention: $n=7$). All remaining eligible participants ($n=388$) continued in the study; however, three intervention participants were not

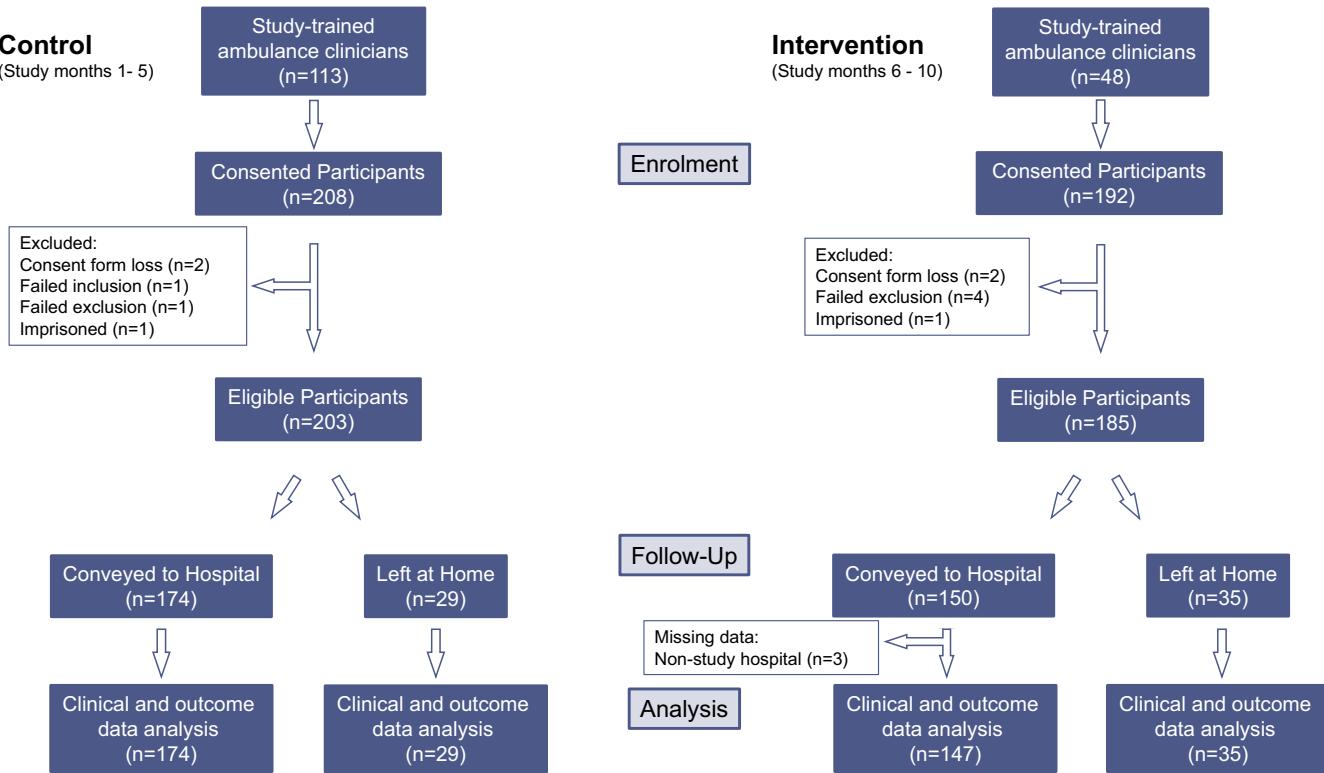


FIGURE 1 KARMA2 Participant overview—CONSORT diagram.

followed up in hospital as they received ongoing care at a non-participating site.

The majority of eligible participants provided informed person consent (control: 84.7%, $n=172$; intervention: 80.5%, $n=149$), with the remainder recruited via personal or nominated consultee consent. Regarding consultee consent, less than one third (control: 32.2%; $n=10$; intervention: 16.7%; $n=6$) of these participants were reconsented on regaining capacity in hospital. Reasons for no reconsent during both phases included discharge from hospital prior to reconsent ($n=14$) and conveyance to a non-study hospital ($n=1$). Permanent loss of capacity ($n=29$), non-conveyance to hospital ($n=6$) and participant deceased ($n=1$) were the reasons for remaining consultee-consented participants not to be reconsented.

To determine the incidence of eligible participants and scope for study recruitment, a service information request indicated study clinicians recruited approximately 11% of adult patient they attended presenting with hyperglycaemia and diabetes (control: 10.9%, $n=208/1909$; intervention: 11.1%, $n=192/1731$).

3.2 | Participant clinical assessment

The key participant clinical findings are summarised in Table 1. Most participants presented with hyperglycaemia to varying extent, that is, ambulance capillary blood glucose

(CBGa) 11.1 mmol/L—‘HI’ (>38.9 mmol/L; out of device range): control: 67.5% ($n=137$); intervention: 54.1% ($n=100$). The incidence of type 1 diabetes was 18.5% (control: 21.2%, $n=43$); intervention: 15.7%, ($n=29$). The incidence of type 2 diabetes was approximately 74% (control: 72.4%, $n=147$); intervention: 76.2%, ($n=141$). Approximately, 7% ($n=28$) of participants reported not having diabetes.

3.3 | Ketonaemia and ‘High-Risk’ DKA incidence

During the control phase, 6.9% ($n=14$) of participants reported elevated ketone levels. This information was obtained from personal issue blood ketone meters and primary care clinicians, which included via urinary testing. With the use of study ketone meters, during the intervention phase this information availability increased to 23.2% ($n=43$).

The incidence of ‘high-risk’ DKA was 2.5% ($n=5$) in control participants and 6.5% ($n=12$) in intervention participants. ED confirmation of DKA status revealed a DKA incidence of 4.4% ($n=9$) and 5.9% ($n=11$) in the control and intervention phases, respectively.

Review of ambulance clinician-reported clinical primary impression codes revealed a high suspicion for DKA as a differential diagnosis during both study phases (control: 77.8%, $n=7$; intervention: 91.0%, $n=10$; see Table 2). DKA participants who were missed included

TABLE 1 Clinical summary of KARMA2 participants.

	Control phase		Intervention phase	
	n	%	n	%
Participants: Total (eligible)	208 (203)	100.0 (97.6)	192 (185)	100.0 (96.4)
Age (years: mean; range)	69; 18–99	N/A	72; 22–102	N/A
Sex (Men)	89	43.8	95	51.0
Conveyed/Left at home	174/29	85.7/14.3	150/35	81.1/18.9
Hyperglycaemia (CBGa >11.0 mmol/L)	137	67.5	100	54.1
Hyperglycaemia—Conveyed (CBGa range; mmol/L)	123 (11.1–‘HI’)	60.7	82 (11.1–‘HI’)	44.3
Hyperglycaemia—Non-conveyed (CBGa range; mmol/L)	14 (11.3–27.8)	6.9	18 (12.3–34.1)	9.7
No diabetes mellitus diagnosis	13	6.4	15	8.1
Diabetes-type 1	43	21.2	29	15.7
Diabetes-type 2	147	72.4	141	76.2
Diabetes-type 2: prescribed insulin	40	19.7	42	22.7
Diabetes-type 2 prescribed SGLT2i	18	8.9	15	8.1
Ketonaemia (CBKa) 0.6–2.9 mmol/L	7	3.4	31	16.8
Urinary ketones (ambulance) High	2	1.0	0	0.0
Ketonaemia (CBKa) ≥3.0 mmol/L to ‘HI’	5	2.5	12	6.5
Ketonaemia (CBKa) ≥3.0 mmol/L + fluids	2	40.0	6	50.0
Ketonaemia (CBKa) ≥3.0 mmol/L + fluid volume (mL; mean)	500	N/A	483	N/A
Ketonaemia (CBKa) ≥3.0 mmol/L + fluid volume (mL; range)		N/A	N/A	250–750
Ketonaemia (CBKa) ≥3.0 mmol/L Systolic Blood Pressure (mmHg; mean; range)	150 (126–183)	N/A	129 (51–196)	N/A
Ketonaemia (CBKa) ≥3.0 mmol/L Systolic Blood Pressure <90 mmHg	0	0.0	2	16.7
Hospital DKA diagnosis	9	4.4	11	5.9
Euglycaemic DKA	1	11.1	2	18.2

Abbreviations: N/A, not applicable; SGLT2i, Sodium-glucose co-transporter-2 inhibitors.

those presenting with euglycaemic DKA. Regarding the extent of hyperglycaemia in ‘high-risk’ DKA participants, five (55.5%) control and seven (63.6%) intervention participants had a CBGa ≥20 mmol/L.

3.4 | ‘High-Risk’ DKA and fluid administration

One third (33.3%; n=3) of control and almost half (45.5%; n=5) intervention phase ‘high-risk’ DKA participants were cannulated and received 0.9% sodium chloride in the ambulance setting. All of these participants were normotensive, except one during the intervention phase (see Table 2).

Unsuccessful cannulation (n=3), participant close to hospital (n=1), and not within scope of practice (i.e. non-paramedic clinician; n=2) were reasons for not

commencing fluids for ‘high-risk’ DKA participants during the intervention phase.

3.5 | Pre-alert messaging

Almost all (91.0%; n=10) of the ‘high-risk’ DKA intervention phase participants received a pre-alert message advising the receiving hospital of their imminent arrival. While pre-alerting is a component of the study intervention, this incidence was approximately twice that of control phase participants (55.6%; n=5).

It was noted that intervention phase ‘high-risk’ DKA participants appeared more unwell than those during the control phase, that is, they were more likely to have a reduced Glasgow Coma Score (GCS <14) (control: 0.0%, n=9; intervention: 45%, n=6) and a raised National Early

TABLE 2 Clinical summary of KARMA2 participants with hospital (Emergency Department) DKA diagnosis.

	Control phase		Intervention phase	
	n	%	n	%
Hospital DKA diagnosis	9	100.0	11	100.0
'High-risk' DKA participants recruited (pre-hospital ketonaemia $\geq 3.0 \text{ mmol/L}$)	1	11.1	12	109.0
Ambulance primary impression: DKA	7	77.8	10	91.0
Age (years: mean; range)	39 (19–63)	N/A	62 (24–89)	N/A
Sex (Men)	5	55.6	4	36.3
Diabetes diagnosis—type 1	6	66.7	7	64.0
Diabetes diagnosis—type 2	3	33.3	3	27.0
New diabetes diagnosis	0	0.0	1	9.0
Previous DKA	7	77.8	7	64.0
Ambulance presentation and management				
Hyperglycaemia (CBGa $> 11.0 \text{ mmol/L}$)	8	88.9	9	82.0
Ketonaemia (CBKa $\geq 3.0 \text{ mmol/L}$)	1	11.1	9	82.0
Glasgow coma score ≥ 14	9	100.0	6	55.0
Systolic blood pressure $> 90 \text{ mmHg}$	9	100.0	10	91.0
NEWS2 ≥ 7	1	11.1	5	45.5
Successful cannulation	5	55.6	5	45.5
Fluid therapy	3	33.3	5	45.5
Hospital pre-alert	5	55.6	10	91.0
Time in ED (minutes: mean; range)	495 (235–748)	N/A	704 (103–1373)	N/A
ED handover to ED fluid initiation $\leq 1 \text{ h}$	3	33.3	6 ^a	60.0
30-day data: Hospital length of stay (days: mean; range)	6.7 (1–30)	N/A	6.6 (0–28)	N/A
30-day data: Participant deaths	0	N/A	2	18.2

^aData obtained for 10 participants.

Warning Score (NEWS2 ≥ 7) (control: 11%, $n=1$; intervention: 45.0%, $n=5$). This may have contributed to the increased pre-alert messaging by ambulance crews.

3.6 | Hospital assessment and management

ED blood glucose and ketone assessment results were obtained for most (88.9%; $n=347$) participants. Of the 'high-risk' DKA cohort, the majority (control: 77.7%, $n=7$; intervention: 91.0%, $n=10$) were hyperglycaemic and had a blood ketone level $\geq 3.0 \text{ mmol/L}$. Glycosylated haemoglobin (HbA1c) data were also collated, but only available for 6.2% ($n=24$) of all participants (data not shown).

The proportion of 'high-risk' DKA participants receiving fluid administration within 1 hr of arrival in ED increased with ketone meter use (control: 33.3%, $n=3$; intervention: 60.0%, $n=6$). However, it is acknowledged these participant sub-cohort numbers are small, and as already identified,

intervention phase 'high-risk' DKA participants appeared more unwell than those in the control phase of this study.

3.7 | 'High-Risk' DKA and hospital admission

Review of hospital participant records at 30 days post-admission revealed the mean admission duration for 'high-risk' DKA participants was approximately 7 days (control: 6.7 days (range: 1–30 days); intervention: 6.6 days (range 0–28 days)). One 'high-risk' DKA control phase participant remained an in-patient at 30 days post-admission, and another (control phase) had a DKA-related readmission.

3.8 | Adverse events

No participant-related adverse events were reported; however, 26 participants (control: $n=11$; intervention: $n=15$)

died within 30 days following recruitment. Independent review by study principal investigators revealed no study-associated causality.

The following protocol deviations were noted: conveyance to a non-KARMA2 hospital ($n=3$), diabetes insipidus, not diabetes mellitus as inclusion criteria ($n=1$); missing meter calibration data ($n=7$).

3.9 | Clinician interviews

Ten ambulance clinicians and ten ED clinicians (see Appendix A) consented to participate in a semi-structured interview (see Appendix S1). Only ambulance clinicians who recruited at least one intervention participant were consented to participate and most ED clinicians ($n=8$) did not recall specifically providing emergency care to a study participant.

Ten key themes were identified and summarised, along with supporting participant quotations (see Table 3):

3.9.1 | Theme 1—clinical assessment

Overall, the capillary blood ketone meters were well received by ambulance clinicians, they reported positive experiences with their use and considered them a beneficial diagnostic tool for clinical assessment and care.

Several practical difficulties were associated with meter use and these included error messages with temperature extremes ($n=2$); calibration value falling outside of manufacturer's range ($n=14$); need for calibration before use with time-critical participants when emergency care was prioritised.

3.9.2 | Theme 2—recognising hyperglycaemia

When considering risk factors for DKA recognition, ambulance clinicians had individualised and varied approaches to determine hyperglycaemia. Some considered hyperglycaemia to have a CBG threshold of 11.0 mmol/L, while others considered 15.0 mmol/L, 'high 20s' and 'in the 30s' to define this glycaemic state. Some clinicians shared that they include the individual's and family members' views when determining atypical CBG levels.

3.9.3 | Theme 3—current ambulance DKA fluid therapy

Paramedic participants indicated that current hyperglycaemia and DKA fluid therapy practice were variable.

While 0.9% sodium chloride may be administered to hypotensive individuals, it may also be administered when not indicated and in accordance with 2022 JRCALC clinical guidelines, that is, the person is normotensive. One student paramedic participant also highlighted operational challenges faced when obtaining paramedic support for pre-hospital fluid treatment.

3.9.4 | Theme 4—ambulance clinical handovers

Ambulance clinician participants reported to value the new ketone information obtained when using the ketone meters and considered it informative for clinical management and triage, care escalation and de-escalation, handover at hospital and when safety-netting with primary care. Most thought other healthcare professionals in hospital and community settings valued the new information shared with them.

3.9.5 | Theme 5—decision support tool

Informed clinical decision making was reported by ambulance clinician participants when using blood ketone meters, in particular, conveyance to hospital versus non-conveyance. Meter use supported appropriate conveyance decisions, while for participants remaining at scene (e.g. home), ambulance clinicians described improved engagement with participant, risk management and primary care provision.

3.9.6 | Theme 6—ambulance diabetes education

Frontline ambulance clinicians appear to rely on experiential and self-directed learning to inform their diabetes and hyperglycaemic emergencies care delivery. During the clinician interviews and study training, it was apparent that euglycaemic DKA and 'sick day rules' were unfamiliar to most participants, potentially placing persons with diabetes at risk of harm in the event of incorrect care decisions and information sharing.

3.9.7 | Theme 7—patient engagement

While this study did not seek the experiences of persons with diabetes, several ambulance clinicians indicated participants felt receptive and positive about blood ketone meters in ambulance clinical practice.

TABLE 3 Interview themes and clinician participant quotations.

Theme	Quotation	Clinician Participant number
Clinical assessment	We've been saying for a long time we need ketone meters on the vehicles, that's something that I commonly hear from people that I work with. ...we've really wanted to do ketones because they look unwell	4
	I've loved the [KARMA2] ketone meters... I think it allows us, as pre-hospital clinicians to make better judgement calls on if we can leave someone at home or if they need to reach out to a GP or whether they need to go to hospital	10
Recognising hyperglycaemia	...you always associated it with a 'HI' reading on the, on the BM [blood glucose] machine or, you know, reading in the 30s or, or high 20s	6
	[It] is just knowing what's normal for that patient and whether they're outside of what's normal for them and whether their concerns and their family and their carers...	2
Ambulance DKA fluid therapy	I would have chosen to use fluids, possibly given them a small bolus [of fluids], depending on the [glucose] reading, probably wouldn't have necessarily looked it up in JRCALC, just given them a little bolus...	3
	...if their sugars are reading high, I'd probably treat them with fluids anyway	5
Ambulance clinical handovers	...it's great to have that information, um, you've got much more of a complete picture	7
	...it would give them another, another nugget of information and it ...will be better, ringing up and saying, 'by the way, do you know Mrs X's blood sugars are 18 today and incidentally the ketones are 1.2 and this is what I've done about it'	3
Decision support tool	...it probably did change my perspective on whether, and whether we should take them to hospital or not. ...just having that extra bit of information to make the decision	9
	I think it's helped having that discussion with the patient and asking them whether they had been following sick day rules and whether they can...you can really gauge how confident you are in leaving that patient to manage their condition and whether they're going to be safe to discharge and whether then it's better to get them somewhere where they can be monitored	2
Ambulance diabetes education	I am embarrassed to say I was not aware of sick day rules...	3
	I had heard of [euglycaemia DKA], but it's not something I would have been very aware...Probably wouldn't be considering DKA if their blood sugars weren't elevated and stuff. Probably wouldn't have crossed my mind previously	2
Participant engagement	...all of the patient have been very receptive... But actually, everybody has been very positive about it. I've been to some patient who have their own ketone meters anyway, and these patient are very happy that that's something that we're considering including	2
	I think it's been really good to have conversations with patient, especially type 2 diabetics, about ketones, which is something they might not know	8
Hospital DKA diagnosis and care	... the more information we can get from you guys actually the, you know, the better informed that we are and actually when we have those phone calls or have that handover that says 'I've got a patient here who's type 1, type 2... they've got high sugars with this background, and we've done the ketones and its saying... ...all I've got to do now is a quick blood gas, or a venous blood gas, so I've got the, I've got the third, third element to, to the DKA...	12
	That information [blood ketones] will change a lot of things. ...Number one will be where to put this patient, the space...If I know the ketones are high, they go to Resus. It's clear cut DKA, initiate fluids, which could be easily done in the back of the ambulance, ...and getting the patient straight to Resus, bypassing the ambulance assessment...Number two, if the information says that it's not DKA, then we can think about the other places where this patient can, er, go	15

TABLE 3 (Continued)

Theme	Quotation	Clinician Participant number
Prioritisation of fluid therapy	...um, getting that fluid in ... does help significantly 'cos it is all about fluid replacement. ...The fluids are the first point of our call where we start treatments. Always start fluids first and then we'll go draw up the insulin...	13
	...at least if [ambulance ketone] reading has already been done and fluids have already been started, it gives us a little bit of time to, um, organise our, our, um, Resus area and get our levels safer to bring this patient then in, um, and get their treatment, like their insulin and things started from their VBG [venous blood gas]	19
Barriers to hospital DKA care	...if we know that they are ...definite like a DKA, we know that they need to go in, and if that's on a pre-alert, say that gives us 15 minutes or 10 minutes to then juggle things around ...and get patient out where we can and escalate it early, we can then try and get that flow to get the patient in quickly	18
	I think gaining access is probably the most helpful, um, because obviously it takes time for us to try and gain access and DKA patient need two points of access. If we've already got one, we can start the treatment	14

Anecdotally, even participants with diabetes and their own ketone meters were supportive of ambulance point-of-care blood ketone meters. Ambulance clinician participants also shared they utilised study-acquired diabetes and hyperglycaemia learning to have informed conversations with participants regarding hyperglycaemia and 'sick day rules' management, including insulin self-administration.

3.9.8 | Theme 8—hospital DKA diagnosis and care

ED participants were overwhelmingly supportive of ambulance blood ketone assessments and 'high-risk DKA' pre-alert messaging to expedite hospital DKA diagnosis, bed allocation and resuscitation-based management. They reiterated the importance of blood glucose and ketone testing for persons with diabetes and in-hospital use of DKA care protocols.

Risk stratification for DKA and other hyperglycaemic emergencies (i.e. hyperosmolar hyperglycaemic state; HHS) was also discussed: in the absence of elevated ketones and DKA, individuals are promptly de-escalated to receive lower-acuity, non-resuscitation-based care.

3.9.9 | Theme 9—prioritisation of fluid therapy

The value of paramedic-led cannulation and 0.9% sodium chloride administration for individuals with DKA was recognised by ED participants. The majority also considered early, pre-hospital fluids beneficial for those with 'borderline DKA', to prevent escalation to DKA,

progression of DKA pathology and need for resuscitation and intensive care. In addition, both interventions enable ED staff to prioritise venous blood gas analysis and insulin infusion in accordance with local DKA care protocols.

3.9.10 | Theme 10—barriers to hospital DKA care

Key barriers to prompt hospital-based DKA care identified by ED participants were resuscitation bed capacity, insufficient nursing and phlebotomy staff, increasing ambulance handover times and lack of intravenous access. All were considered to reduce patient flow. A need for DKA assessment and treatment in ambulances (prior to hospital entry) was noted by some clinicians, and this was experienced by some study participants. Ambulance 'high-risk DKA' pre-alert messaging was seen to be key for preparing appropriate bed and staff resourcing.

4 | DISCUSSION

It is understood that this is the first evaluation of point-of-care blood ketone testing in the ambulance setting. Medical devices, such as capillary blood ketone meters and continuous ketone monitors, that provide quantitative analysis of β -hydroxybutyrate are the preferred methods for monitoring ketone levels, DKA risk stratification and care: urine ketone dipstick and breath ketone analysis measure the presence of acetoacetate and acetone.^{12–14} More than one in four individuals with DKA in the community do not have access to ketone testing,¹⁵ and in the absence of ambulance ketone meters,

ambulance clinician access to ketone status is limited in the pre-hospital setting.^{6,10} An alternative method for ambulance DKA recognition has been demonstrated utilising end-tidal carbon dioxide monitoring.⁸ Provision of blood ketone meters for ambulance clinicians could offer early ketosis recognition to facilitate in-hospital DKA diagnosis and management, and impact morbidity and mortality.

The KARMA2 feasibility study has evaluated the recruitment and management of people with hyperglycaemia and those at risk of DKA in the ambulance setting. It demonstrated paramedic and non-paramedic ambulance clinician use of capillary blood ketone meters is feasible for the safe identification of individuals with elevated ketone levels and DKA, commencement of fluid therapy (regardless of participant blood pressure) and provision of hospital pre-alert messages for those at 'high risk' of DKA ($\text{CBKa} \geq 3.0 \text{ mmol/L}$). Meter use by these clinicians also enabled the identification of individuals with elevated blood ketones requiring ongoing care, but not at immediate risk of DKA (i.e. $\text{CBKa} = 0.6\text{--}2.9 \text{ mmol/L}$). Ambulance clinicians considered meter use acceptable and beneficial for not only DKA recognition, but appropriate decision making for non-conveyance, improving clinical handovers with community, primary and secondary care healthcare professionals, 'sick day rules' support and safety-netting. ED clinicians supported the use of ketone meters by ambulance staff, such that they considered blood ketone meter use, appropriate pre-alert messaging and pre-hospital fluid therapy opportunities to expedite in-hospital DKA triage and care delivery.

Despite these findings, a full-scale, controlled trial with a stepped-wedge design is deemed not feasible, owing to the recruitment threshold progression criterion not being met, that is, at least 70% of eligible participants consented to study participation. The original planned study recruitment target in each phase was 400 participants over 4 months, and this was not met even when both study phases were extended by 1 month and various clinician recruitment and support strategies were implemented. Anecdotal evidence collected from clinicians (see Appendix S2) highlighted the impacts of the COVID-19 pandemic on ambulance staff, service delivery and capacity for research activities, including participant recruitment. Recruitment difficulties have been observed in other ambulance-based feasibility studies,^{16–18} highlighting the challenges researchers can encounter in this clinical research setting. Feedback received from participating KARMA2 ambulance clinicians indicated cluster or randomised controlled trial designs and revised eligibility criteria, in particular, inclusion of legal representatives for consent, may facilitate participant recruitment. Lowering the recruitment

threshold criterion and screening missed recruitment opportunities may also be warranted. It is worth noting that even with the lower KARMA2 recruitment rate, the planned minimum DKA sample size (i.e. 20 participants) was met. A potential explanation for this is the increased incidence of DKA associated with new diabetes diagnosis and unwell patients with type 2 diabetes during the COVID-19 pandemic.^{19,20}

It was beyond the scope of this feasibility study to address the apparent low recruitment rate; however, it should be noted that KARMA2 was designed prior to COVID-19 and subsequently delivered during the initial phase of the pandemic. As in other clinical and research settings at this time, the ambulance workforce experienced personal and service delivery challenges.^{21,22} It was recognised that despite clinician support throughout the study, notable clinician attrition occurred. We suggest alternative methods are explored for clinician engagement, for example, mandatory participation and study training as ongoing professional development activities.

The following study limitations are acknowledged which offer important learning opportunities for future ambulance hyperglycaemia and DKA-related research: (i) only a single UK ambulance service participated in this study, so the generalisability of the findings to other settings may be limited; (ii) due to the feasibility nature of the study, differences between the control and intervention phase participants have not been formally tested and should be considered with caution; (iii) the planned transition phase was removed and both phases were extended by 1 month to optimise participant recruitment; (iv) it is possible that due to recruiting clinician unconscious bias or increased study confidence, intervention 'high-risk' DKA participants were older and more unwell than those recruited during the control phase. This could have contributed to the differences observed in the management of these participants; (v) not all eligible 'high-risk' DKA participants received fluid therapy prior to hospital arrival indicating there is scope to improve this clinical practice; (vi) it was beyond the scope of this study follow-up participants who were not conveyed to hospital via their primary care provider and to explore effects of seasonality on participant recruitment and management.

In summary, we believe this is the first clinical trial evaluating capillary blood ketone meter use in the ambulance setting. It has been demonstrated that ambulance clinicians can safely undertake capillary blood ketone assessments and adhere to new ambulance 'high-risk' DKA fluid therapy guidance, to support early, pre-hospital fluid administration for these individuals. However, it appears a powered research trial with a stepped-wedge controlled design is not warranted. Recently, JRCALC revised the national ambulance glycaemic emergencies guidelines,

taking into consideration the KARMA2 study methodology and findings.²³ Service provision of capillary blood ketone meters is now recommended for UK ambulance care and guidance for pre-hospital ketone testing and DKA management have been updated.

AUTHOR CONTRIBUTIONS

LP, TF, AL, AB, KD, GR, MS and JW developed the study question and methodology; as Research Paramedics, LP and TS provided daily oversight for study delivery and performed the data analysis, with TF, AL, AB, AC, KD, GR, and JW contributing to the interpretation of data. LP drafted the manuscript, with co-authors reviewing and approving the final version for publication. LP and TF are the guarantors of this work.

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CONFLICT OF INTEREST STATEMENT

Professor Rayman was the Chair of the Diabetes UK Clinical Studies Group 4; Lake was the Deputy Chair of the Diabetes UK Clinical Studies Group 4; Professors Dhatariya and Sampson were members of the Diabetes UK Clinical Studies Group 4.

CLINICAL TRIAL REGISTRATION

Clinicaltrials.gov registration identifier: NCT04940897.

HUMAN STUDIES AND PARTICIPANTS

This study was approved by North East—Newcastle & North Tyneside 2 Research Ethics Committee (Reference: 21/NE/0134) and conforms to the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Employment profile of KARMA2 interview participants.

Interview number	Clinician type	Clinical setting	Emergency care experience (years)
1	Student ambulance paramedic	Ambulance	7.0
2	Newly qualified paramedic	Ambulance	3.5
3	Paramedic	Ambulance	6.0
4	Student ambulance paramedic	Ambulance	4.5
5	Paramedic	Ambulance	7.0
6	Nurse	Emergency department	1.0
7	Deputy sister	Emergency department	3.0
8	Staff nurse	Emergency department	1.0
9	Senior paramedic	Ambulance	15.0
10	Senior paramedic	Ambulance	22.0
11	Senior sister	Emergency department	4.0
12	Sister	Emergency department	9.5
13	Newly qualified paramedic	Ambulance	2.0
14	Deputy sister	Emergency department	5.0
15	Advanced clinical practitioner (trainee)	Emergency department	15.0
16	Paramedic	Ambulance	7.0
17	Senior paramedic	Ambulance	18.0
18	Emergency medicine doctor (specialty trainee)	Emergency department	8.0
19	Emergency medicine doctor (specialty trainee)	Emergency department	6.0
20	Staff nurse	Emergency department	18.0