BMJ Open

Intravenous ketamine for emergency department treatment of suicidal ideation in a paediatric population: protocol for a double-blind, randomised, placebo-controlled, parallel-arm pilot trial (KSI study)

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To cite: Schlegelmilch M, Plint AC, Barrowman N, *et al*. Intravenous ketamine for emergency department treatment of suicidal ideation in a paediatric population: protocol for a double-blind, randomised, placebo-controlled, parallel-arm pilot trial (KSI study). *BMJ Open* 2024;**14**:e085681. doi:10.1136/bmjopen-2024-085681

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-085681).

Received 22 February 2024
Accepted 20 May 2024

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ABSTRACT

Introduction Suicidal ideation (SI) is a common and severe cause of morbidity in adolescents. Patients frequently present to the emergency department (ED) for care, yet there is no acute therapeutic intervention for SI. A single dose of intravenous ketamine has demonstrated efficacy in rapidly reducing SI in adults; however, ketamine has not been studied in paediatrics. We aim to determine the feasibility of a trial of a single intravenous ketamine dose to reduce SI for patients in the paediatric ED.

Methods and analysis This will be a single-centre, double-blind, randomised, placebo-controlled, parallel-arm pilot trial of intravenous ketamine for ED treatment of SI in a paediatric population. Intervention: one intravenous dose of 0.5 mg/kg of ketamine (max 50 mg), over 40 min. Placebo: one intravenous dose of 0.5 mL/kg (max 50 mL) of normal saline, over 40 min. Participants will be randomised in a 1:1 ratio. SI severity will be measured at baseline, 40 min, 80 min, 120 min, 24 hours and 7 days. We aim to recruit 20 participants. The primary feasibility outcome is the proportion of eligible patients who complete the study protocol. We will pilot three SI severity tools and explore the efficacy, safety and tolerability of the intervention.

Ethics and dissemination This study will be conducted according to Canadian Biomedical Research Tutorial, international standards of Good Clinical Practice and the Health Canada, Food and Drug Act, Part C, Division 5. The study documents have been approved by the CHEO Research Institute Research Ethics Board (CHEO REB (23/02E)). Participants must provide free and informed consent to participate. If incapable due to age, assenting participants with parental/legal guardian consent may participate. On completion, we will endeavour to present results at international conferences, and publish the results in a peer-reviewed journal. Participants will receive a results letter.

Trial registration number NCT05468840.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Robust assessment of clinical outcome measurement tools is essential to effectively measure rapid changes in suicidal ideation severity.
⇒ Results of the pilot study will inform the development of a fully powered, definitive randomised controlled trial of intravenous ketamine for the rapid treatment of suicidal ideation in a paediatric emergency department.
⇒ Our study is limited by small sample size and use of unproven outcome measurement tools in this population.
⇒ There is potential for unblinding given there could be subjective (dizziness, mild euphoria) and objective (tachycardia and hypertension) effects from the ketamine infusion.
⇒ Loss to follow-up may threaten the study validity as these are one-time patient interactions and follow-up may be difficult.

INTRODUCTION

In 2019, death by suicide (9.5 per 100 000 population) was second only to accidents (9.7 per 100 000) as the leading cause of death for Canadians aged 15–19 years. This incidence is three times greater than cancer deaths (3.4 per 100 000), which is the third leading cause in this age group.[1] Suicide is also the third leading cause of death for Canadians aged 10–14 years.[1] The magnitude of the problem is likely underestimated as an unknown proportion of suicide deaths are counted as accidental.[2]

Suicide attempts are estimated to be 50–100 times more prevalent than completed suicides and the prevalence of suicidal ideation (SI), although difficult to quantify, is even greater.[3] Over the past 5 years, paediatric emergency departments (EDs) across North America have seen increased numbers of suicide-related complaints.[4] SI is a medical emergency and the ED is a critical point of

contact for primary and secondary suicide prevention, yet methods to rapidly and effectively reduce the risk of attempts or to alleviate distress associated with acute and chronic SI are severely lacking.

Over the past decade, clinical and research interest has emerged around the use of ketamine for rapid relief of suicidal symptoms in adult patients. Two systematic reviews of placebo-controlled trials of ketamine therapy for the treatment of SI in adults concluded a single dose of intravenous ketamine may be an effective option for rapid and sustained relief of SI.[5 6] Wilkinson *et al*.[6] reported a moderate to large effect size of single-dose intravenous ketamine on SI (d=0.48–0.85), although a better understanding of the optimal dose and population was recommended. Abbar *et al*[7] conducted the largest trial to date with 156 adult participants with SI who were voluntarily admitted to hospital. Participants receiving ketamine demonstrated greater odds of complete SI remission by day 3, compared with those receiving placebo (OR 3.7; 95% CI 1.9 to 7.3).

The majority of studies of intravenous ketamine for SI use a subdissociative ketamine dose of 0.5 mg/kg administered over 40 min; however, three published ED studies have used rapidly administered ketamine at lower doses. Kashani *et al* (2014) conducted a single-blind uncontrolled study of 49 adult patients with SI.[8] Participants received 0.2 mg/kg ketamine over 1 min and showed reduced SI at 40, 80 and 120 min. Domany *et al* (2020) conducted a randomised controlled double-blind trial of 18 adult patients with SI in the ED.[9] Eighty-eight per cent of patients receiving intravenous ketamine dosed at 0.2 mg/kg over 5 min no longer had suicidal thoughts at 90 min compared with 33% of controls. In 2022, Domany *et al* used a fixed dose (40 mg) of ketamine administered intranasally and found improved depressive symptoms 4 hours post administration.[10] These studies showed rapidly administered, lower dose ketamine was effective with no detriment to patient safety and may be more feasible to use in an ED setting.

To our knowledge, there are only two published studies investigating the use of ketamine for mental health conditions in adolescents. An open-label study by Cullen *et al*[11] studied 13 adolescents with treatment-resistant depression who received intravenous ketamine at 0.5 mg/kg over 40 min every 2 weeks for a total of six treatments. They found a 43% absolute reduction of symptoms of depression following the final infusion. More recently, Dwyer *et al* published the first randomised controlled trial of intravenous ketamine in adolescents with depression using intravenous ketamine dosed at 0.5 mg/kg over 40 min. They reported a significant reduction in mean depression scores 24 hours after infusion.[12]

Ketamine is a commonly used medication for sedation and analgesia in the paediatric ED with excellent safety and patient tolerability.[13] Theoretical concerns of neuronal apoptosis on animal fetuses have been described in primate models who received ketamine for >5 hours, although standard ED use differs significantly in terms of older patient populations and much shorter dosing administrations.[14] Additionally, risk of drug dependence to ketamine remains theoretical. Studies in adult populations of ketamine for mental health conditions report no drug cravings or drug-seeking behaviour following a single, subdissociative dose of ketamine.[15]

Despite a very favourable safety profile and early evidence for efficacious treatment of depression, ketamine has never been studied for rapid treatment of SI in adolescents. High-quality research for youth with SI is urgently needed and the paediatric ED is a critical point of contact for this population. If ED treatment of SI with intravenous ketamine is efficacious, as it is in adults, ketamine therapy has the potential to improve patient safety, reduce symptoms and minimise patient and family distress. We aim to conduct a pilot randomised clinical trial of a low-dose intravenous ketamine infusion for adolescents presenting to the paediatric ED with moderate to severe SI. The results of this feasibility pilot study will inform the development of a larger, definitive trial.

METHODS AND ANALYSIS

Trial design

This study will be a single-centre, double-blind, pilot randomised controlled trial of intravenous ketamine versus placebo for the rapid treatment of adolescents (aged 12–17 years) with SI in the paediatric ED. Two study groups will be examined: (1) intravenous ketamine 0.5 mg/kg (50 mg maximum) over 40 min and (2) intravenous normal saline 0.5 mL/kg (50 mL maximum) administered over 40 min. Participants will be recruited from the ED at CHEO, the tertiary care academic children's hospital in Ottawa, Canada with an annual census of over 75 000 patient visits. Our study launched on 15 January 2024 and is expected to complete enrolment by summer 2024.

Sample size

We aim to enrol 20 patients in this feasibility trial. Although this trial is not designed with adequate power to detect a clinical efficacy of ketamine therapy, enrolling 10 patients per group will provide information on our feasibility outcomes as well as estimates of distribution of our SI severity tools.

Randomisation, allocation concealment and blinding

The statistician will prepare a randomisation list with a 1:1 allocation ratio between the intervention (intravenous ketamine) and control (intravenous normal saline) groups. The list will be provided to the research pharmacist. The active and placebo drugs will be identical in appearance and volume. Study drugs will only be identified by a sequential study number. Study participants, research nurses (administering the intervention and assessing the outcomes), ED staff and data analysts will be blind to group assignment. If it is medically necessary for

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Age 12–17 years 2. Responds 'yes' to ASQ at triage, which asks "Are you having thoughts of killing yourself right now?" 3. Moderate to severe suicidal ideation, defined as score ≥3 on the first 5 questions of the Beck Scale for Suicidal Ideation[17] 4. Medically clear (deemed fit for participation in the trial), as judged by the treating physician. Minimum criteria required to be deemed medically clear are: 1. No evidence of serious physical injury requiring urgent intervention 2. No evidence of acute ingestion requiring monitoring, blood tests, imaging or ECG or in the context of acute ingestion they have satisfied the requisite number of hours of postingestion monitoring with no further need for intervention	1. Acute intoxication, from any substances, including alcohol 2. Previously enrolled in the current study or currently enrolled in another clinical trial 3. History of intellectual disability, cognitive developmental delay or autism spectrum disorder by patient/parent report 4. Active, or history of, psychosis or psychotic disorder 5. History of non-psychiatric neurological disorder associated with seizures 6. Any of the following contraindications to ketamine based on the drug monograph: 1. Known allergy or hypersensitivity to ketamine by patient history 2. History of cerebrovascular accident (stroke or aneurysm) 3. History of elevated intracranial pressure or idiopathic intracranial hypertension 4. Significant hypertension requiring daily medication 5. Severe cardiac decompensation 7. On an involuntary psychiatric hold 8. Requires physical or chemical restraint 9. History of violence while in hospital 10. Pregnant or breastfeeding 11. Received opioids in the 24 hours prior to study screening

ASQ, Ask Suicide Screening Questions.

treating physicians to know which intervention a participant received, the study blind can be broken by the clinical team after discussion with the sponsor-investigator or their qualified delegate. The unblinding procedure will enable only the treating physician to be aware of the participant's allocation. In addition, the data safety monitoring board (DSMB) may request unblinding from the research pharmacist if they deem it necessary to consider the results of the interim safety analysis or to review possible adverse events.

Eligibility assessment and consent

Adolescents presenting to the ED with a mental health complaint will be eligible to participate if they meet all of the following inclusion criteria: (1) aged 12–17 years; (2) respond 'yes' to question 5 of the Ask Suicide Screening Questions (ASQ)[16] at triage, which asks "Are you having thoughts of killing yourself right now?"; (3) have moderate to severe SI, defined as score ≥3 on the first 5 questions of the Beck Scale for Suicidal Ideation (SSI5)[17]; (4) are medically clear (deemed fit for participation in the trial), as judged by the treating physician. They must also meet none of the exclusion criteria. Detailed inclusion and exclusion criteria are summarised in table 1.

The consent process will be carried out by a trained and delegated research team member and done in a private room in the ED. The research team member will review the participant informed consent forms with the participant and their parent or guardian (online supplemental appendix A). The informed consent forms will discuss the specific risks and benefits of participating or not participating in the research study.

Patient and public involvement

Patients and family members with lived experience in mental health emergencies were engaged during the external peer-review process required by our funding agency and the REB. Two independent family leaders were identified by the granting agency's Research Institute and provided an anonymous evaluation of the pilot study protocol. Collated feedback was provided to the study team to inform the ongoing development of the pilot design. At the conclusion of the pilot, our study team plans to re-engage members of the public, through similar mechanisms, to further guide the development of the planned subsequent trial.

Interventions

Intervention group

Participants randomised to receive intravenous ketamine (1 mg/mL) will be administered a subdissociative dose of 0.5 mg/kg (maximum 50 mg) over 40 min. This is the current standard dosing protocol in the majority of ketamine trials for mental health disease.

Control group

Participants randomised to receive intravenous normal saline will be administered a dose of 0.5 mL/kg (maximum 50 mL) over 40 min.

Participants will be under continuous cardiorespiratory and oxygen saturation monitors and have a caregiver, study team delegate or patient sitter present for the duration of the infusion and for 120 min following the start of the infusion. Patient vitals will be centrally monitored at the ED nursing station.

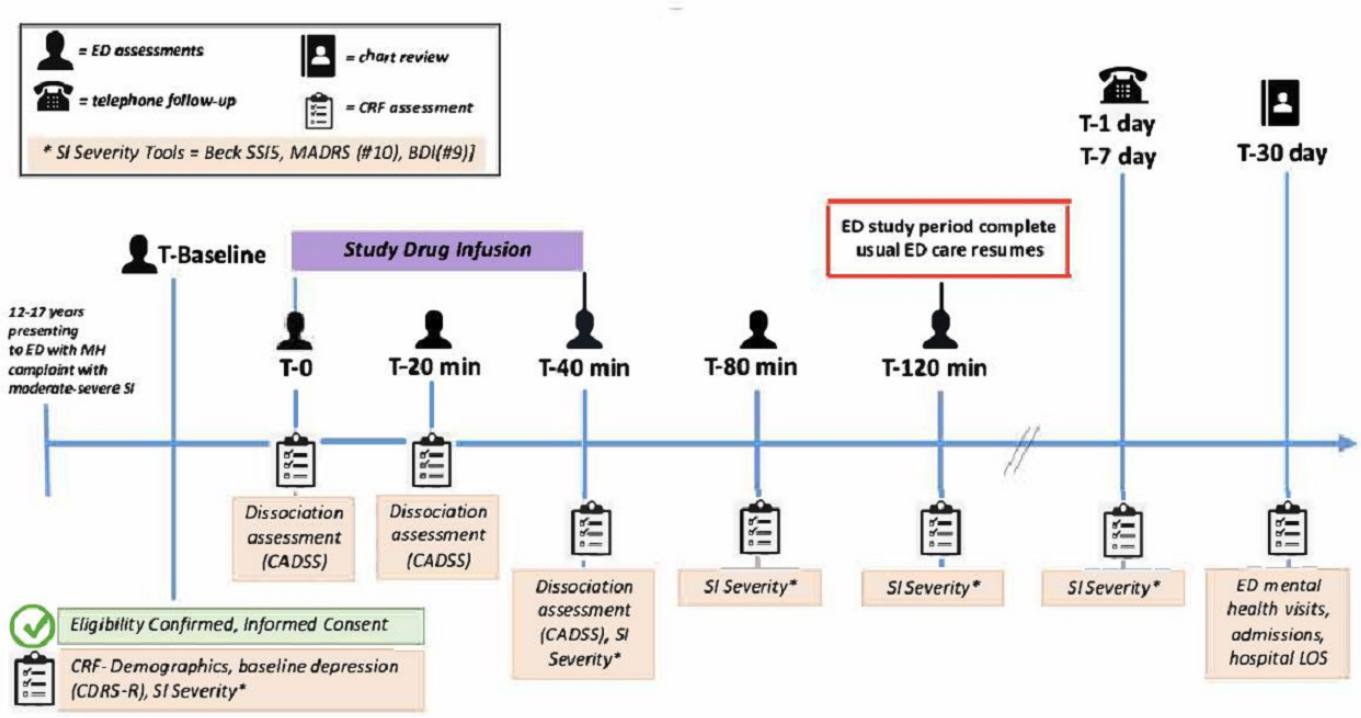

Figure 1 Participant timeline. *SI severity measured by the Beck SSI5, the MADRS item 10, and the BDI item 9. CADSS, Clinician Administered Dissociative States Scale; CDRS-R, Children's Depression Rating Scale-Revised; CRF, case report form; ED, emergency department; LOS, length of stay; MH, mental health; SI, suicidal ideation.

Modifications and concomitant care

If the infusion is interrupted, it may be restarted to administer the remainder of the prescribed dose so long as the infusion is restarted within 30 min. If the infusion is interrupted and restarted within the allowable timeframe, the first outcome assessment of SI severity (T-40) will occur when the infusion is complete. If the intravenous infusion cannot be re-established, the study does not permit the intervention to continue because the initial metabolic clearance of intravenous ketamine has a half-life of 10–15 min.[18] Participants will be able to continue in the study; however, instances where they are unable to complete the intervention will be documented.

All patients approached for enrolment in the study will receive usual ED care, irrespective of their decision to participate.

Participant evaluation

Participants will undergo two phases of assessment: (1) in the ED and (2) post-ED. The participant's timeline is shown in figure 1.

Measurements in the ED

Baseline demographic data will be collected on enrolment and measure: (1) age; (2) assigned sex at birth; (3) current gender; (4) sexual orientation; (5) current weight; (6) languages spoken at home; (7) combined average yearly household income and (8) current medications. A baseline mental health assessment performed using the Children's Depression Rating Scale-Revised (CDRS-R).[19]

Severity of SI will be assessed at baseline, 40 min (T-40), 80 min (T-80) and 120 min (T-120) following the start of the infusion, using three SI assessment tools: (1) the first five questions from the Beck SSI5[17 20]; (2) the suicide item (number 10) from Montgomery-Asberg Depression Rating Scale (MADRS10)[21] and (3) the suicide item (number 9) from the Beck Depression Inventory (BDI9).[22]

Participants will be under continuous cardiorespiratory and oxygen monitors for the duration of the infusion and for 80 min following the end of the infusion. They will be monitored with the Clinician Administered Dissociative States Scale-Abbreviated Version (CADSS-6),[23 24] a standardised measure of dissociative symptoms.

Rationale for outcome measurement tool selection

There is currently no gold standard against which to validate the outcome assessment tools. Previous studies of adult patients have shown all three measures are responsive to rapid change in SI but none of these tools have been studied in our population for this indication, with this intervention. There are three challenges we anticipate. One, the MADRS10 loses sensitivity in adult patients by day 3 and we do not know if this will also be an issue in our population.[25]

Two, the SSI5 may be challenging for youth as it is a multi-item scale with potentially confusing language. For example, one question asks to rate passive suicidal desire by selecting, 'would avoid steps necessary to save or maintain life', which may or may not be comprehensible to

Table 2 Schedule of activities

Evaluation	Prescreening	Screening	Baseline (–60 min)	Intervention (0 min)	Monitoring (20 min)	Immediate follow-up (40, 80, 120 min)	Follow-up (1 and 7 days)	Chart review (30 days)
ASQ 5	X							
Capacity assessment*		X						
Consent		X						
Urine pregnancy test		X						
Demographics			X					
CDRS-R			X					
Beck SSI5		X	X			X	X	
MADRS10			X			X	X	
BDI9			X			X	X	
Drug infusion				X				
Vital signs				X	X	X		
CADSS-6				X	X	X (40 min)		
Adverse events					X	X	X	X
Follow-up chart review							X	X

*See box 1 for details of the capacity assessment.
BDI9, Beck Depression Inventory; CDRS-R, Children's Depression Rating Scale-Revised; MADRS10, Montgomery-Asberg Depression Rating Scale; SSI5, Beck Scale for Suicidal Ideation.

children and youth, especially in an acute state of active SI. Third, the single item questions of the MADRS10 and BDI9 are pragmatically appealing for speed and ease of application, but may not give enough breadth to the complex assessment of SI.

Measurements post-ED

Participants will be followed-up by telephone at 24 hours and 7 days following enrolment. This follow-up will consist of SI severity assessment using the SSI5, MADRS10 and BDI9.

Each participant's medical chart will be reviewed to examine the 30 days following enrolment. This will determine: (1) number of ED visits for mental health complaints in the 30 days since enrolment, (2) whether the participant was admitted to hospital at the enrolment ED visit and (3) adverse events (AEs) and (4) death. If hospitalised at the enrolment visit, we will also determine (1) length of admission (days) and (2) indication for admission. Participant schedule of activities is shown in table 2.

Safety assessments

During the intervention phase of the study, the research assistant will record on a designated paper or electronic case report form any AEs that occur. AEs that could be related to the administration of ketamine (dissociation, amnesia, hypertension, tachycardia, respiratory depression, laryngospasm, vomiting) will be specifically solicited from participants or recorded from participants' vital signs.

Although we expect low rates of dissociation, participants will be assessed at T-0 (start of infusion), 20 min (midinfusion) and 40 min (T-40, end of infusion) using the Clinician Administered Dissociative States Scale-Abbreviated Version (CADSS-6).[23 24] A total score over 6, or a score of 4 on any single question will trigger an assessment by a nurse or physician. These cut-off points are conservative estimates of distressing levels of dissociation based on previous studies.[26]

During the follow-up phase at 24 hours and 7 days postintervention, participants will be directly screened for any active SI at each of these timepoints. We have established a safety management plan to outline the steps that our research personnel must take when they identify potential AEs during the study intervention or follow-up phases, in order to ensure the sponsor-investigator is informed in a timely fashion.

Outcomes

Feasibility outcomes

The primary outcome is study feasibility, and will be measured by the number and percentage of eligible patients who complete the study protocol. Specifically, we will measure and report the number of patients who:

(1) are screened for participation; (2) are eligible; (3) are eligible and who given consent; (4) complete the intervention; (5) complete study follow-up; (6) receive the maximum dose of ketamine or placebo and finally (7) we will measure the time (min) from triage to the study intervention start.

Assessment tool outcomes

There is currently no gold standard against which to validate the clinical outcome assessment tools. Due to the uncertainty of the short-term and long-term responsiveness to ketamine, ease of use and appropriateness in our population, we will administer all three of the following tools: the SSI5, MADRS10 and BDI9. For each, we will measure and report: (1) estimates of central tendency and variance; (2) minutes taken to complete the assessment at each timepoint; (3) proportion of assessments with missing data; (4) a pragmatic assessment of the tool validity by asking each participant, which tools best captures how they are feeling.

Clinical outcomes

Although this pilot is not powered to detect changes in clinical outcomes, our primary clinical outcome is SI severity, measured by the SSI5, MADRS10 and BDI9, at the end of the 40 min medication infusion (T-40). Secondary clinical outcomes are: (1) change in SI severity from baseline, measured by SSI5, MADRS10 and BDI9 at 80 min (T-80), 120 min (T-120) poststart of the infusion and at 24 hours (T-1 day) and 7 days (T-7 days) following enrolment; (2) hospital admission at the enrolment ED visit; (3) length of hospital stay for patients admitted at the enrolment visit and (4) ED visits for mental health complaints within 30 days following enrolment. Adequacy of blinding will be assessed by asking participants which intervention they think they received at the end of the 40 min infusion.

Safety outcomes

AEs will be carefully monitored, documented and reported. Safety outcomes during the ED phase include: (1) clinically significant tachycardia or hypertension requiring intervention by the treating team, (2) vomiting and (3) dissociation, measured by CADSS-6, with a score over 4 on any single question or a total score of over 6[23,26] and (4) all-cause mortality within 30 days of enrolment.

Statistical analysis

Feasibility outcomes

We will report number and percentage of patients screened, enrolled, randomised, lost to follow-up and analysed to align with the Consolidated Standards of Reporting Trials reporting of randomised controlled trials.[27] We will also examine the mean time to completeness of SI severity measurements. We will report measures of central tendency and variance, as well as change over time at specific timepoints, for each SI severity measurement tool.

Clinical outcomes

Baseline participant characteristics and participant safety data will be reported by number and percentage, or by mean and SD as appropriate. The primary clinical outcome analysis will be an analysis of covariance to examine between-group differences in SI severity at 40 min adjusting for SI severity at baseline, as well as sex, age and CDRS-R scores.

To analyse change in SI severity over the four timepoints following the end of the intervention (80 min, 120 min, 24 hours and 7 days postintervention), constrained longitudinal data analysis will be used.[28 29] Additional analyses will examine between-group differences in the proportion of participants admitted following intervention, and in the length of admission for those admitted. The proportion of participants who represent to the ED with mental health complaints, admission to hospital and death within 1 month following intervention will also be calculated and compared between groups.

All statistical hypothesis tests will be two-sided. All main efficacy analyses will be based on the intention-to-treat principle. All reports and publications will distinguish these analyses.

Data management and monitoring

Data for this study will be collected using the CHEO Research Institute's validated instance of Research Electronic Data Capture. The application and data are housed on secure servers at CHEO. Data will be derived from participants directly via questionnaires completed at the time of the ED visit and in follow-up, over the telephone. Retrospective data will be extracted from the medical record at 30 days to determine subsequent ED visits, length of stay in hospital if admitted at the enrolment ED visit and all-cause mortality. Urine for beta-human chorionic gonadotropin testing is the only biological specimen to be collected. All urine specimens will be destroyed at the index visit and will not be stored.

Safety oversight will be under the direction of an independent DSMB. The DSMB is chaired by Dr Jocelyn Gravel and two other individuals with expertise in trial methodology, epidemiology, biostatistics and paediatric emergency medicine.

Monitoring for quality and regulatory compliance will be performed by the CHEO Research Institute. Details of the clinical monitoring plan are included in a Trial Monitoring Plan.

All records will be kept in a secure, locked location and only research staff will have access to the records. The assigned monitor will be given direct access to the source documents, case report forms and other study documents. All research records pertaining to studies that fall under Health Canada Division 5 regulations must be retained for a minimum of 15 years after study closure.

Box 1 Capacity assessment

Questions for the participant

1. What is the study about? What do the researchers want to learn?
2. What are some possible good things that might happen in this study? *OR* Can you tell me the benefits of this study?
3. What are some possible bad things that might happen in this study? *OR* Can you tell me the risks of this study?
4. Do you have to be in this study?

ETHICS AND DISSEMINATION

This study will be conducted according to Canadian Biomedical Research Tutorial, international standards of Good Clinical Practice and the Health Canada, Food and Drug Act, Part C, Division 5, Drugs for clinical Trials Involving Human Subjects. The study will be federally monitored by Health Canada and approval has been granted for the conduct of this study (HC6-024-c272395). The Research Ethics board at CHEO has further approved the study protocol and consent documents (23/02E). Any amendments to the study protocol and/or consent documents will be submitted to Health Canada and the CHEO REB for formal approval to conduct the study.

Participants who satisfy all inclusion, and no exclusion criteria are eligible to participate in the trial. The consent process will be carried out by a trained and delegated research team member and done in a private room within the ED. The research team member will read through the participant informed consent forms with the participant and their parent or guardian. The informed consent forms will discuss the specific risks and benefits of participating or not participating in the research study. Once the informed consent discussion has taken place, the same research team member will conduct a capacity assessment (box 1). The appropriateness of the participant responses will be assessed by the research team member and verified by the treating physician. Capable patients have the option to provide informed, voluntary and ongoing consent (online supplemental appendix A). If there is concern about capacity, participants will be asked to provide their assent to participate. If an incapable patient is assenting, free and informed consent from a parent or legal guardian with medical decision-making authority can be obtained. Dissenting or capable non-consenting participants will not be enrolled.

At the conclusion of the study, the research team will endeavour to present the study results at national and international conferences, and to publish the study results in a high-impact, peer-reviewed journal. Participants will be provided with a letter with the results of the study.

Contributors MS and MB contributed to the study conception and initial drafting of the study protocol. All authors contributed to the design of the trial. NB was responsible for the design of the statistical analysis. CG and ACP provided critical review of the study protocol. The final manuscript was approved by all authors.

Funding This project has received peer-reviewed grant funding from the CHEO Research Institute Research Growth Award (20221382) and the CHEO Psychiatry Associates (cc9906). Neither funding body has any role in study design, data collection, analysis or manuscript writing.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the 'Methods' section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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