Study Protocol

Sensitivity, specificity, and acceptability of a bedside formate assay as a diagnostic tool in methanol poisoning: prospective observational and randomised studies

Methanol POC studies

Sponsors	The University of Edinburgh The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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PROTOCOL APPROVAL SIGNATURE PAGE

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Methanol POC

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

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For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

Name			
Principal Investigator	**Signature**	**Site**	**Date**

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
ADE	Adverse Device Effect
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CRRT	Continuous renal replacement therapy
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMD	Clinical Trial of Investigational Medicinal Device
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic case record form
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IHD	Intermittent high-flow haemodialysis
IMD	Investigational Medicinal Device
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LMICs	Low- and middle-income countries
NIMP	Non-Investigational Medicinal Product
PGIMER	Postgraduate Institute of Medical Education and Research
PI	Principal Investigator

POC	Point-of-Care
QA	Quality Assurance
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UADE	Unanticipated Adverse Device Effect
UoE	University of Edinburgh

TRIAL SUMMARY

Trial Title	Investigation of a bedside formate assay as a diagnostic tool in methanol poisoning
Study Acronym	Methanol POC
Clinical Phase	**Study 1a** - Phase IIb study of a medical device **Study 1b** - Feasibility phase III cluster RCT of a medical device
Trial Design	**Study 1a** - Observational study. **Study 1b** - Three-arm, open, feasibility phase III, cluster RCT, comparing use of (1) laboratory and POC formate assays, (2) laboratory formate assay only, and (3) current routine care (no assays, treatment on suspicion) on time to diagnosis and appropriate care.
Trial Participants	Patients with suspected methanol poisoning or metabolic acidosis of unknown cause
Planned Number of Participants	**Study 1a** - 1,620 **Study 1b** - 4,500
Planned Number of Sites	**Study 1a** - 5-10, depending on case incidence **Study 1b** - 12-15
Countries Anticipated to be Involved in Trial	Bangladesh, India
Treatment Duration	Diagnostic test. NIMP for up to 7 days
Follow up Duration	Until hospital discharge (most commonly 5 days)
Total Planned Trial Duration	**Study 1a** - 12 months **Study 1b** - 24 months
Primary Objective	**Study 1a** - To determine the sensitivity and specificity of the POC formate assay (index test) in comparison to the laboratory formate assay (Gold standard, reference test). **Study 1b** - To determine whether it is possible to recruit hospitals to a cluster RCT of formate diagnostic approaches.
Secondary Objectives	**Study 1a** Evaluate whether POC formate assay (index test) can be used to identify methanol poisoning in diverse healthcare systems **Study 1b** Evaluate the use of the POC formate assay for methanol poisoning Compare clinical and resource use of using the POC formate assay by introducing the assay into routine clinical use

Primary Endpoint	**Study 1a** The sensitivity and specificity of POC formate test (index test) for diagnosis of methanol poisoning (target condition, as per the Gold standard laboratory formate assay) **Study 1b** Number of hospitals successfully recruited to the study
Secondary Endpoint	**Study 1a** • Time interval (in minutes) from the patient's arrival at the emergency department until the sample is drawn from the patient • Time interval (in minutes) from when the sample is drawn to when the result is displayed by the POC assay • Time interval (in minutes) from when the sample is drawn to when the result is displayed to laboratory staff by the Gold standard assay • Delay between time of the Gold standard assay result being displayed and the time of the POC assay result being displayed • Time interval (in minutes) from when the sample is drawn until the clinician is informed about the result of the assays • Time interval (in minutes) to initiation of antidote treatment in patients with methanol toxicity from arrival at the emergency department • Time interval (in minutes) to stopping fomepizole in patients who do not have methanol poisoning (after starting it) • Use of unnecessary fomepizole therapy in patients who do not have methanol poisoning **Study 1b** • Time (in minutes) to stopping fomepizole in patients who do not have methanol poisoning (after starting it) • Use of unnecessary fomepizole therapy in patients who do not have methanol poisoning • Proportion of patients with changed management (buffer, antidote, dialysis) based on the laboratory formate assay • Clinical outcomes (deaths, intubation, need for dialysis where available) • Cost of therapy of the POC formate assay vs. the LAB-assay vs. no assays.
IMD(s)	Point-of-Care formate assay device (Orphan Diagnostics, Norway) Classified as a IVD type A medical device (Low Individual Risk and Low Public Health Risk)
IMD Method of Use	Finger prick or venous blood sample analysis at bedside
NIMP(s)	Sodium bicarbonate, fomepizole, folinic acid

Lay Summary of Trial	Every year, thousands of people are poisoned by methanol, often in outbreaks affecting the poorest of the poor, devastating communities in low-and middle-income countries (LMICs). Diagnosis is difficult because methanol poisoning is a great imitator, resembling many medical conditions, and classical diagnostic techniques have required expensive laboratory equipment. Because methanol poisoning is difficult to diagnose, doctors often do not even consider the diagnosis. Methanol is not itself particularly toxic; however, it is broken down in the body to formate, which is highly toxic, causing brain swelling and death. We have developed a new method for diagnosing methanol poisoning that uses a single drop of blood in a device that can be used at the bedside, removing the need for any laboratory equipment. This 'point of care' (POC) assay measures formate which is only present when a patient has methanol poisoning. This project involves two studies, one after the other. The first aims to determine how well the POC formate assay works at diagnosing methanol poisoning in comparison to the standard laboratory formate assay, which at best usually takes several hours to be performed. We will take this information into the second study. This feasibility cluster randomised controlled trial (in which hospitals rather than individual patients are randomly allocated – like tossing a coin – to the different approaches) aims to see whether it is possible to use this design in a future larger-scale (cluster randomised) research study of clinical outcomes. Such a study would determine whether the POC formate assay speeds up accurate diagnosis - allowing appropriate treatment to be started as soon as possible and deaths prevented. This study will determine whether hospitals can be recruited to the study and if so whether they can be retained until the study is complete. This would reduce wastage of valuable healthcare resources that results from treating people who do not have methanol poisoning. We hypothesise that the POC formate assay will speed the start of appropriate treatment and reduce unnecessary costs. The studies will provide data to allow us to design a large cluster study that will definitively show whether the use of the new bedside test helps patients and healthcare workers and reduces deaths. These studies will also allow us to set up a high-quality protocol for evaluation, diagnosis, and treatment of future patients admitted to these hospitals. Further, it will lay the ground for other studies on the topic, inspire junior doctors to take an academic career path, and encourage a good approach to clinical practice. Finally, it will put a 'forgotten crisis' on the global clinical agenda, raising awareness and increasing the likelihood of methanol poisonings being detected early and treated effectively.

1. INTRODUCTION

1.1 BACKGROUND

Every year, thousands of people are poisoned by methanol, often in outbreaks affecting the poorest of the poor, devastating communities in low-and middle-income countries (LMICs) [1-3]. Diagnosis is difficult because methanol poisoning is a great imitator, resembling many medical conditions, and diagnosis has required expensive laboratory equipment [4]. The number of outbreaks reported (figure 1) is likely to represent the tip of the iceberg [4], with an unknown number of people dying, or surviving with brain damage/ blindness, without getting a diagnosis. Covid-19 has surprisingly resulted in many deaths from drinking hand-sanitizers incorporating methanol (rather than ethanol) [5]. Several Asian countries have seen a surge of poisoning while Iran has reported its largest ever outbreak with >7,000 cases recorded so far. Recently, the Dominican Republic, Ecuador, Peru, Uganda, Vietnam, Cambodia, Bangladesh India, and Turkey have all had major outbreaks with hundreds of victims with case fatality as high as 40%.

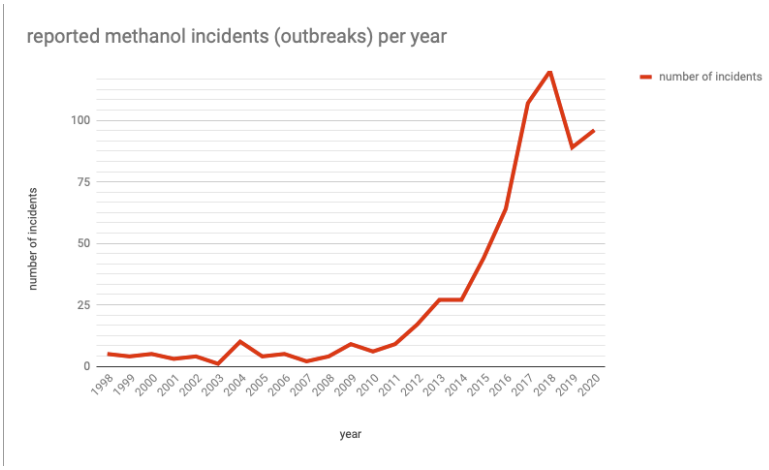

Figure 1. Number of methanol incidents being reported to Médecins sans Frontières (MSF) showing increased awareness over recent years (https://methanolpoisoning.msf.org).

Methanol is not itself particularly toxic. However, it is metabolised via the alcohol dehydrogenase (ADH) enzyme to formaldehyde, which is then metabolised to the main toxin, formate (formic acid) (figure 2). Formate is highly toxic, causing cell death, typically leading to blindness and potentially lethal brain damage.

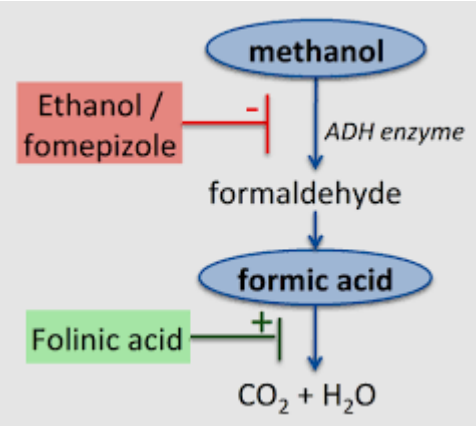

Figure 2. Pathogenesis of methanol poisoning, showing the production of formate from methanol via alcohol dehydrogenase (ADH) and the protective inhibition of this enzyme by ethanol and fomepizole.

Despite deaths occurring with even small amounts of methanol, effective treatment is possible by blocking the metabolism of methanol to formate via inhibition of alcohol dehydrogenase (ADH) with fomepizole or ethanol [4]. Fomepizole is preferred and since 2013 has been listed as a WHO Essential Medicine. Twelve-hourly fomepizole doses inhibit ADH, allowing the methanol to be eliminated (mostly) by the lungs, and partly by the kidneys (or by haemodialysis where available). However, such treatment can only follow early diagnosis of methanol poisoning, ideally within 12-24 hrs [4, 6]. Without a clear objective method of diagnosis, methanol toxicity is often missed, and treatment not started. Late diagnosis and delayed therapy produce poor outcomes.

Diagnosis has previously been complex, expensive, and slow, requiring measurement of blood methanol concentrations [4, 7]. This uses GC-MS or GC-FID and experienced lab personnel and may be negative in patients who present late to hospital (when the methanol has already been totally metabolised to formate).

We have developed a laboratory-based technique (based on simple equipment that is available in LMICs - spectrophotometry) by measuring the toxic metabolite formate rather than the parent alcohol [8]. Without formation of formate, methanol has no significant toxic effects; the formate concentration is tightly correlated with methanol toxicity. Formate assay threshold is 1 mM, well below the 15-20 mM concentration associated with severe toxicity. A concentration of 1-10 mM is associated with no clinical symptoms and less toxicity, but clear evidence of methanol exposure.

The high sensitivity and specificity of the assay allows detection of formate up to 10 hrs before symptoms become apparent. It also allows diagnosis of late presenters, when all methanol has been converted to toxic formate. The method was successfully established in local laboratories during two large LMIC epidemics [3]. It is now recommended as the global standard of care (refs [7, 9] and [https://legerutengrenser.no/mpi/assets/msf-methanol-poisoning-protofcol.pdf].

However, this method requires a well-functioning laboratory, a freezer for reagents, and laboratory-competent personnel. There is an urgent need for a rapid, affordable, point-of-care (POC) formate assay to differentiate methanol poisoning from other common conditions with similar clinical features to allow timely and appropriate treatment (Box 1). Such a diagnostic test will save thousands of lives, especially in areas where hospitals have limited laboratory infrastructure. Currently, in the absence of such a diagnostic test, methanol is usually not considered in diagnoses, unless a large epidemic occurs resulting in public health notification that hospitals should seek out cases.

Box 1: characteristics of an ideal diagnostic test. It should:

- be ***bedside and easy to perform*** (e.g., a single drop of blood from the finger)
- be ***quick*** (reliable answer in less than 5 min)
- have a ***high sensitivity and specificity***
- be ***independent of laboratory equipment***
- *be* ***easy to ship and stable at room temperature***
- be available for a ***reasonable price (e.g., less than Euro 10/assay)***.

We have therefore further adapted the method to use a single drop of blood (10μL) in a POC device, removing the need for any laboratory capabilities [10]. The device is this far tested for only 3 months storage, and storage in fridge is preferred (4-8 degrees Celsius). In testing, the assay has a sensitivity of 100%, specificity of 97% [11].

It can detect formate in a single drop of blood, using four ranges (<1 mM, 1-5 mM, 5-10 mM, and >10mM). A 'positive/high' (>10mM) result indicates methanol poisoning that requires antidotes, while 'positive/low' results (1-10mM formate) indicate the presence of low concentrations that may rise to cause toxicity [4]. In this case, further blood samples are taken after 1-2 h to determine whether the concentration is rising to the 'positive/high' range, requiring antidotes.

There is an urgent need to test the use, sensitivity, specificity, and performance of the POC formate assay in clinical practice. External validity will come from testing the diagnostic in different healthcare systems, hence our choice of hospitals in both India and Bangladesh.

1.2 RATIONALE FOR STUDY

We propose an initial observational study (Study 1a) to assess the sensitivity, and specificity of the POC formate assay in comparison to the laboratory formate assay (Gold standard, reference test). If the sensitivity is greater than >0.80, this will be followed by a feasibility 3-arm cluster randomised controlled trial (RCT) (Study 1b) to determine whether it is possible to recruit hospitals to a cluster RCT of formate diagnostic approaches. If successful, this design will be used in a future study to test the clinical- and cost-effectiveness of introducing the formate POC assay into routine clinical use. Because ruling out methanol toxicity is most important, for part 1b (see below) to be started.

We hypothesise that ultimately the POC formate test will speed the start of appropriate treatment and reduce the cost of unnecessary treatment (in patients subsequently shown not to have methanol poisoning). Evidence for this will need to come from a large RCT testing clinical outcomes, of death and use of dialysis.

This study will provide data on the accuracy of the diagnostic test and then allow selection of the appropriate primary and secondary outcomes, as well as data for the power calculations, and information on the practicalities of performing a future definitive cluster RCT. Ultimately, such a cluster RCT will establish whether the POC test enables earlier diagnosis, use of appropriate therapy, reduces waste, and will also provide limited data on whether this improves clinical outcome.

These studies will also provide us with the opportunity to set up a high-quality protocol for evaluation, diagnosis and treatment for patients being admitted to these hospitals. Further, it will lay the ground for other studies within the topic, encourage junior doctors into an academic career path, and stimulate good habits that will be carried into their clinical practice. Finally, use of the formate assays will put a 'forgotten crisis' on the global clinical agenda, raising awareness and increasing the likelihood of methanol poisonings being detected early and treated effectively. Increasing awareness will enable the public to be warned about dangerous alcohol in their midst, increasing the chance of identifying the source, and stopping further poisonings with that batch of toxic alcohol.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

- **Study 1a** - To determine the sensitivity and specificity of the POC formate assay (index test) in comparison to the laboratory formate assay (Gold standard, reference test).

- **Study 1b** - To determine whether it is possible to recruit hospitals to a cluster RCT of formate diagnostic approaches.

2.1.2 Secondary Objectives

- **Study 1a -** Evaluate whether POC formate assay (index test) can be used to identify methanol poisoning in diverse healthcare systems
- **Study 1b -** Evaluate the use of the POC formate assay for methanol poisoning
  - Compare clinical and resource use of using the POC formate assay by introducing the assay into routine clinical use

2.2 ENDPOINTS

2.2.1 Primary Endpoint

- **Study 1a -** Sensitivity and specificity of POC formate test (index test) for diagnosis of methanol poisoning (target condition, as per the Gold standard laboratory formate assay)
- **Study 1b -** Number of hospitals successfully recruited to the study

2.2.2 Secondary Endpoints

Study 1a

- Time interval (in minutes) from the patient's arrival at the emergency department until the sample is drawn from the patient
- Time interval (in minutes) from when the sample is drawn to when the result is displayed by the POC assay
- Time interval (in minutes) from when the sample is drawn to when the result is displayed to laboratory staff by the Gold standard assay
- Delay between time of the Gold standard assay result being displayed and the time of the POC assay result being displayed
- Time interval (in minutes) from when the sample is drawn until the clinician is informed about the result of the assays
- Time interval (in minutes) to initiation of antidote treatment in patients with methanol toxicity from arrival at the emergency department
- Time interval (in minutes) to stopping fomepizole in patients who do not have methanol poisoning (after starting it)
- Use of unnecessary fomepizole therapy in patients who do not have methanol poisoning

Study 1b

- Time (in minutes) to stopping fomepizole in patients who do not have methanol poisoning (after starting it)
- Use of unnecessary fomepizole therapy in patients who do not have methanol poisoning
- Proportion of patients with changed management (buffer, antidote, dialysis) based on the laboratory formate assay
- Clinical outcomes (deaths, intubation, need for dialysis where available)
- Cost of therapy of the POC formate assay vs. the LAB-assay vs. no assays

We will also record the number of device failures and report this to the manufacturers.

These outcomes are of key importance to LMIC health services. There are no relevant diagnostic alternatives available, while these deadly poisonings usually have a good outcome if specific treatment is started early. Simple and robust diagnostic tests should allow for an early diagnosis and treatment.

3. STUDY DESIGN

Study 1a is an observational study performed at hospitals in two different LMIC public health care systems (Bangladesh, India) (figure 4). The study is expected to complete in 12 months after first recruitment. All recruited participants, considered by treating clinicians or research team to be at risk of methanol toxicity, will be tested on admission with the bedside POC formate assay (index test) and then, using the same blood sample, with the laboratory formate assay (reference test). We will inform the responsible consultant physicians that the laboratory formate assay is available to all patients (irrespective of their participation in the study) and that they can receive fomepizole antidote for methanol poisoning until no longer required. Patients will be followed up until hospital discharge or death. Primary outcome will be recorded at the time of reporting the laboratory formate assay to the treating clinician. As an observational study, with no interim analyses planned, there are no rules for stopping the study ahead of completion of planned recruitment. A DMC will be established for this study, which will take any decisions to stop the study based on unblinded data.

Because ruling out methanol toxicity is most important, the sensitivity will need to be >0.80 for part 1b (see below) to be started.

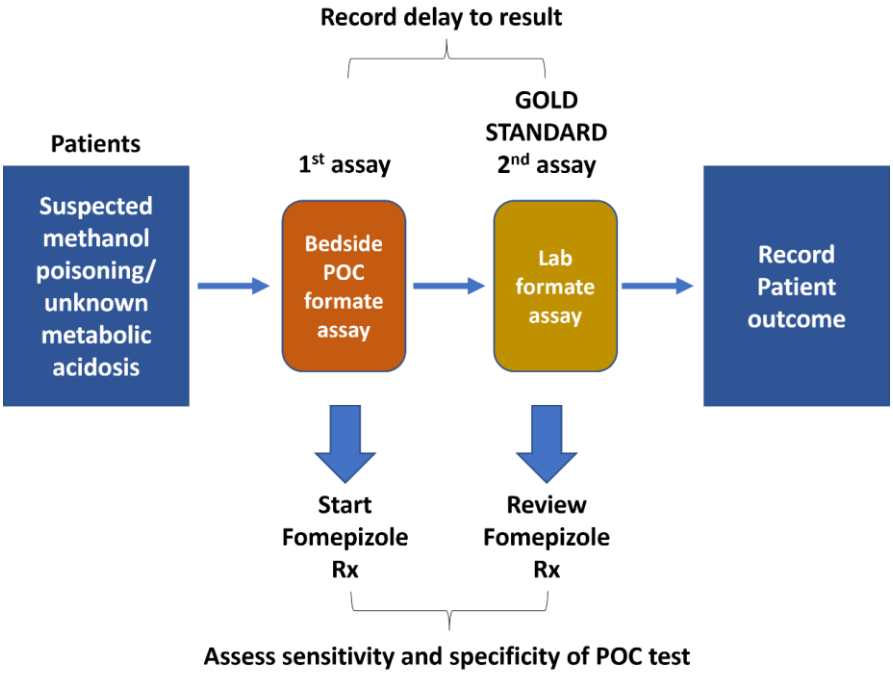

Figure 4. Design of study 1a (observational study).

Study 1b is a three-arm, open, feasibility phase-III cluster RCT, comparing **(1)** laboratory and POC formate assays, **(2)** laboratory formate assay only, and **(3)** current routine care (no assays, treatment on suspicion) (figure 5). It will be performed at hospitals in two diverse LMIC public health care systems (Bangladesh, India). The study is expected to last for 24 months after first recruitment. All patients (irrespective of their participation in the study) will be able to receive appropriate antidotes for methanol poisoning until improvement or until absence of methanol poisoning is confirmed by the laboratory formate assay. Diagnosis for all patients will be as per hospital allocation. Patients will be followed up until hospital discharge or death, at which point primary outcome will be recorded. There are no stopping rules for this study. A DMC will be established, which will take any decisions to stop the study based on unblinded data.
It is possible that the Indian or Bangladeshi Ministries of Health will change standard practice during the progress of the study. It is possible that this will involve implementing the laboratory

formate assay across all hospitals. If this happens, the no assay arm will be dropped from the study after consultation with the Sponsor and ethics/drug regulatory committees. Other changes will be noted and reported.

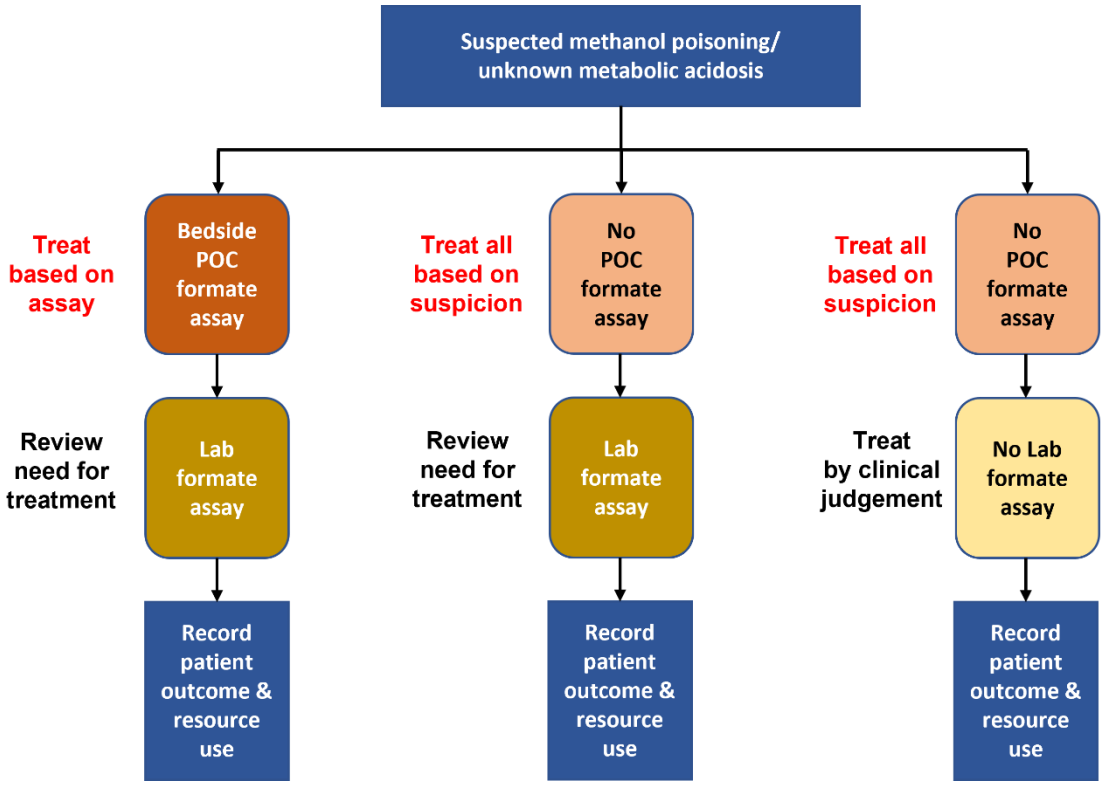

Figure 5. Design of Study 1b (feasibility cluster RCT)

4. STUDY POPULATION

The study population will include patients presenting to large referral hospitals in 2 countries (Bangladesh, India) with suspicion of methanol poisoning or unexplained metabolic acidosis.

4.1 NUMBER OF PARTICIPANTS

- Study 1a: 1,620 participants
- Study 1b: 4,500 participants

Recruitment is expected to take place over a minimum 12 and 24 months, respectively. The number of participants for Study 1a is estimated based on a conservative 5% formate positive proportion (using the laboratory formate assay); if the observed proportion is substantially greater than this, the number of participants will be reviewed by the TSC and the sample size for both studies revised.

4.2 INCLUSION CRITERIA

Pathways to inclusion in the study are summarised in Figure 6. The main inclusion criteria are

- Patients presenting with suspected methanol poisoning or metabolic acidosis of unknown cause, including:
  - Children aged 16-17 years, who are willing to provide assent.

- Parents/Guardians of children aged 16-17 years who are able and willing to provide consent.
- Adults (aged 18 years with no upper age limit) who are willing to provide informed consent.
- Participants who lack capacity to consent for themselves but who have a relative who is willing and able to provide informed consent on behalf of the participant.

Suspected methanol poisoning will be based on clinician judgement using the following typical indicators of possible methanol ingestion:

1. ***History of:***
   - Intake of illegal/bootleg/spurious alcohol, and/or
   - Other patients admitted with confirmed/suspected methanol poisoning and/or
   - Time from intake to symptoms >6-12 h

2. ***Symptoms/clinical findings***
   - Coma, and/or
   - Hyperventilation (respiratory rate [RR] >20/min) and/or dyspnea, and/or
   - Visual disturbances (blurred vision, blindness), and/or
   - Gastrointestinal symptoms (vomiting, abdominal pain), and/or
   - Chest pain, and/or
   - Severe/unusual 'hang-over': Feeling very sick the following day, and/or
   - Pseudopapillitis

Metabolic acidosis of unknown origin will be based on the following features:

- Metabolic acidosis of unknown origin = origin not identified. The acidosis is **not of unknown origin** if the metabolic acidosis can be explained by another cause eg. lactic acidosis (e.g. where base deficit [BD] = 15 mM [i.e., base excess (BE) = -15 mM] and lactate is 12-15mM).
- An initial ABG shall be drawn. If the BD is >15mM (BE<-15mM), the patient shall be included (as long as "unknown origin" – see above). If the patient has a BD between 5-15, the acidosis is only moderate, and there is time to do the "fluid trial" (see below). If the acidosis improves within 1-2 hours after the fluid trial, the acidosis is unlikely to be because of methanol and the patient should not be included. If the acidosis does not improve, the patient should be included.

"The fluid trial": Give 1-2L of Ringer Acetate* or Ringer Lactate* + thiamine + glucose (e.g., 500 mL of 100 mg/dL) (+ insulin if needed). This should all be given within 30-60 minutes ***without giving bicarbonate or antidote*** (this will make the test inconclusive).

*Preferably *not* NaCl as it will create a temporary hyperchloremic acidosis itself

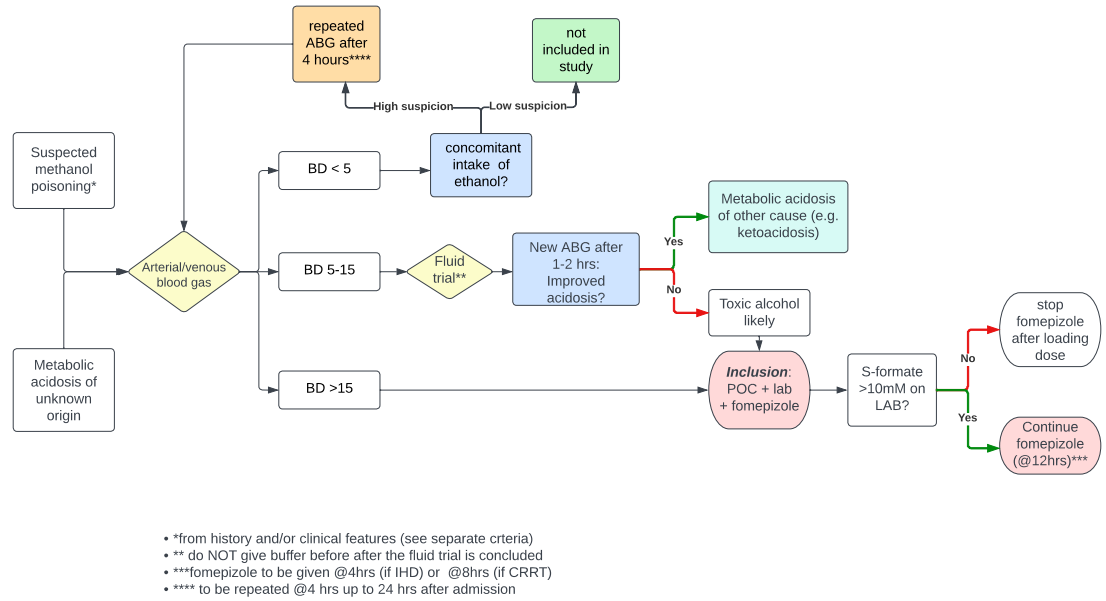

Figure 6.
An arterial or venous blood sample is taken from each potential participant. If the base deficit (BD) is greater than 15, then the patient (and/or relatives) will be approached for recruitment. If the BD is 5 to 15, then a fluid trial is given. If the BD (acidosis) improves, then the toxic alcohol is unlikely, and the patient excluded. If there is no improvement (or worsening), the patient will be recruited as toxic alcohol poisoning is likely. If BD is less than 5, then a 2nd blood gas analysis will be done at 4 hours if alcohol co-ingestion is suspected. The results of this blood gas will feed back into the pathway. Training on the pathway will be provided to the study team

4.3 EXCLUSION CRITERIA

- Children aged less than 16 years.
- Children aged 16-17 years, who are unwilling to provide assent.
- Parents/Guardians of children who are unable or unwilling to provide consent.
- Adults (aged 18 years with no upper age limit) who are unwilling to provide informed consent.
- Participants who lack capacity to consent for themselves and who do not have a relative who is willing and able to provide informed consent on behalf of the participant (i.e. unaccompanied unconscious patients and others)
-
- Individuals previously recruited to the study.

4.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

For ineligible participants or eligible participants who are not subsequently entered into the study, the reason for ineligibility or non-recruitment will be entered on into the study CRF to allow the CONSORT flow chart to be produced

4.5 JUSTIFICATION FOR INCLUSION OF VULNERABLE POPULATIONS

Children (adolescents) between the age of 16 and 17 will be included in the study because they can suffer from formate poisoning, will potentially benefit from early diagnosis, and are cared for adult wards (individuals under 16 years are treated in paediatric wards). The research findings should benefit this participant group. Consent will also be requested from the parent/guardian.

4.6 CO-ENROLMENT

As these are diagnostic studies, co-enrolment will be permitted for both interventional and non-interventional studies in this same study population following ACCORD Co-enrolment Policy (POL008), provided it does not place undue burden on participants and will not compromise the end point of either study. Co-enrolment for particular studies will be discussed between CIs and then recorded for each participant.

For co-enrolment with CTIMPs, co-enrolment will be permitted as per the sponsor co-enrolment policy and the appropriate co-enrolment checklist will be completed by the Sponsor's representative in conjunction with the CI prior to the co-enrolment proceeding.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Potential participants will be identified by their clinical care team after admission to the emergency department or medical wards in study hospitals.

These clinicians will approach the patients - if alert and orientated - or their family - if not - as soon as a diagnosis of possible methanol poisoning is considered, based on history, clinical features or unexplained metabolic acidosis on blood tests, to provide initial information about the study. Potential participants with metabolic acidosis of unknown origin will have not improved to routine early therapy (IV fluids, thiamine, and glucose) over the previous hour.

5.2 CONSENTING PARTICIPANTS

Study 1a. Due to the emergency situation of acute poisoning, it will not be possible to offer a 24-hour period for reflection and discussion concerning recruitment. As in other RCTs of acute poisoning, 30 min will be available for participants to consider and discuss the PIS. This will ensure that the patient can be treated early and is therefore able to obtain the full potential benefit of the treatment with fomepizole (offered to all patients via their consultant physician, irrespective of their participation in the study).

Written informed consent in their own language will be sought by the GCP-trained clinical research team who have undergone training about consent taking. A delegation log will be set up for appropriately trained and qualified individuals to take consent from potential participants. We will take the time to explain the study carefully in words familiar to the patients and their families as done previously for our studies in poisoned patients.

The participants and relatives/guardians (first degree relatives) will read the participant information sheet for the study and questions answered by the researchers. Where the participant and relatives/guardians cannot read, the contents of the participant information sheet will be read to them by the researchers. Where participants or relatives are unable to write, thumb prints will be accepted instead of signatures.

Severely poisoned patients will be in a coma and lack capacity, but have the greatest potential to benefit from improved diagnosis. Consent will be sought from their relatives (first degree legally acceptable representative such as spouse, parent, adult child, brother or sister) or their guardians, in their own language, by the clinical research team. There will be an information sheet and consent form for the relative to provide consent on behalf of the patient who lacks capacity.

When participants recover capacity, we will not formally seek their consent. However, researchers will routinely make the trial documents and PIS/consent forms available and discuss the trial with the patient after her/his recovery; if the individual wishes to withdraw from

the trial, this request will be respected (see section 5.6 for description of data handling in case of withdrawal). The consent discussion will be documented as standard.

Assent will be sought from the 16-17 year old individuals themselves in addition to consent from their parents/ guardians. There will be an assent form and participant information sheet specific to this age group, and an information sheet and consent form for the parent/guardian.

Study 1b. Randomisation (as a cluster RCT) will occur at the hospital level. Consent for randomisation will not be sought from individual patients or relatives. Implementation of any intervention (POC assay, lab formate assay only, or no assay) is a marked improvement in care due to the provision of fomepizole antidote for all patients at risk of methanol toxicity. Randomisation of hospitals will be 1:1:1 allocation, stratified by country, in blocks of size 3 within country, to ensure there is at least one hospital in each randomised group for each country.

Consent will be requested for collection of observational data, following the same procedures as those outlined above for study 1a. Patients who do not consent will still receive the allocated intervention, including fomepizole, but their data will not be included in the trial and analysis.

5.3 SCREENING FOR ELIGIBILITY

Study 1a - Participant eligibility will be verified by a clinical trial team member after written informed consent has been obtained. Confirmation of eligibility and the consent process will be recorded within the participants' medical records. No pre-randomisation assessments will be performed before a participant can enter the trial. The presence of history, clinical features, or unexplained metabolic acidosis suggestive of methanol poisoning will be recorded at recruitment.

A screening log will be maintained including sex, age, and decision taken by the patient or relative concerning recruitment to allow the CONSORT flow diagram to be constructed.

Study 1b - Patient eligibility will be verified by a clinical trial team member after admission to the study hospitals. Confirmation of eligibility will be recorded within the participants' medical records. Data on the history, clinical features, or unexplained metabolic acidosis suggestive of methanol poisoning will be recorded at recruitment.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Ineligible and non-recruited patients with suspected methanol toxicity will be cared for by the ward staff, with the support of research staff as preferred, following standard treatment guidelines as per hospital treatment policy. They will receive fomepizole and laboratory formate assay diagnosis as per the wishes of the responsible consultant physician and patient.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

Study 1a - Study 1a does not involve randomisation. All patients will have their blood sample tested using the POC formate assay and the laboratory formate assay.

Study 1b - Will be randomised (as a cluster RCT) at the hospital level at a ratio of 1:1:1 to: (i) POC and laboratory formate assays, or (ii) laboratory formate assay only, or (iii) current routine care (no assays, treatment on suspicion only). All patients with suspected methanol poisoning or metabolic acidosis of unknown cause presenting to each hospital will be diagnosed and treated with antidote using the randomised intervention specific to that hospital.

Randomisation of the hospitals to the diagnostic approach will be done using a centrally-held online randomisation list (to maintain allocation concealment), created by a programmer

(Maxsol Pro (Pvt) Ltd) with no other involvement in the study using computer-generated pseudo-random numbers. The randomisation will be stratified to ensure hospitals participating in Study 1a are allocated to either POC or laboratory formate assays. Hospitals using these assays in Study 1a will not be allocated to the no-assay arm.

This list will be accessed by the trial manager to randomise a site and then inform the site of allocation. This will take place within one week of the site consenting to participate.

Since the hospitals do not currently have any of the diagnostic tests (POC or laboratory formate assays) available, or give fomepizole on suspicion to all patients, all study arms will represent an improvement in care compared to the existing situation.

5.5.2 Treatment Allocation

Study 1a. All patients will receive the same diagnostic tests and treatment.

Study 1b. Treatment will be directed by the diagnostic approach, consistent with the hospital's allocation in the cluster RCT.

Tests for formate and methanol will be performed by ward, laboratory, or research staff. The laboratories will be located within the hospitals, affiliated universities, or local commercial sector.

Uptake of the treatment allocation (i.e. proportion of eligible participants receiving the diagnostic tests their hospital is randomised to receive), and the proportion of participants in each hospital for whom treatment on suspicion is actioned, will be recorded.

5.5.3 Emergency Unblinding Procedures

The non-investigational study treatment is open and fomepizole treatment is similar across groups, thus unblinding procedures are not required. The randomised allocation of hospitals in Study 1b is open and there will therefore be no requirement for emergency unblinding of individual participants. The diagnostic test result will be recorded in the medical notes and be accessible throughout the patient's stay.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point, for any reason. If this occurs, the primary reason for withdrawal will be documented in the case record form. The participant will have the option of withdrawing from:

- all aspects of the trial but continued use of data collected up to that point,
- all aspects of the trial with the removal of all previously collected data, or
- all aspects of the trial with the removal of previously collected data and stored participant samples.

Participants who wish to withdraw from the study before any diagnostic test will be taken out of the study and another participant recruited to replace them. Data already collected on the participant will be kept on the CRF/database if the participant agrees to this.

6. INVESTIGATIONAL DIAGNOSTIC AND REFERENCE TEST

6.1 STUDY DIAGNOSTIC (INDEX TEST) (See Investigator's Brochure Appendix 4)

6.1.1 Identification

THE UNIVERSITY of EDINBURGH

accord
Academic and Clinical Central Office for Research and Development

6.1.2 Study PoC Manufacturer

Orphan Diagnostics A/S, Oslo, Norway, is the legal manufacturer of the test kit. Its manufacture is outsourced VelixX Gmbh (https://www.velixx.com/en/).

6.1.3 Marketing Authorisation Holder

Orphan Diagnostics A/S, Oslo, Norway

6.1.4 Labelling and Packaging

Original device labelling and packaging, Orphan Diagnostics A/S, Oslo, Norway. Secondary research labelling will be in English language and affixed to each device stating 'For Clinical Trial Use Only' with study ID (see Appendix 5 for cartridge label and Appendix 6 for outer label).

6.1.5 Instructions for Use

The Bedside PoC formate assay will be used by appropriately trained clinical professionals according to the Instructions for Use (Appendix 7) supplied with the device. Training in usage and handling will be provided to investigators.

6.1.6 Assay results

The POC assay read-out will be photographed and uploaded to the database, as well as being recorded in the eCRF.

6.1.7 Storage

The PoC device is packed in dry, sealed pouches. To be stored at temperature 4-25ºC, with temperature logs. Should a temperature excursion occur, the device will be quarantined until the manufacturer has been contacted. Shelf life is 3 months. Temperature control not required during couriering to study site.

6.1.8 Regulatory Release to Site

The devices will be distributed from VelixX directly to TSB and PGIMER. Regulatory release will be the responsibility of the manufacturer. The Trial Manager will oversee distribution of the device subsequent to regulatory release once the required approvals are in place.

During couriering, the temperature does not need to be controlled.

6.1.9 Destruction of Unused/Expired Devices

Local study coordinators will be responsible for collecting unused/expired devices and destroying them.

6.1.10 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

Device documentation will be provided in a separate document (Appendix 4) with a cover sheet and signature page (signed and verified by the CI and Sponsor) and filed in the TMF which will be located in Toxicology Society of Bangladesh (TSB)'s office in Chattogram, Bangladesh. The Chief Investigator will archive the TMF. The same IB will be submitted to regulatory authorities in India and Bangladesh.

6.1.11 Risk classification

Classified as a IVD type A medical device (Low Individual Risk and Low Public Health Risk) by country regulatory agencies in India (CDSCO-IVD-FAQ-03-2022-.pdf) and Bangladesh (file dgdagov.info, page 33)

6.2 REFERENCE TEST

6.2.1 Identification

Laboratory spectrophotometer-based assay, using the formate dehydrogenase (FDH) enzyme, reading at 340 nM [8].

6.2.2 Study Kit Manufacturer:

FDH enzyme produced by Roche Diagnostics GmbH, Germany. Spectrophotometer available in the clinical laboratory.

6.2.3 Marketing Authorization Holder:

FDH: Roche Diagnostics GmbH, Sandhofer Strasse 116, 68305 Mannheim, Germany
Spectrophotometer: not applicable

6.2.4 Labelling and Packaging

Original device labelling and packaging

6.2.5 Storage

In solid form (powder) stable at +2 to +8°C with temperature logs until the expiration date printed on the label. Stable for more than 5 years at +2 to +8°C as a liquid suspension [12]. To be kept frozen at -20ºC after dilution; practical experience in Oslo has shown formate dehydrogenase to have excellent activity more than 3 years after freezing.

6.2.6 Regulatory Release to Site

Not applicable

6.2.7 Assay set up

The laboratory formate assay will be set up as a clinical laboratory assay using standard operating procedures in a hospital, clinic or university laboratory for each site. The standard operating procedures will be provided by Oslo University Hospital where the assay is routine. The laboratories will perform standard quality control tests before the study starts.

6.2.8 Assay results

The spectrophotometer assay result read-out will be photographed and uploaded to the database. The results will also be recorded in a laboratory Excel spreadsheet against study number and these data merged with the database.

6.3 OTHER MEDICATIONS

6.3.1 Non-Investigational Medicinal Products

For the patients fulfilling the criteria for inclusion (irrespective of recruitment), the following treatment will be provided by the study (or offered via the responsible consultant physician):

- **Sodium bicarbonate** to correct the metabolic acidosis: For full correction of the acidosis, the formula **patient weight (kg) x base deficit (mmol/L) x 0.3 = bicarbonate needed (mmol)** should be used.
- **Folinic acid** to enhance the endogenous metabolism of formic acid/formate produced by the body. To be dosed 50 mg IV q6h for 24 h.
- **Fomepizole** will be given as a loading dose of 15 mg/kg, followed by 10 mg/kg q12h. During intermittent dialysis, fomepizole will be dosed q4h; during continuous renal replacement therapy, fomepizole will be given q8h. Dosing will be increased to 15 mg/kg after the 4th dose (dose 5 onwards) due to auto-induction of metabolism by fomepizole.

  Fomepizole will be provided to all study hospitals to ensure that patients can be treated safely while awaiting their diagnostic test results.

  The fomepizole will be provided by Proclin Research Pvt Ltd (Bhopal, M.P, India) and couriered to TSB and PGIMER for local distribution.

  Participants who withdraw from the study will continue to receive fomepizole and other standard treatments for methanol poisoning.

The SmPC for the above treatments are provided in an SmPC NIMP Booklet Appendix 8.

Standard care: all participants will receive standard treatment for methanol poisoning, including IV fluids, oxygen, ventilatory support and dialysis, as necessary and available. The treatments will be sourced from the study hospital medical wards. Management will be guided by locally adapted versions of established guidelines (MSF) on which clinical ward staff will receive training.

Dialysis (intermittent high-flow (IHD) or continuous modalities (CRRT)) will be used according to availability. When available, it will be used if suspect/verified methanol poisoning/formate analysis or metabolic acidosis and newly developed visual disturbances, and/or positive formate test + moderate to severe metabolic acidosis (pH <7.1, BE<-15) or ingestion of more than 1g/kg methanol and a positive methanol test/clinical suspicion as per protocol. IHD is preferred (to be used for a minimum of 6-8 hours), whereas CRRT should be used for a minimum of 18 hours.

6.3.2 Permitted Medications

Any medication required for the treatment of methanol poisoning (e.g., fomepizole, bicarbonate, folic-/folinic acid, or supportive treatment as necessary) will be permitted, as well as medication used by the patient before the poisoning.

6.3.3 Prohibited Medications

No medicines are specifically prohibited for this clinical trial.

7. STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

Study 1a. All patients will receive the same diagnostic approach with both POC and laboratory formate assays.

Study 1b. Patients will be allocated to the diagnostic strategy to which their hospital has been randomised.

No specific safety assessments are envisaged for either study of additional diagnostic testing. The DMC will be requested to review the incidence of complications in the study arms.

7.2 STUDY ASSESSMENTS

All patients will have a venous or arterial blood sample taken before being considered for the study as this assessment is core to the diagnosis of 'suspected methanol toxicity' or 'metabolic acidosis of unknown cause'.

A screening log will be maintained, including sex, age, and the decision taken concerning recruitment to allow the STARD (Study 1a, [13]) or CONSORT (Study 1b, [14]) flow diagram to be constructed.

Study 1a.

After consent and recruitment, only essential demographic, and clinical details (including study ID, name, initials, age, sex, time of poisoning, poison ingested, treatment received, Glasgow Coma Score, arterial/venous blood gas results (including pH/H+ concentration, pCO2, base excess, and/or lactate) will be recorded to minimize time to intervention.

A blood sample will be taken for laboratory formate analysis + POC formate analysis.

A loading dose of fomepizole will be given to all patients in the study as part of their standard care. Other standard supportive care and medicines will be given as required for the poisoning. The timing of medicine administration will be recorded in the electronic case record form (eCRF).

POC formate analysis will be performed, and results (high/intermediate/none) recorded in the participant's eCRF. No action will be taken as a result of this assay as the sensitivity and specificity of the test will then be unknown. The time of the result will be recorded.

Arterial or venous blood gases will be collected intermittently as required for clinical care.

The laboratory formate analysis will be performed following standard laboratory procedures, including frequency of analysis. The results of the laboratory formate analysis will be documented (with times) in the eCRF and rapidly reported to the clinician caring for the patient.

- Patients with a raised formate on the laboratory formate assay (>10mM) will be considered poisoned and treatment continued following standard MSF protocols until the patient has recovered.
- Patients with an intermediate concentration (1-10 mM) will have blood samples taken and formate assay done again at least 2-4 h after the previous blood sample was taken. Fomepizole and other therapies will be continued at this time. Further samples will be taken for POC and/or laboratory assay until treatment is no longer required.
- Patients with undetectable formate (<1 mM) on the initial or repeat testing will have their osmolal gap and metabolic acidosis status calculated. If the osmolal gap is low (below 15), the second fomepizole dose will be delayed until at least 15 hours later and until after a blood gas and/or POC formate test is completed.

Any resulting change in management/plans for further testing will be recorded in the eCRF.

All events, including seizures, need for ventilation, problems with vision, and death will be recorded as soon after they occur as possible and at least twice per day.

Cognition and vision will be formally assessed just prior to discharge.

	Study 1a Assessments	Timing
1	Identification of potential participants - based on history or blood gas analysis (routine clinical care)	Following presentation to hospital
2	Consent and recruitment	In ED or medical ward

3	Screening log (sex, age, recruitment decision)	Following decision re consent
4	Essential demographic and clinical details recorded (study ID, name, initials, age, sex, time of poisoning, poison ingested, pre-admission therapy received, GCS, blood gas results [pH, base excess, lactate])	For patients giving consent, data collected at baseline
5	Blood sample collection for laboratory formate analysis +/- POC formate analysis (time recorded)	As baseline data (#4) collected
6	Loading dose of fomepizole administered (time recorded)	Following collection of blood sample
7	POC formate analysis with results recorded as high, intermediate, or negative)	Following start of fomepizole administration
8	Collect additional baseline data (additional to #4)	While awaiting lab result
9	Collection of blood gas blood samples as required over 48 hours	At 2-4 hr intervals as clinically required
10	Laboratory formate analysis (time & results recorded)	When available
11	Results presented to the treating clinician (time recorded)	Following completion of laboratory analysis
12	Clinician makes treatment decision based on the laboratory format assay result (stop or continue fomepizole)	Following provision of the result to the clinician
13	Calculation of osmolal gap and metabolic acidosis status for patients with undetectable formate (<1 mM)	Following provision of the result to the clinician
14	Delayed administration of further fomepizole for patients with low osmolal gap and undetectable formate	Following calculation of osmolal gap
15	Additional POC and/or laboratory assay samples until treatment is no longer required for patients	Over following 12-48 hours
16	Recording of events (seizures, ventilation, vision problems, death)	Every 12 hours for duration of hospital stay
17	Formal assessment of brain injury and visual defects using visual evoked potentials (VEP) and magnetic resonance imaging of the brain (MRI)	Prior to discharge

Study 1b.

Study 1b will be performed once the clinical accuracy of the POC formate assay has been assessed in Study 1a. These results will allow the POC formate assay result to be used on admission to determine management.

Overall, study procedures and assessments will take place as per Study 1a.

Patients presenting to hospitals randomised to use the POC assay will only receive fomepizole on recruitment to the study if the result is high positive (>10 mM) or clinicians consider the risk of methanol toxicity to be high (because the sensitivity in Study 1b is unlikely to be 100%).

Patients with suspected methanol poisoning in hospitals without the POC assay will be treated with 12-hrly fomepizole on suspicion only. In hospitals with the laboratory assay, this will be reviewed when results are available. In hospitals allocated current routine care, fomepizole will be continued as per the judgement of local clinicians.

Data collection for participants in both studies after recruitment and treatment

Clinical and laboratory data collected will include time of methanol intake (if known), estimated amount ingested (if known), treatment received before admission, clinical features (Glasgow Coma Score, blood pressure, pulse, respiratory rate), symptoms (chest pain/dyspnoea/GI-symptoms/visual disturbances), arterial (or venous) blood gas, formate test results, pre-existing medical conditions, treatment received, imaging results, complications, and outcome (death, visual and cognitive outcome, discharge with/without sequela).

Blood-borne virus infection from blood samples is not a high risk situation in South Asia due to a low prevalence of such infections. However, standard infection control practices will be followed at all times. Local standard procedures will be followed regarding blood sampling and disposal of sharps.

	Study 1b Assessments	POC	Lab	No Dx	Timing
1	Identification of potential participants - based on history or blood gas analysis (routine clinical care)	x	x	x	Following presentation to hospital
2	Consent and recruitment	x	x	x	In ED or medical ward
3	Screening log (sex, age, recruitment decision)	x	x	x	Following decision re consent
4	Demographic and clinical details recording (study ID, name, initials, age, sex, time of poisoning, poison ingested, pre-admission therapy received, GCS, blood gas results [pH, base excess, lactate])	x	x	x	For patients giving consent, data collected at baseline
5	Blood sample collection for laboratory formate analysis +/- POC formate analysis (time recorded)	x	x		As baseline data (#4) collected
6	Loading dose of fomepizole administered (time recorded)	x	x	x	Following collection of blood sample
7	POC formate analysis with results recorded as high, intermediate, or negative)	x			Following start of fomepizole administration
8	Collect additional baseline data (additional to #4)	x	x	x	While awaiting lab result
9	Collection of blood gas blood samples as required over 48 hours	x	x	x	At 2-4 hr intervals as clinically required
10	Laboratory formate analysis (time & results recorded)	x	x		When available
11	Results presented to the treating clinician (time recorded)	x	x		Following completion of laboratory analysis
12	Clinician makes treatment decision based on the laboratory format assay result (stop or continue fomepizole)	x	x		Following provision of the result to the clinician
13	Calculation of osmolal gap and metabolic acidosis status for patients with undetectable formate (<1 mM)	x			Following provision of the result to the clinician
14	Delayed administration of further fomepizole for patients with low osmolal gap and undetectable formate	x			Following calculation of osmolal gap
15	Additional POC and/or laboratory assay samples until treatment is no longer required for patients	x	x		Over following 12-48 hours
16	Recording of events (seizures, ventilation, vision problems, death)	x	x	x	Every 12 hours for duration of hospital stay
17	Formal assessment of brain injury and visual defects using visual evoked potentials (VEP) and magnetic resonance imaging of the brain (MRI)	x	x	x	Prior to discharge

7.3 COMPLIANCE ASSESSMENTS

We do not envisage any issues with compliance since all diagnostics and treatments will be carried out by researchers with the support of ward staff.

7.4 LONG TERM FOLLOW UP ASSESSMENTS

Follow-up post-discharge will not be performed as part of this study.

7.5 STORAGE AND ANALYSIS OF SAMPLES

Blood samples will be collected from all patients to measure methanol and for collaborative research (including serum, plasma, whole blood). A maximum of 40 mL of blood will be taken over the whole hospital stay for research purposes with a maximum of 15 mL at any one time. Samples will be collected as near as possible to the required times, with actual times of collection recorded in the CRF.

Samples will be stored in a 2-8 °C fridge and -20 or -80 °C freezers following standard protocols that will be set up for the study. They will be stored at individual study sites (for fridge and -20 °C freezer) before being transferred to central facilities in each country (at Bangabandhu Sheikh Mujib Medical University (BSMMU) and Postgraduate Institute of Medical Education and Research (PGIMER)) for longer -80 °C storage. Samples will be shipped on dry ice for both local and (potentially in the case of future collaborative research only) overseas shipments. Labels will be hand-written and include the ID number, and date and time of sampling.

All stored specimens will be kept for up to 10 years in these facilities and will be available for further analyses by study investigators, for example, immunological studies, after ethics review. Any newly proposed analyses on these specimens will be submitted to the designated Ethics committee. If the Ethics committees require that specimens should be destroyed, the PI and Co-PIs will inform the same when this has been done. Prior consent will be sought from every participant for storing and utilizing the samples in future. DNA and RNA will not be collected.

8. TRANSCRIPTION AND TRANSLATION

8.1 TRANSCRIPTION SERVICES

N/A

8.2 TRANSLATION SERVICES

This will be done by a professional translator in each country with experience of writing trial documentation in the local language. Study documents will be translated to Bangla, Hindi, and Punjabi.

9. DATA COLLECTION

We will collect data on baseline characteristics and then all clinical events that occur at least every 12 hours during the patient's hospital stay, until hospital discharge or death. The primary and secondary outcomes are simple and objective. They will be directly recorded by research staff onto an encrypted handheld device.

Laboratory data (including blood gas results) will be recorded and kept using standard systems set up for each assay system and incorporated into the primary study database. Scanned

copies will also be taken for records on a locked PC in a locked office; access will be provided using password protected logons to study staff and monitors. Laboratories will be located in hospitals, affiliated universities, or local commercial sector.

Study 1a consent forms will be collected, copied, and stored. The reasons why patients are not recruited will be recorded for the STARD [13] flow diagram.

All potential participants will be recorded in this database at first contact. Recruited patients will be assigned a study number (specific to each of the study hospitals, which will have separate databases that will be combined for data analysis). This anonymous study number (eg FCMC0001) will be used for all data and samples collected from that person. Data entry will be date/time stamped.

9.1 SOURCE DATA DOCUMENTATION

All clinical findings and activities will be directly entered into the eCRF from direct observation of the patient. The paper-based medical notes will not be used as source data.

9.2 CASE REPORT FORMS

An eCRF similar to that we have used previously in poisoning RCTs will be used [15]. All case report forms will be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation).

9.3 TRIAL DATABASE

An electronic database will be developed and filled from the eCRF. The data will be automatically entered from the eCRF as it is filled in by the researchers. At the end of the trial, the data will be made available for other researchers following NIHR rules.

The database will be provided by Maxsol Pro (Pvt) Ltd and held on fully secure local servers (supplied by Line Reflection Pvt Ltd in Bangladesh, Getontheweb Technologies Pvt Ltd in India) in each country. Only deidentified data will be provided to statisticians at ECTU, Edinburgh. Data collection, storage, transfer, and archiving will be fully compliant with national laws in Bangladesh and India.

The database will be held securely by the host organisations in Bangladesh (TSB) and India (PGIMER) for ten years after the study is finished.

See Data Management Plan (DMP) appended within Protocol (Appendix 1).

10. DATA MANAGEMENT

10.1.1 Data Management Plan

All aspects of data collection, data processing (entry/uploading, cleaning, and query management), and the production of the final dataset ready for analysis and/or archiving are detailed in the Data Management Plan (Appendix 1). A data manager will be employed in South Asia to oversee data collection, checking and quality. This person will coordinate with an ECTU data manager (working part time on the study) to support them in their work.

10.1.2 Personal Data

The following personal data will be collected as part of the research:

- name, hospital number, age/date of birth, sex, and contact details (address, contact telephone numbers), medical records

10.1.3 Data Information Flow

Personal data will be collected after consent using the eCRF and transferred automatically to the database held on secure local servers. It will be reviewed and cleaned by local data managers and the Trial Manager before an extract is performed and deidentified (pseudo-anonymised as still linked by study number). This deidentified dataset can then be transferred to ECTU for analysis. The person identifiable data will remain with the local host organisations.

10.1.4 Data Storage

All paper files containing personal data will be stored by the research team in locked cupboards in a locked research office at each study site. Only GCP-trained research staff will have access to the data. The key to these locked cabinets will be kept by research staff/coordinator at each site.

Investigator Site Files will be stored in secured cabinets in respective local research sites. The Trial Master File will be held in locked cabinet in a locked office at the TSB main office in Chattogram, Bangladesh.

10.1.5 Data Retention

Personal data (both paper and electronic) and de-identified electronic data will be stored securely by the host organizations for 10 years after the study finishes.

10.1.6 Disposal of data

Once the retention period is over, the data can be deleted as per the guidance of the UoE Research data service and local regulations as applicable.

10.1.7 External Transfer of Data

Personal identifiable data will not be transferred to any external individuals or organisations outside of the sponsoring institution. Only de-identified data will be transferred to researchers outside of study sites.

The aggregated results only will be shared with Orphan Diagnostics under a contract.

10.1.8 Data Controller

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.

The data controllers for the study will be the host institutions in each country, along with the University of Edinburgh as sponsor of the study.

10.1.9 Data Breaches

Any data breaches will be reported to the University of Edinburgh (dpo@ed.ac.uk) who will onward report to the relevant authority according to the appropriate timelines if required. There are no requirements in Bangladesh or India to report such data breaches.

11. STATISTICS AND DATA ANALYSIS

11.1 SAMPLE SIZE CALCULATION

Study 1a. 1,620 participants will be recruited over 12 months (810/site). With an anticipated 5% of admissions expected to have methanol poisoning, this sample size will allow sensitivity to be estimated with a (2-sided, 95%) confidence interval width of ±0.066, for a true sensitivity of 0.90. In the event that the sensitivity is lower (0.86) or higher (0.94), the confidence interval

widths would be ±0.076 and ±0.052 respectively. The corresponding confidence interval width for a true specificity of 0.95 would be ±0.011.

The TSC will observe recruitment rates and event proportion (proportion of cases that are formate positive) within 3 months of the study starting. Additional hospitals will be recruited as necessary to ensure recruitment to target.

Study 1b: With 5% of patients in this patient population expected to have methanol poisoning, a sample size of 4,500 participants over 24 months will include approximately 225 methanol-poisoned patients (75 in each arm). This study size will provide good evidence of the practicalities and feasibility of the study as well information on the time to treatment, costs, and clinical outcome. The proposed study size and power will be re-evaluated once data, including positive case proportion, from Study 1a are available and at regular intervals during the study.

The study hospitals are all major referral hospitals that have 1000-2000 hospital beds and commonly see patients with metabolic acidosis and/or methanol poisoning.

11.2 PROPOSED ANALYSES

Study 1a. Quantitative statistical analyses will be governed by a comprehensive Statistical Analysis Plan finalised prior to database lock and prepared blinded to the results of the POC and laboratory formate assays.

The sensitivity/specificity of the POC formate assay (index test) will be calculated in comparison to the laboratory formate assay (reference test; [8, 9] [https://legeruten-grenser.no/mpi/assets/msf-methanol-poisoning-protofcol.pdf]. Formate POC test diagnostic accuracy will be summarised using an ROC curve with corresponding measures of area under the curve (AUC), sensitivity, specificity, positive and negative predictive values for (1) a cut-off of >10mM (versus 10mM or less) which is associated with clinically relevant methanol toxicity [8, 10] and (2) a cut-off of 1 mM, which is the true threshold for any toxicity.

Sensitivity at the cut-point giving 95% specificity will be reported, as will specificity at the cut-point giving 95% sensitivity. Each measure will be summarised using the proportion and its exact binomial 95% CI. Supporting measures will be the positive and negative likelihood ratios; and the Youden and modified Youden indices.

The delay from blood sample collection to the completion of the laboratory assay, and to informing clinicians (so that they can review treatment decisions), will be collected for all patients. We will record and present how the laboratory formate analysis results alter treatment of patients with fomepizole. These data will be presented using simple descriptive statistics.

As per the STARD checklist of essential items for reporting of diagnostic accuracy studies [13], the frequency and percentage of participants experiencing an ADE or SADE (see Section 12.1) related to the testing will be summarised for each of the index test and reference standard.

The flow of participants will be reported in a diagram containing the features recommended in the STARD reporting guidance [13].

Study 1b. Statistical analyses will be governed by a comprehensive Statistical Analysis Plan finalised prior to database lock and prepared blinded to the results of the POC and laboratory formate assays.

We will report the number of hospitals agreeing to join the study and following the allocated protocol for diagnosis and management of methanol poisoning.

We will also assess the Study 1b secondary outcomes listed in section 2.2.2: These data will be presented using simple descriptive statistics.

As per the STARD checklist of essential items for reporting of diagnostic accuracy studies [13], the frequency and percentage of participants experiencing an ADE or SADE (see Section 12.1) related to the testing will be summarised for each of the index test and reference standard.

The flow of participants will be reported in a diagram containing the features recommended in the CONSORT reporting guidance extension for cluster randomised trials [14].

12. PHARMACOVIGILANCE/SAFETY REPORTING

The CI and Principal Investigators are responsible for the detection and documentation of safety events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the NIMPs can be found in the relevant SmPCs (Appendix 8).

Study 1a is an observational study of a diagnostic medical device and Study 1b is an RCT of a diagnostic medical device, not a medicine.

The medical device is defined as being of low risk (category A) by the regulatory authorities in India and Bangladesh (see above for references). No advice is provided on the reporting requirements for the device issues except that only category B to D devices require post-marketing surveillance reporting. No reporting is required for category A devices.

All patients will receive appropriate treatment regardless of the index test result, until the reference test result is available. Therefore, any adverse event noted will most likely be related to the poisoning or non-investigational medicines used to treat poisoning.

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after informed consent until hospital discharge or death will be recorded in the eCRF or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

12.1 DEFINITIONS

12.1.1 Medical Device:

A medical device is defined as any instrument, apparatus, appliance, material or other article whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception and does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, even if it is assisted in its function by such means.

12.1.2 Investigational Medical Device

An investigational medical device is a medical device being assessed for safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

12.1.3 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device, and whether anticipated or unanticipated. This definition includes events related to the investigational device or the comparator. This definition includes events related to the procedures involved. This definition is restricted to events related to investigational medical devices.

12.1.4 Adverse Reaction (AR)

Any untoward and unintended response to a NIMP which is related to any dose administered to that participant.

12.1.5 Serious Adverse Event (SAE)

An adverse event is defined as serious if it:

a. Led to death,

b. Led to a serious deterioration in health of the subject, that either resulted in;

- A life threatening illness or injury, or
- A permanent impairment of body structure or a body function, or
- Inpatient hospitalisation or prolongation or existing hospitalisation, or
- In medical or surgical intervention to prevent life threatening illness

c. Led to foetal distress, foetal death or a congenital abnormality or birth defect.

A planned hospitalisation for a pre-existing condition, or a procedure required by the risk analysis plan/protocol/Clinical Investigation Plan (CIP), without a serious deterioration in health, is not considered a serious adverse event.

12.1.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any AR that is classified as serious, is suspected to be caused by an NIMP, and is not consistent with the Reference Safety Information (RSI) found, for example, in the Summary of Product Characteristics (SPC) or Investigator's Brochure (IB) for that NIMP.

NB: Fatal and life-threatening SARs should usually be considered unexpected even if previous fatal and life-threatening SARs have occurred. Fatal SARs can only be considered expected for NIMPs with a Marketing Authorisation (MA) in the European Union (EU) when it is clearly stated in the table or list of ARs in Section 4.8 of the SPC, that the NIMP can cause these fatal SARs. Thus the RSI of a product that has not received an MA in the EU should never include fatal SARs

12.1.7 Device Deficiency

Is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Device deficiencies include malfunctions, user errors and inadequacy in the information supplied by the manufacturer including labelling.

12.1.8 Adverse Device Effect (ADE)

An **Adverse Device Effect** (ADE) is an adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

An ADE includes any event that is a result of a use error or intentional misuse. Use error refers to an act or omission of an act that results in a device response than intended by the manufacturer or expected by the user. Use error includes the inability of the user to complete a task. An unexpected physiological response of the subject does not in itself constitute a use error.

12.1.9 Serious Adverse Device Effect (SADE)

A SADE is an adverse event effect that has resulted in any of the consequences characteristics of a SAE.

A **serious adverse device effect** (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or led to a characteristic of a SAE. SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances has been less opportune.

12.1.10 Anticipated Serious Adverse Device Effect (ASADE)

A serious adverse device effect, which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report, protocol or Clinical Investigation Plan.

12.1.11 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect, which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report, protocol or Clinical Investigation Plan.

12.2 IDENTIFYING AEs, ADEs, SAEs AND SADEs

Participants will be asked about the occurrence of AEs/SAEs at every review during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. As patients will be in-patients with acute poisoning during their time on the study, many possible events will not be relevant (eg. hospital admission). If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

12.2.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

12.2.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition will be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

Death, brain injury, and blindness are expected consequences of formate poisoning and will not be considered SAEs. The DMC will consider all deaths and other complications of poisoning at the planned intermediate analyses. As stated above, deaths arising as reactions to the NIMPs (and not as a consequence of the poisoning) will still be considered SUSARs and will be reported as described in section 12.4.

The following specific events are common complications of methanol/formate poisoning and not the study medicines. They will therefore not be routinely reported as SAEs unless considered linked to the study medicines

- death,
- brain injury
- blindness,
- intubation,

- ventilation,
- use of dialysis
- low blood pressure
- use of vasopressors
- seizures
- pneumonia, pneumonitis

12.2.3 Assessment of AEs

Each AE must be assessed for seriousness, causality, severity and expectedness by the Principal Investigator (PI) or another suitably qualified physician in the research team who is trained in recording and reporting Aes and who has been delegated this role. During PI absences appropriately qualified, experienced, and trained site staff may assess causality and report SAEs if they have been delegated this task on the delegation log by the PI.

12.2.4 Assessment of Seriousness

The Investigator will make an assessment of seriousness (as defined in section 12.1.5).

12.2.5 Assessment of Causality

The Investigator will also make an assessment of whether the AE is likely to be related to the device according to the following definitions:

• **Unrelated:** where an event is not considered to be related to the device.

• **Possibly related**: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the device.

Where there are two assessments of causality (e.g. between PI and Chief Investigator (CI)), the causality assessment by the Investigator cannot be downgraded. In the case of a difference of opinion, both assessments are recorded and the 'worst case' assessment is used for reporting purposes.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

12.2.6 Assessment of Expectedness

If the AE is judged to be related to the device, the Investigator will make an assessment of expectedness based on knowledge of the event and any relevant product information as documented in the risk analysis report. The event will be classed as either;

- **Expected:** the reaction is consistent with the effects of the device listed in the risk analysis report/protocol/CI (NIMPs SmPC section 4.8) and the POC device (section 7 in the IB). N/A for the device.
- **Unexpected:** the reaction is not consistent with the effects listed in the risk analysis report/protocol/CIP.

Fatal and life-threatening SADEs should usually be considered unexpected.

12.2.7 Assessment of Severity

The Investigator will make an assessment of severity for each AE according to the following categories:

• **Mild:** an event that is easily tolerated by the research participant, causing minimal discomfort and not interfering with every day activities.

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- **Moderate:** an event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe:** an event that prevents normal everyday activities.

The term 'severe' used to describe the intensity of an event should not be confused with the term 'serious', as defined in section 12.1.5, which is a regulatory definition based on trial participant/event outcome action criteria. For example, a headache may be severe but not serious, while a minor stroke may be serious but is not severe.

12.3 RECORDING AEs, ADEs, SAEs AND SADEs

When an AE/SAE/Sade/ASADE/USADE/DEVICE DEFICIENCY occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report the safety event, to review all documentation (eg. hospital notes, laboratory, and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the relevant SAE form (if the AE meets the criteria of serious).

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

12.4 REPORTING SAES/SADES/ASADES/USADES/DEVICE DEFICIENCIES TO THE SPONSOR

The following events are considered reportable events and require reporting to the Sponsor:

- Any SAE that occurs irrespective of the causality and expectedness
- Any Investigational Medical Device Deficiency that might have led to a SAE if:
    1. Suitable action had not been taken or
    2. Intervention had not been made or
    3. If circumstances had been less fortunate
- Post-study USADEs that occur after the trial participant has completed a clinical trial should also be notified by the investigator to the Sponsor.

12.5 RECORDING OF AEs

All adverse events for each participant will be recorded on the AE log and will be assigned the appropriate MedDRA Systems Organ Class (SOC) code. AE logs will be stored locally on the ISF and then made available in the TMF at completion of the study.

12.6 REPORTING OF SAEs/SADEs

Once the Investigator becomes aware that a SAE/SADE/ASADE/USADE/ has occurred in a study participant, the information will be reported using Template report SAE CTIMD Form CR012-T01 and the Cover Sheet and Return Receipt (CR012-F01) and sent to the Sponsor (safety@accord.scot) and manufacturer (fridtjof@orphandiagnostics.com) within 24 hours of becoming aware of the event. Only forms in a pdf format will be accepted by the sponsor via email. Where missing information has not been sent to the sponsor after an initial report, the sponsor representative will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

The SAE CTIMD Form CR012-T01 will provide an assessment of causality and expectedness at the time of the initial report to the sponsor according to Sections 12.2.5 (Assessment of Causality) and 12.2.6 (Assessment of Expectedness).

If the Investigator does not have all information regarding an SAE/SADE/ASADE/USADE, s/he should not wait for this additional information before notifying the sponsor. The SAE CTIMD

Form CR012-T01 form can be updated when the additional information is received. Reports will be complete as far as possible and will be signed and dated by the Investigator.

All reports sent to the sponsor and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

12.7 REPORTING OF DEVICE DEFICIENCIES

Once the Investigator becomes aware that a Device Deficiency has occurred in a study participant, the information will be reported using Template report CR012-T02 Medical Device Deficiency Form and sent to the Sponsor (safety@accord.scot) and manufacturer (fridtjof@orphandiagnostics.com) within 24 hours of becoming aware of the event.

If the Investigator does not have all information regarding a Device Deficiency, s/he should not wait for this additional information before notifying the sponsor. The CR012-T02 Medical Device Deficiency form can be updated when the additional information is received. Reports will be complete as far as possible and will be signed and dated by the Investigator.

All reports sent to the sponsor and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

12.8 REGULATORY AND ETHICS REPORTING REQUIREMENTS

Reporting to regulatory authorities is not required. We will submit an annual report about the progress of the study to the regulatory authorities and to the relevant ethics committees. This will include a list of all SADEs reported during that time period.

There is no requirement to report NIMP SUSARS to the health authorities or ethics committee

The Trial Manager, as the representative of the Sponsor, will arrange all onward submissions on behalf of the sponsor.

12.8.1 Expedited Reporting of SADEs/USADEs to the Research Ethics Committees

All SADEs/USADEs, where appropriate, should be reported to the relevant ethics committees in each country within 15 calendar days of the Sponsor becoming aware of the event.

The Trial Manager, as the representative of the Sponsor, will arrange the reporting of SADEs/USADEs to the relevant ethics committees, on behalf of the sponsor.

12.9 FOLLOW UP PROCEDURES

After initially recording an AE/ADE or recording and reporting a SADE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SADE will be reported to the ACCORD office.

If the outcome of an initial report of an event is one of the following outcome options:
- Condition still present and unchanged
- Condition deteriorated
- Condition improving

Then the investigator must follow-up with the participant(s). Unless otherwise defined in the protocol, a safety report will not be considered complete until the outcome is:

- Completely recovered (including date of recovery)
- Recovered with sequelae (including date of recovery)
- Death (including date of death)

All new information/follow-up information must be initialled and dated on the follow-up reports. Follow-up reports should be submitted to the Sponsor (ACCORD) as per section 13.6

If, after follow-up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of the SADE form.

12.10 MEDICAL DEVICE QUARANTINE

If the event is defined as serious i.e. a SAE or device deficiency that could have led to SADE or USADE the Investigator must quarantine the device as soon as possible e.g. segregating the device from other equipment and labelling as not for use with contact details attached.

Until the Regulatory Authority and Sponsor has been given the opportunity to carry out an investigation, all items (together with relevant packaging materials) should be quarantined. They should not be repaired, or discarded or returned to the manufacturer without agreement from the sponsor.

Medical devices should not be sent to the Regulatory Authority unless this has been specifically requested. Investigators should contact the manufacturer to obtain information relating to the procedure for returning the device, where considered appropriate.

The device should be cleaned and decontaminated where appropriate, securely packaged, and clearly labelled, including the Regulatory Authority or manufacturer reference number if needed. Documentation regarding shipment and receipt of the device, where available, will be retained in the ISF.

13. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Trial Management Group, consisting of the grant investigators working on WP1 (Chief Investigator), the principal investigators at each site, the Trial Manager, and senior research staff.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the eCRFs and database for completeness, plausibility, and consistency. Any queries will be resolved by the local Principal Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

Members of the trial management group:

- Prof Michael Eddleston, CI University of Edinburgh, UK
- Prof Christopher Weir, Trial Statistician, University of Edinburgh
- Prof Knut Erik Hovda, Co-I & PI Oslo University Hospital, Norway
- Prof Aniruddha Ghose, Co-I & PI Chattogram Medical College Hospital, Bangladesh
- Prof Dr Ashish Bhalla, Co-I and PI Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India
- Prof Dr Fazle Rabbi Chowdhury, Co-I Bangabandhu Sheikh Mujib Medical University, Bangladesh
- Prof Shishir R Chakraborty, PI MAG Osmani Medical College Hospital, Sylhet, Bangladesh
- Prof Md. Shafiqul Bari, PI Dhaka Medical College Hospital, Bangladesh
- Prof Abu Shahin, PI Rajshahi Medical College, Bangladesh
- Dr Md. Halimur Rashid, PI Shaheed Ziaur Rahman Medical College Hospital, Bogura, Bangladesh
- Prof Gurinder Mohan, PI SGRD Amritsar, India
- Prof Ravinder Garg, PI GGSMC, Fardikot, India

- Dr Suvodip Shaw, Senior Trial Manager, University of Edinburgh

13.2 TRIAL STEERING COMMITTEE (TSC)

A TSC will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting, and the names and contact details are detailed in CR015 DMC & TSC Charters.

13.3 DATA MONITORING COMMITTEE (DMC)

An independent DMC will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee, and the names and contact details are detailed in CR0015 DMC & TSC Charters.

The DMC Charter will be signed by the appropriate individuals prior to the trial commencing.

13.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Principal Investigator agrees to allow inspectors direct access to all study records and source documentation.

13.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the sponsor, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

13.6 STUDY MONITORING AND AUDIT

The sponsor, clinical trial monitors, or designees will perform monitoring activities in accordance with the study monitoring plan. This will involve remote monitoring activities as far as is practical and some onsite monitoring as necessary. Sponsor's QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary.

14. GOOD CLINICAL PRACTICE

14.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

Ethics review and approval will be sought from the following committees:

- Bangladesh: Directorate General of Drug Administration , Bangladesh Medical Research Council
- India: Central Drugs Standard Control Organization, Indian council for Medical Research

14.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authorities in each participating countries. The protocol and study conduct will comply with the relevant local regulatory legislations (Bangladesh: Directorate General of Drug Administration, and India: Central Drugs Standard Control Organization). A CRO. A contract research organisation (CRO) will be responsible for regulatory submissions in each country (India: Proclin Research Private Ltd, Bangladesh: Devcare Foundation).

14.3 INVESTIGATOR RESPONSIBILITIES

The Principal Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

14.3.1 Informed Consent

The Principal Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor.

The Principal Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

14.3.2 Study Site Staff

The Principal Investigator must be familiar with the Medical Device, NIMP, protocol, and study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the Device, NIMP, protocol, and their trial related duties.

14.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

14.3.4 Investigator Documentation

Prior to beginning the study, Principal Investigators will be asked to provide specific essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (part of Clinical Trial Agreement documents).

- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

14.3.5 GCP Training

All study staff will hold evidence of appropriate GCP training.

14.3.6 Data Protection Training

All University of Edinburgh employed researchers, students and study staff will complete the Data Protection Training through Learn.

14.3.7 Information Security Training

All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules through Learn and will have read the minimum and required reading setting out ground rules to be complied with.

14.3.8 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.3.9 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the UK General Data Protection Regulation, with consideration of the 'data protection by design and default' principles) with regard to the collection, storage, processing and disclosure of personal information.

Access to personal information will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

15. STUDY CONDUCT RESPONSIBILITIES

15.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Sponsor for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate ethics committees and Regulatory Authorities for approval prior to implementation.

15.2 PROTOCOL NON-COMPLIANCE

15.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

15.2.2 Protocol Waivers

Prospective protocol deviations, i.e., protocol waivers, will not be approved by the Sponsor and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the appropriate ethics committees and Regulatory Authorities for review and approval if appropriate.

15.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsor every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. Deviation logs / violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

15.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the appropriate ethics committees and the Regulatory Authorities. This is defined as an urgent safety measure and the investigator must contact the Regulatory Authorities and discuss the issue.

The Investigator will then notify the Regulatory Authorities, the ethics committees and ACCORD, in writing, of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

15.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the -sponsor (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the sponsor to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

15.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 10 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor. Archiving will be done locally with research partners in each country.

15.6 END OF STUDY

The end of study is defined as the discharge from hospital or death of the final patient.

The Investigators and/or the trial steering committee and/or the sponsor has the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the appropriate ethics committees, the Regulatory Authorities and sponsor within 90 days, or within the specific timelines specified by the individual ethics committees who approved the study. If the study is terminated prematurely, the end of study will be reported to the relevant ethics committees and sponsor within 15 days. The Investigators will inform participants still in the study of the premature study closure and ensure that the appropriate follow up is arranged. End of study notification will be reported to the sponsor via email to resgov@accord.scot.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and the ethics committees within 1 year of the end of the study.

Within one year of the end of trial, the Investigator will publish summary results on the public accessible database that the trial was registered with on behalf of the Sponsor.

The Investigator will submit a short confirmatory e-mail to the Regulatory Authorities once the result-related information has been uploaded to the public register with 'End of trial: result-related information: Ref number' as the subject line. The Sponsor will be copied in this e-mail (QA@accord.scot).

15.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Not relevant.

15.8 INSURANCE AND INDEMNITY

The sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the sponsor responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The sponsor requires individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying the device has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where

there is any modification to the study drug (including without limitation re-packaging and blinding).

16. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

16.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

16.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the ISRCTN database within 1 year of the end of the study.

Summaries of results will also be made available to Investigators for dissemination within their hospitals and universities (where appropriate and according to their discretion).

16.3 DATA SHARING

Please refer data management plan (appendix 1).

16.4 PEER REVIEW

The study was peer-reviewed as part of its funding review by the NIHR.

17. REFERENCES

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APPENDIX 1: Data Management Plan

0. Proposal name
Sensitivity, specificity, and acceptability of a bedside formate assay as a diagnostic tool in methanol poisoning: prospective observational and randomised studies
1. Description of the data
1.1 Type of study A field validation study followed by a three-arm, open, feasibility phase III, cluster RCT, comparing use of (1) laboratory and POC formate assays, (2) laboratory formate assay only, and (3) current routine care (no assays, treatment on suspicion) on time to diagnosis and appropriate care. The studies will recruit up to 1,620 and 4,500 patients with suspected methanol poisoning or metabolic acidosis of unknown cause presenting to Bangladeshi and Indian referral hospitals. **1.2 Types of data, including personal data** The study will generate clinical data on participants, in particular their baseline characteristics at recruitment, their diagnosis during their hospital stay, their vital status at hospital discharge, and secondary outcomes, including time to initiation of antidote treatment, time to stopping fomepizole in patients who do not have methanol poisoning, use of unnecessary fomepizole therapy, interval from sample collection to completion of the POC formate assay or the laboratory formate assay, and proportion of patients with changed management based on the laboratory assay. Patient blood samples will be collected to measure formate and methanol concentrations and for collaborative research. Consent forms will be collected, copied, and stored. The reasons why patients are not recruited will be recorded for the Consort flow diagram. Personal data will also be collected, including name, hospital number, age or date of birth, gender, home address, and telephone numbers. **1.3 Format and scale of the data** File formats will include standard Microsoft .docx, .xlsx, .mdb, .accdb, .pptx files; Adobe .pdf, .psd, .jpg, .tiff files; Graphpad Prism .pzf files; Stata .dta; or standard text .txt files. Data will be collected on all patients potentially recruited to the study as well as more simple data on those not recruited to the study. The standard formats and software will enable sharing and long-term validity and validation of data.
2. Data collection / generation
2.1 Methodologies for data collection / generation Clinical data will be collected into an encrypted handheld computer using bespoke programming, based on Android platform, as previously (Eddleston 2007, https://www.ncbi.nlm.nih.gov/pubmed/17498281, and Knipe 2014, https://www.ncbi.nlm.nih.gov/pubmed/25027231). All potential participants will be recorded in the WP1 study database (MaxSol Pro (Pvt) Ltd) at first contact and assigned a study number (specific to each of the study hospitals, which will have separate databases that will be combined for data analysis). This study number (e.g. CF0001) will be used for all data and samples collected from that person. Study doctors will recruit patients at the bedside in study 1 using a handheld device. In Study, allocation will determined by randomising the hospital (not patient). All clinical events will be entered directly into the database by research staff, including vital status at hospital discharge. Data entry will be date/time stamped. Laboratory analysis data will be collected using standard systems set up for each assay system and provided to the study in Excel file format for linking with the primary study database. **2.2 Data quality and standards** This data collection will be guided by standard clinical trial methodology under the supervision of the Edinburgh Clinical Trials Unit. A formal clinical data management plan will be written before the study starts, agreed by the co-investigators, Trial Steering Committee and Data Monitoring Committee, and published on the web. During data entry, after each short page, the researcher will be asked to check and confirm. Particularly important data will be explicitly checked with a pop-up box before the recruitment can proceed. Data entry will not be able to proceed unless all the required boxes are complete. Daily printouts of patients

remaining within the study will be checked at each study hospital by clinical and admin staff for accuracy. Alterations will be made to the data set after logging on for identification of the person revising data; all revisions will be data/time and person stamped. Data quality will be constantly monitored by a full-time data manager in Bangladesh, together with a data manager at the Edinburgh Clinical Trials Unit (ECTU). Equipment used for laboratory analyses will undergo regular quality control as per laboratory standard operating procedures. Laboratory results will be discussed regularly between the PI and laboratory managers.

3. Data management, documentation and curation

3.1 Managing, storing and curating data.

Clinical data will be entered directly into a database on the encrypted handheld device. These data will be backed up onto a local secure server (supplied by Line Reflection Pvt Ltd in Bangladesh, Getontheweb Technologies Pvt Ltd in India) when the handheld device comes into wireless connection. Back-ups will be done soon after any additional data is added to the handheld. The devices will be encrypted to prevent unauthorized access to data.

The local data managers will visit the study sites to review systems and their application when required. They will review the data on the server from the main study offices in Bangladesh and India.

The data controllers for the study will be the Toxicology Society of Bangladesh and PGIMER in Bangladesh and India, respectively, along with the University of Edinburgh as sponsor of the study.

Extracted deidentified data will be sent to Edinburgh securely through Data Sync for statistical review and analysis and stored on the University of Edinburgh's DataStore server.

3.2 Metadata standards and data documentation

File naming and indexing will be by the study participant, operator, and date/time. User-generated indexing will be documented in protocol sheets and on spreadsheets in .xlsx formats

3.3 Data preservation strategy and standards

All raw and processed data will be retained and archived in industry-standard file formats on volatile (RAM) and non-volatile (paper, ROM) media for at least 10 years.

4. Data security and confidentiality of potentially disclosive information

4.1 Formal information/data security standards

The study will be compliant with the University of Edinburgh information security policy) Information security policy (ed.ac.uk).

4.2 Main risks to data security

The main risk is unauthorized access to personal data. Personal electronic data will be collected onto password-protected, encrypted handheld computers and uploaded to a secure server located in Bangladesh and, India. Access to identifiable data will be minimized using role-specific secure computer log-ins. Data from the study will be deidentified by the data manager before transfer to Edinburgh, using standard secure pathways. User compliance with these procedures will be audited by the data manager and by ECTU in turn.

5. Data sharing and access

Deidentified data will be stored in the University of Edinburgh's DataStore via DataSync for review and analysis, and then on University of Edinburgh's DataShare data repository for a minimum of 10 years following the end of the study (see https://datashare.is.ed.ac.uk/) as per University of Edinburgh data policy

5.1 Suitability for sharing

Yes - for future individual patient meta-analysis.

5.2 Discovery by potential users of the research data

The study will have a readily discoverable website to provide up-to-date summary information about the study purpose, the cohort profile, and the kinds of information (being) collected. It will be provided in sufficient detail to inform the general public about the study and be consistent with the expectations and sensitivities of the study participants. The website will report the criteria, processes and timeframe by which data requests will be assessed.

5.3 Governance of access

The PI in discussion with the TSC and its independent chairman will be responsible for reviewing and deciding access requests to study data.

It is not envisaged that the study will receive many requests for data. An advisor with appropriate expertise, independent of the study, will be appointed to periodically review the outcomes of access requests that have been submitted. Individual requests will be referred to the advisor for advice if: difficult issues are apparent (e.g. risk to the data, participants or study, or to depletable resources) or if the PI intends to decline a request.

5.4 The study team's exclusive use of the data

The study team will have exclusive use of data up until three months after the first publication of findings based on the data

5.5 Restrictions or delays to sharing, with planned actions to limit such restrictions

Following this three-month exclusive use of the data, we will positively encourage facilitated collaboration with external researchers through the website

5.6 Regulation of responsibilities of users

External users will be bound by a data-sharing agreement, setting out their responsibilities as per the NIHR and MRC Policy and Guidance on Sharing of Research Data. Agreements will prohibit any attempt to identify study participants from the released data or otherwise breach confidentiality and to make unapproved contact with study participants.

5.7 Data Breaches

Any data breaches will be reported to the University of Edinburgh Data Protection Officer (dpo@ed.ac.uk). There are no requirements in Bangladesh or India to report such data breaches.

6. Responsibilities

Alongside the PI, the responsibilities lie with the Co-Investigators and Research staff employed on the project regarding all direct handling of data, local security, metadata generation and quality assurance.

7. Relevant institutional, departmental or study policies on data sharing and data security

Policy	URL or Reference
Data Management Policy & Procedures	https://www.ed.ac.uk/information-services/about/policies-and-regulations/research-data-policy
Data Security Policy	https://www.ed.ac.uk/records-management/data-protection/data-protection-policy
Information Security Policy	https://www.ed.ac.uk/information-services/about/policies-and-regulations/security-policies/security-policy

8. Author of this Data Management Plan (Name) and, if different to that of the Principal Investigator, their **telephone & email contact details**
Prof Michael Eddleston

APPENDIX 2: Trial Steering Committee (TSC)

Chair: Paul Dargan, Consultant Physician and Professor of Clinical Toxicology, Guy's and St Thomas' NHS Foundation Trust, London UK

Statistician: Christian Holm Hansen, Statistician and Epidemiologist, Dept Infectious Disease Epidemiology and Prevention, Statens Serum Institut, Denmark

Member: Sergey Zakharov, Professor of Clinical Toxicology, Charles University, Prague, Czech Republic

Sponsor representative: Ellie McMaster, University of Edinburgh

APPENDIX 3: Data Monitoring Committee (DMC)

Chair: Sophie Gosselin, Chief, Emergency Department, Centre Hôpital Charles-Lemoyne, Greenfield Park, QC, Canada

Statistician: Laura Sutton, University of Sheffield

Member: Darren Roberts, Medical Director NSW Poisons Information Centre, Sydney, New South Wales, Australia

Member: Cynthia Aaron, clinical toxicologist, Michigan Poison and Drug Information Centre, Wayne State University School of Medicine, Detroit, Michigan, USA

APPENDIX 4a: Investigators' Brochure (separate document)

APPENDIX 4b: Investigator's Brochure Supplementary Files (separate document)

APPENDIX 5: Cartridge Label (separate document)

APPENDIX 6: Outer Label (separate document)

APPENDIX 7: Instructions for Use (separate document)

APPENDIX 8: SmPC NIMP Booklet (separate document)