ISRCTN17516192 https://doi.org/10.1186/ISRCTN17516192

A trial of normal versus higher dose acetylcysteine in patients with paracetamol overdose

Submission date
12/05/2023

Recruitment status
Recruiting

Registration date
21/11/2023

Overall study status
Ongoing

Last Edited
24/03/2025

Condition category
Injury, Occupational Diseases, Poisoning

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Paracetamol overdose is very common. Someone presents to the hospital following an overdose every 5 minutes across the UK. This rate is the same as the rate for heart attacks. Despite having an effective antidote called acetylcysteine (NAC), 1 in 10 patients go on to develop liver damage. NAC causes side effects such as allergic reactions that are unpleasant for the patient and may result in this essential treatment being stopped. It is unknown whether increasing the dose of NAC is more effective at preventing liver damage partly because, until recently, dose increases have not been possible due to the side effects. To address this, we designed a new protocol for giving NAC (the SNAP regimen) that is now used across the UK and has dramatically reduced the risk of patients experiencing side effects. The improved safety of the SNAP regimen allows us to look at the potential benefits of treating patients with higher NAC doses. This trial will determine whether increasing the NAC dose results in an increase in the breakdown of paracetamol, without causing an unacceptable rate of side-effects.

Who can participate?
Patients who have had a paracetamol overdose from the Emergency Department at participating sites in Scotland.

What does the study involve?
The trial will compare the effects of NAC given for 12 hours at 1.5 times and double the standard dose with standard treatment (dose groups: standard = 300 mg/kg; 1.5 = 450 mg/kg and double=600 mg/kg). Paracetamol breakdown will be assessed by measurement of the breakdown products (metabolites) in the blood. Side effects will be assessed using a patient questionnaire. Participants will be followed up for 7 days using their medical notes to review their recovery. The results of this trial are essential information for the next step, a UK-wide trial to determine whether a higher dose of NAC improves the outcome for patients.

What are the possible benefits and risks of participating?
Patients treated with NAC may experience side effects such as nausea, vomiting, feeling flushed, feeling wheezy or skin rash. In rare cases, patients have more side effects such as lowering of

their blood pressure or swelling of the tongue or lips. In most cases, the symptoms subside after stopping the medicine temporarily and the medical team will can give treatment to help with side effects. The SNAP protocol helps minimise the likelihood of these symptoms. The need for one additional blood sample may cause minor discomfort.

Where is the study run from?
University of Edinburgh (UK)

When is the study starting and how long is it expected to run for?
January 2023 to June 2026

Who is funding the study?
Chief Scientist Office, Scottish Government Health and Social Care Directorate (UK)

Who is the main contact?
HiSNAP Trial Management Team, Edinburgh Clinical Trial Unit, HiSNAP.Trial@ed.ac.uk (UK)

Contact information

Type(s)
Scientific

Contact name
Ms Kat Oatey

Contact details
Usher Institute
NINE, Usher Building
57 Little France Road
Edinburgh Bioquarter
Edinburgh
United Kingdom
EH16 4UX
+44 (0)131 651 9913
Hisnap.trial@ed.ac.uk

Type(s)
Principal Investigator

Contact name
Dr James Dear

Contact details
Queen's Medical Research Institute
Room E3.20
47 Little France Crescent
Edinburgh
United Kingdom
EH16 4TJ
+44 (0)131 242 9214
James.dear@ed.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1007520

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
AC23035, IRAS 1007520, CPMS 59286

Study information

Scientific Title
A multi-centre, randomised, open-label, blinded end-point, safety and efficacy trial of conventional (300 mg/kg) versus higher doses of acetylcysteine (450 mg/kg and 600 mg/kg) in patients with paracetamol overdose (HiSNAP)

Acronym
HiSNAP

Study objectives
Testing whether increasing the dose of acetylcysteine (NAC) increases the breakdown of paracetamol in patients who have had paracetamol overdose.

Safety - reviewing the side effects patient experience when taking the different doses, particularly those related to allergic reactions.
Efficacy (how well NAC works) - see if there is evidence of reduced liver injury with higher NAC doses

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 26/09/2023, East Midlands - Derby Research Ethics Committee (2 Redman Place, London, EC20 1JQ, UK; Tel: Not Applicable; derby.rec@hra.nhs.uk), ref: 23/EM/0129

Study design
Multi-centre randomized open-label blinded-end-point safety efficacy study

Primary study design
Interventional

Secondary study design
Randomized open-label blinded-end-point

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Paracetamol overdose

Interventions
Participants will receive a 12-hour infusion of acetylcysteine (NAC) of either conventional (300 mg/kg), 1.5 times (450 mg/kg) or double (600 mg/kg) the conventional dose. Any preparation of acetylcysteine which has marketing authorisation in the UK to be used for this indication and is stocked by local hospital pharmacies at the participating sites may be prescribed in this study. Standard dosing (300 mg/kg) will be infused as per the SNAP regime: initial loading dose (100 mg /kg in 200 mL) given intravenously over 2h, followed by a second dose (200 mg/kg in 1000 mL) infused over 10h. OR HiSNAP group 1 (450 mg/kg): initial loading dose (150 mg/kg in 200 mL) given intravenously over 2h, followed by a second dose (300 mg/kg in 1000 mL) infused over 10h. OR HiSNAP group 2 (600 mg/kg): initial loading dose (200 mg/kg in 200 L) given intravenously over 2h, followed by a second dose (400 mg/kg in 1000 mL) infused over 10h. The dose of NAC assigned to each patient will be randomised using a centralised online randomisation system. Participants will be followed-up for 7 days following the infusion using their medical notes to review.

Intervention Type
Drug

Pharmaceutical study type(s)
Dose response

Phase
Phase II

Drug/device/biological/vaccine name(s)
Acetylcysteine

Primary outcome measure
Glutathione (GSH) derived paracetamol metabolite concentration as a percentage of total metabolites (%GSH) in the circulation at the end of the infusion of the second NAC dose

Secondary outcome measures
Safety: Incidence of adverse events and serious adverse events occurring from the time of starting NAC until the end of follow-up. There are expected adverse reactions listed in the product summary of product characteristics (SPC). The protocol defines two adverse events of special interest (AESI). Symptoms of anaphylactoid reactions reported on Likert scale at baseline and 12h after starting NAC.

Efficacy: Full paracetamol metabolite panel (APAP-Cys, APAP-Glu, APAP-Sul, APAP-GSH, APAPMer) in serum and urine. Measured at baseline (pre-NAC) for serum and urine. For serum, at 12h after NAC started. All urine is collected for the trial period. ALT (gold standard diagnostic liver injury marker), high sensitivity liver injury markers (keratin-18, microRNA-122, GLDH) and INR (a prognostic marker of liver synthetic function) measured at baseline and after 12 hrs NAC from blood. Length of hospital admission, repeat hospital admission within 7 days, acute liver failure, transfer to Scottish Liver Transplantation Unit, liver transplantation and death recorded from medical notes at 7 days follow-up.

Overall study start date
01/01/2023

Completion date
30/06/2026

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 25/10/2024:
1. Paracetamol overdose* presenting to hospital within 24 hours of taking their last dose of paracetamol. *All patterns of overdose (single, staggered overdoses and therapeutic excess); Accidental or deliberate; Paracetamol alone or mixtures of tablets are eligible.
2. Patient deemed to need NAC treatment by the clinical team
3. Blood paracetamol concentration and ALT results are available (clinical care bloods)
4. Provision of informed consent
5. Adult (16 years old or above)

Previous participant inclusion criteria:
1. Single acute paracetamol overdose presenting to hospital within 24h of overdose. All tablets ingested over a period of 2 h or less. Accidental or deliberate overdoses are eligible. Overdose of paracetamol alone or mixtures of tablets are eligible.
2. Overdose at risk of toxicity: blood paracetamol concentration over ‘200 line’ on nomogram
3. Provision of informed consent
4. Adult (16 years old or above)

Participant type(s)
Patient

Age group
Mixed

Lower age limit
16 Years

Sex
Both

Target number of participants
At least 90

Key exclusion criteria
Current participant exclusion criteria as of 25/10/2024:
1. Patients that do not have the capacity to consent
2. Patients who are pregnant or breastfeeding
3. Patients who have previously participated in the study
4. Patients who, in the opinion of the responsible clinician/nurse, are unlikely to complete the full course of NAC e.g. expressing wish to self-discharge
5. Patients detained under the Mental Health Act
6. Patients already started on NAC treatment
7. Patients with known viral hepatitis or HIV
8. Prisoners

Previous participant exclusion criteria:
1. Patients that do not have the capacity to consent
2. Patients who are pregnant or breastfeeding
3. Patients who have previously participated in the study
4. Patients who, in the opinion of the responsible clinician/nurse, are unlikely to complete the full course of NAC e.g. expressing wish to self-discharge
5. Patients detained under the Mental Health Act
6. Patients already started on NAC treatment
7. Known overdose of a modified/extended-release preparation of paracetamol
8. Patients with known viral hepatitis or HIV

Date of first enrolment
19/02/2024

Date of final enrolment
31/01/2026

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
Royal Infirmary of Edinburgh at Little France
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian
United Kingdom
EH16 4SA

Study participating centre

St Johns Hospital
Howden W Road
Howden, Livingston
Lothian
United Kingdom
EH54 6PP

Study participating centre
Victoria Hospital
Hayfield Road
Kirkcaldy
United Kingdom
KY2 5AH

Sponsor information

Organisation
Accord (United Kingdom)

Sponsor details
Usher Building
57 Little France Road
Edinburgh Bioquarter
Edinburgh
Scotland
United Kingdom
EH16 4UX
+44 (0)131 242 6226
resgov@accord.scot

Sponsor type
Hospital/treatment centre

Website
http://accord.scot/

ROR
https://ror.org/01x6s1m65

Funder(s)

Funder type
Government

Funder Name
Chief Scientist Office, Scottish Government Health and Social Care Directorate

Alternative Name(s)
Chief Scientist Office, Scottish Government Health Directorate CSO, Chief Scientist Office, Scottish Government Health Directorates, Chief Scientist Office of the Scottish Government Health Directorates, Scottish Government Health and Social Care Directorate of the Chief Scientist Office, Scottish Government Health Directorate Chief Scientist Office, The Chief Scientist Office, CSO

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on the website
5. Submission to regulatory authorities

Intention to publish date
31/12/2026

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from ECTU Data Sharing Committee.
Consent will be sought from participants to permit sharing of anonymised data with funders and collaborators or publishing on publicly available resources as appropriate. Following the publication of the primary HiSNAP Trial results, a de-identified individual participant data set will be prepared for sharing purposes. Access to de-identified data may be granted to other researchers upon reasonable request in line with ECTU policies at that time. Further information including contact information for the ECTU Data Sharing Committee can be accessed here: https://www.ed.ac.uk/usher/edinburgh-clinical-trials/publications/data-sharing.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Protocol article	22/03/2025	24/03/2025	Yes	No