**THE INTOXICATE (ex-TOXIC-EUROPE) STUDY**

Non-interventional Study Agreement

The undersigned,

1. University Medical Center Utrecht, Division of Anesthesiology, Intensive Care and Emergency Medicine, whose registered office is at Heidelberglaan 100, 3584 CX Utrecht, The Netherlands, lawfully represented by Drs. S. Vernie, Division Manager and Prof. dr. A.M.G.A. de Smet, Medical Scientific Manager

(hereinafter referred to as “**Sponsor**”)

and

1. [*insert name study site*], department of [*insert name department*], whose registered office is at [*insert address*], lawfully represented by [*insert name(s) and function(s*)]

(hereinafter referred to as “**Study Site**”)

in the presence of:

[NAME SITE Investigator].

(hereinafter referred to as “**Site** **Investigator**”)

WHEREAS,

* the Parties each are involved in patient care, research and education;
* the Sponsor and in particular Claudine C. Hunault, MD, PhD (hereinafter “**Investigator**”), researcher employed by Sponsor has designed the Non-interventional Study identified hereof;
* The ‘**INTOXICated pAtients ouTcome in Europe and other continents”** study (INTOXICATE) is an international, prospective, observational, multicentre cohort study using medical data that is stored in Electronic Health Records (EHR).
* the Study Site has facilities and personnel with the requisite skills, experience, and knowledge required to support the performance of the Non-interventional Study by the Site Investigator;
* the Sponsor wishes to engage the Study Site and Site Investigator to perform part of the Non-interventional Study and Site Investigator and Study Site, having reviewed the Protocol and relevant Non-interventional Study information, is willing to participate in the Non-interventional Study.

In consideration of the undertakings and commitments set forth herein, the Parties agree to enter into this Non-interventional Study Agreement.

1. **DEFINITIONS**

The following words and phrases have the following meanings:

* + 1. “**Agreement**” means this agreement comprising its clauses, schedules and any appendices attached to it, including the Protocol and including any amendments to the Agreement agreed between the Parties;
    2. **“Coordinating Centre”** located at the University Medical Centre and mentioned on page 1 in the Protocol;
    3. “**Confidential Information**” means any and all information, data and material of any nature belonging or entrusted to a Party and/or its affiliates, or which is a trade secret, which such Party (the “**Disclosing Party**”) may disclose in any form to the other Parties (each a “**Receiving Party**”) pursuant to this Agreement, the release of which is likely to prejudice the interests of the Disclosing Party;
    4. “**CRF**” means the form in a format prepared by Sponsor and documenting the observations related to the Non-interventional Study and attached as Annex 3 and “**eCRF**” means a CRF in electronic form;
    5. “**Effective Date**” the date this Agreement comes into effect, being the date of the last Party’s signature to this Agreement;
    6. **“Executive Committee”** members from the Coordinating Centre as mentioned in the Protocol on page 1 and will act as Study Monitor;
    7. **“ICF”** means the Informed Consent Form, in which the Non-interventional Study Subject consents to his participation in the Non-interventional Study;
    8. “**Intellectual Property Rights**” means intellectual property rights including but not limited to patents, trademarks, trade names, service marks, domain names, copyrights, rights in and to databases (including rights to prevent the extraction or reutilisation of information from a database), design rights, topography rights and all rights or forms of protection of a similar nature or having equivalent or the similar effect to any of them which may subsist anywhere in the world, whether or not any of them are registered and including applications for registration of any of them;
    9. “**Know How**” means all technical and other information which is not in the public domain (other than as a result of a breach of confidence), including but not limited to information comprising or relating to concepts, discoveries, data, designs, formulae, ideas, inventions, methods, models, procedures, designs for experiments and tests and results of experimentation and testing, processes, specifications and techniques, laboratory records, manufacturing data and information contained in submissions to regulatory authorities, whether or not protected by Intellectual Property Rights;
    10. “**Law**” means any International, European Union and Dutch law and regulations, as well as generally accepted international conventions applicable to the performance of the Non-interventional Study. Such Law including but not limited to:
* the Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation or GDPR)
* the Dutch Medical Treatment Agreements Act (*Wet op de geneeskundige behandelingsovereenkomst* or *Wgbo*)
* and/or any successors of the above mentioned Laws.
  + 1. “**Non-interventional Study**” means the investigation as defined in the cadre on page 1 of this Agreement, (also) to be conducted at the Study Site in accordance with the Protocol as mentioned below;
    2. **“National Coordinator”** is a coordinator which will be chosen to assist with identification of eligible ICUs and to serve as a national resource for ethics applications and logistical support as set out in the Protocol article 3.5;
    3. “**Non-interventional Study Subject**” means a person enrolled to participate in the Non-Interventional Study;
    4. “**Party**” means the Sponsor or the Study Site and “Parties” shall mean the two of them jointly;
    5. “**Personal Data**” means personal data as defined in the GDPR, i.e. any information relating to an identified or identifiable natural person;
    6. “**Protocol**” means the document as defined in the cadre on page 1 of this Agreement, detailing all aspects of the Non-Interventional Study, a copy of which is at Annex 1 to this Agreement. The Protocol includes all amendments thereto;
    7. “**Research Staff**” means the persons who will undertake the conduct of the Non-interventional Study at the Study Site on behalf of the Site Investigator and under the supervision of the Site Investigator;
    8. “**Site Investigator**” means the person who will take primary responsibility for the conduct of the Non-interventional Study at the Study Site or any other person as may be agreed from time to time between the Parties as a replacement;
    9. **“Site Coordinator(s)”** local site coordinator for each ICU participating under this Agreement as set out in article 3.7 of the Protocol.
    10. **“Steering Committee”** the members of this Committee are mentioned on page 1 and 2 of the Protocol;
    11. **“Site Parties”** means Study Sites, all participating centres and Site Investigator;
    12. “**Study Monitor**” means one or more persons appointed by the Sponsor to monitor compliance of the Non-interventional Study with the Protocol and to conduct source data verification;

1. **OBLIGATIONS** 
   1. The Site Parties agree to perform the Non-interventional Study in accordance with the terms and conditions of this Agreement.
   2. The Site Parties represent and warrant that they each have the authority to enter into this Agreement. The Site Investigator will ensure the availability of and/or access to any resources necessary to perform the Non-interventional Study at the Study Site, including departments, facilities and Research Staff and support personnel, and represents that he/she holds the necessary registration and has the necessary qualifications, expertise and time to perform the Non-interventional Study.
   3. The Site Investigator shall notify the Sponsor if he/she ceases to be associated with the Study Site where the Non-interventional Study will be conducted or if he/she is otherwise unavailable to continue as Site Investigator, and Study Site shall use all reasonable endeavours to find a qualified successor acceptable to the Sponsor. If subject to the foregoing no mutually acceptable replacement can be found, within reasonable time as not to hinder the safe continuation of the Non-interventional Study at the Study Site, and provided that the Sponsor will not unreasonably withhold its approval of the proposed replacement of Site Investigator, each Party may terminate this Agreement pursuant to clause 11.2.d below.
   4. The responsibilities and obligations of the National Coordinator, the Site Parties, the Site Coordinators, the Executive Committee, the Coordinating Centre and the Steering Committee are further set out in the Protocol.
2. **NON-INTERVENTIONAL STUDY GOVERNANCE AND COMPLIANCE**
   1. The Sponsor shall be responsible for obtaining the decision of an accredited medical research ethics committee that the Dutch Medical Research Involving Human Subjects Act does not apply to the Non-interventional Study.
   2. The Non-interventional Study shall be performed at the Study Site. The Site Coordinator shall be responsible for obtaining permission from the representatives of the Study Site to perform the Non-interventional Study at the Study Site, which shall include the engagement of the Research Staff and, to the extent applicable clinical chemists.
   3. The Parties shall conduct the Non-interventional Study in accordance with the Protocol, this Agreement and applicable Law.
   4. The National Coordinator shall apply for regulatory approval at a national level where applicable and ensure that ethical committee approvals, or waivers of approvals, are obtained for all the participating hospitals in their country prior to the initiation of the Study and assist the Executive Committee in communicating with the participating sites regarding data queries. The National Coordinator does not have the power of attorney to sign any agreement relating to the Study.
   5. The Site Coordinator shall submit CRF/eCRFs to the Sponsor as outlined in the Protocol in article 3.7. Further responsibilities of the Site Coordinator are set out in article 3.7 of the Protocol.
3. **LIABILITIES, INDEMNIFICATION AND INSURANCE**
   1. Except in the event of intentional behaviour or gross negligence of a Party, in no event will a Party’s liability towards the other Party include any indirect damages (indirect damages meaning: loss of profit, loss of revenue and loss of business opportunities).
   2. The aggregate liability of a Party for a claim or proceeding of the other Party under this Agreement shall be limited to EUR 500.000, except and to the extent such claim or proceeding is made for damages caused by intentional behaviour or gross negligence (in Dutch: bewuste roekeloosheid of opzettelijk handelen of nalaten).
   3. Nothing in this clause 4 shall operate so as to restrict or exclude the liability of any Party vis-à-vis the other Party which cannot be so restricted or excluded by applicable law.
   4. Both Study Site and Sponsor shall take out and maintain an insurance cover in respect of their potential liability in connection with the conduct of the Non-interventional Study.
4. **SUBJECT RECRUITMENT AND ENROLLMENT**
   1. The Site Investigator shall use reasonable endeavours to recruit Non-interventional Study Subjects to the Non-interventional Study within the timelines specified in the Protocol. Site Investigator is obligated to make sure that the Study is in accordance with the Protocol and the GDPR.
   2. If circumstances or events have occurred or will occur that will substantially delay or are likely to substantially delay the progress of recruitment or enrolment of the Non-interventional Study Subjects, the Site Investigator shall immediately inform the Sponsor in writing. In each such event Parties shall discuss the consequences of the delay and each Party shall undertake reasonable endeavours to agree on measures to overcome the delay.
   3. In the event that the Non-interventional Study is part of a multi-centre study, the Site Investigator acknowledges and agrees that recruitment may be competitive and that Sponsor may stop further recruitment of Non-interventional Study Subjects at the Study Site when the recruitment target for all investigational sites for this Non-interventional Study has been met, even if the Study Site has not yet recruited the amount of Non-interventional Study Subjects pursuant to clause 5.1.
5. **QUALITY ASSURANCE AND CONTROL**
   1. The Study Site shall permit the Executive Committee and any official with a legal right to inspect and access all relevant documentation and source data for monitoring of the progress of the Non-interventional Study, the proper collection and recording of Non-interventional Study data, the welfare of the Non-interventional Study Subjects, and altogether the good quality of the Non-interventional Study and compliance with applicable Law and Sponsor’s standard operating procedures. The Executive Committee ’s access will be arranged at mutually convenient times and on reasonable notice with no additional costs for the Executive Committee or Sponsor, after Sponsor has provided Study Site the contact details of the Executive Committee . The Executive Committee will comply with all internal policies and regulations of the Study Site during such inspection. For the avoidance of any doubt, the Sponsor shall be responsible for the confidential handling of all personal data of Non-interventional Study Subjects and other patients which the Executive Committee or Sponsor comes across with during such inspection and will let the Executive Committee sign a confidentiality declaration prior to such inspection.
   2. The Site Investigator or the Study Site shall promptly inform the Sponsor of any intended or actual inspection, written enquiry and/or visit to the Study Site by any regulatory authority in connection with the Non-interventional Study and forward to the Sponsor copies of any correspondence from any such regulatory authority relating to the Non-interventional Study. The Site Parties shall allow Sponsor’s representatives to be present during any such visit.
   3. The Site Investigator shall take appropriate measures and/or corrective actionswithout delay as the Sponsor may reasonably require in order to solve all problems found and reported by the Executive Committee s or officers from regulatory authorities or during an inspection under clause 6.2.
6. **CONFIDENTIALITY AND DATA PROTECTION**

*Medical Confidentiality, data protection and data controlling*

* 1. The Study Site and Sponsor are considered joint controllers for the processing of the Clinical Data and will both handle all Clinical Data in accordance with the GDPR and any other to the performance of the Non-interventional Study applicable laws or regulations covering the protection of Personal Data (collectively “**Data Protection Law**”). Parties, as joint controllers, will fully cooperate with each other as joint controllers and shall take the necessary measures in order to comply with the Data Protection Law, such cooperation shall duly reflect the respective roles and relationships of the joint controllers vis-à-vis the Non-interventional Study Subjects as data subjects, in particular as regards the exercising of the rights of these data subjects and the Parties’ respective duties to provide the information referred to in Articles 13 and 14 of the GDPR. Each joint controller shall maintain a record of processing activities under its responsibility.
  2. Each Party shall be responsible for its own processing of Clinical Data in accordance with all Data Protection Law and with the ICFs obtained from Non-interventional Study Subjects and to the extent applicable, Personal Data consents obtained from the Site Investigator and Research Staff.
  3. Both Sponsor and Study Site shall implement appropriate technical and organizational measures to meet the requirements of the GDPR.
  4. If any Party becomes aware of a Personal Data breach that concerns its performance of the Non-interventional Study, that Party shall promptly notify the other Party/-ies, and, the Party that is the controller of the relevant Personal Data shall also document the Personal Data breach and report the breach to the applicable regulatory authorities. In such case, Parties will fully cooperate with each other in order to fulfil the (statutory) notification obligations timely. A Personal Data breach refers to a personal data breach as defined in article 4 paragraph 12 GDPR and further determined by articles 33 and 34 of the GDPR.
  5. Each Party agrees to co-operate with any competent supervisory authority and to allow such supervisory authority to audit each Party’s compliance with the GDPR.
  6. The Parties agree to adhere to the principles of medical confidentiality in relation to Non-interventional Study Subjects.
  7. Sponsor acknowledges that Non-interventional Study Subjects – and/or their legal representatives on their behalf – may withdraw, in whole or in part, their initial informed consent. Site Investigator shall promptly notify Sponsor of any such withdrawal of the informed consent of a Non-interventional Study Subject, which may affect the use of such Non-interventional Study Subject’s Personal Data under this Agreement. The Site Investigator will communicate with Sponsor on behalf of the Non-interventional Study Subject. However, the procedure followed upon such withdrawal of a Non-interventional Study Subject’s consent will be according to the instructions, to the extent laid down in the Protocol and the ICF, and in accordance with the Applicable Law.
  8. Sponsor shall refrain from tracing and/or identifying any Non-interventional Study Subject, except where Sponsor is under a legal obligation to do so. In the event any Non-interventional Study Subject, for any other than aforementioned reason, becomes identifiable to Sponsor, Sponsor agrees to preserve, at all times, the confidentiality of information pertaining to such Non-interventional Study Subjects.

*Confidential Information*

* 1. The Receiving Party shall ensure that only those of its officers and employees concerned with the carrying out of this Agreement have access to the Confidential Information of the Disclosing Party. The Receiving Party shall take all practicable steps to ensure that such persons abide by the same obligations of confidentiality as apply to the Receiving Party under this Agreement. The Receiving Party undertakes to treat as strictly confidential and not to disclose to any third party any Confidential Information of the Disclosing Party, except where disclosure is required by a regulatory authority or by law, in which case the Receiving Party shall inform the Disclosing Party of such requirement and the information to be disclosed. Notification will be within a reasonable time prior to being required to make the disclosure or if such time is not available, immediately upon becoming known of the requirement to disclose, Confidential Information. The Receiving Party undertakes not to make use of any Confidential Information of the Disclosing Party, other than in accordance with this Agreement, without the prior written consent of the Disclosing Party.
  2. The obligations of confidentiality and non-use set out in clause 7.4 shall not apply to information which the Receiving Party can show by competent evidence:
     1. is or becomes part of the public domain by any other means than a wrongful act or breach of this Agreement by the Receiving Party;
     2. was or becomes in the Receiving Parties’ lawful possession prior to the disclosure without restriction on disclosure;
     3. has been independently developed by the Receiving Party without the use of Confidential Information of the Disclosing Party;
     4. has been obtained by the Receiving Party from a third party without breach of a confidentiality obligation; or
     5. is published in accordance with clause 10 hereof.

*Site Investigator and Research Staff’s Personal Information*

* 1. Where applicable, Sponsor shall inform the Site Investigator, and to the extent applicable other Research Staff, of the collection, the use and the transfer of his/her/their Personal Data and his/her/their rights in respect of such processing as set forth in articles 13 and 14 GDPR. Site Parties agree to help Sponsor obtain any express consent, as may be necessary in accordance with applicable Data Protection Law from the Site Investigator, and to the extent applicable and necessary from other Research Staff, for any intended processing of his/her/their Personal Data by Sponsor.

1. **INTELLECTUAL PROPERTY**
   1. All Intellectual Property Rights and Know How owned by or licensed to any of the Parties prior to and after the date of this Agreement other than any Intellectual Property Rights and Know How arising from the Non-interventional Study are and shall remain the property of that Party.
   2. The Sponsor shall own the Intellectual Property Rights and Know How arising from and directly relating to the Non-interventional Study and the Protocol, but excluding any clinical procedure and improvements thereto that are clinical procedures of the Site Investigator or of Study Site.
   3. The Site Investigator will promptly inform the Sponsor of any invention or discovery arising from and directly relating to the Non-interventional Study or the Protocol, and Study Site hereby assigns rights in relation to all Intellectual Property Rights in relation to such invention or discovery, and will provide reasonable assistance to the Sponsor in filing or prosecuting Intellectual Property Rights, at the expense of the Sponsor.
   4. Nothing in this clause 8 shall be construed so as to prevent or hinder the Study Site or the Site Investigator from using the Know How generated in the Non-interventional Study for its normal hospital, research and education activities to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Rights of the Sponsor.

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1. **PUBLICITY**

The Sponsor will not use the logo or name of the Study Site, Site Investigator, nor of any member of the Research Staff, for promotional purposes, in any publicity, advertising or news release without the prior written approval of the Study Site or Site Investigator, such approval not to be unreasonably withheld. The Study Site and Site Investigator will not, and will ensure that the Research Staff will not, use the name or logo of the Sponsor or of any of its employees for promotional purposes, in any publicity, advertising or news release without the prior written approval of the Sponsor, such approval not to be unreasonably withheld.

1. **PUBLICATION AND AUTHORSHIP**
   1. Publication and authorship between the Parties is regulated in clause 8.3. of the Protocol.
   2. Publications will be in accordance with international recognized scientific and ethical standards concerning publications and authorship, including the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, established by the International Committee of Medical Journal Editors. Copyrights concerning Publications of the Non-interventional Study remains with the authors of the Publication, regardless of any other provisions regarding intellectual property rights.
2. **TERM and TERMINATION**
   1. This Agreement commences on the Effective Date and shall continue in force until the earlier of:

a. completion of the Non-interventional Study, close-out of the Study Site and completion of the obligations of the Parties under this Agreement; or

b. early termination in accordance with clauses 11.2 or 11.3 of this Agreement;

11.2 Each Party may terminate this Agreement upon written notice to the other Parties with immediate effect in the following events:

a. if the Sponsor and/or the Institution become or are declared insolvent or a petition in bankruptcy has been filed against it or if one of them is dissolved;

b. if circumstances beyond a Party’s control occur that render continuation of the Non-interventional Study unreasonable;

c. if one of the Parties fails to comply with the obligations arising from the Agreement and, if capable of remedy, is not remedied within 30 days after receipt of notice from the other Party specifying the non-compliance and requiring its remedy, unless the severity of the failure to comply does not reasonably justify the premature termination of the Non-interventional Study; or

d. if the Site Investigator is no longer able (for whatever reason) to act as Investigator and no mutually acceptable replacement has been found in accordance with clause 2.3.

11.3 At close-out of the Study Site following termination or expiration of this Agreement the Site Investigator and the Study Site shall immediately return to the Sponsor all Confidential Information, equipment and/or unused materials provided by Sponsor in accordance with Sponsor’s instructions, except for one copy of the Confidential Information for archival and evidentiary purposes.

1. **FINANCIAL PROVISIONS / EQUIPMENT**
   1. The DPIC is the sponsor of the study. For instance, costs related to Castor (Electronic Data Capture) and Wordpress (for the making of a website) will be covered by the DPIC. There is no financial compensation for participation(s) and/or inclusion(s). Participation in the study is completely voluntary.
2. **FORCE MAJEURE**

13.1 No Party shall be liable to the other Parties or shall be in default of its obligations hereunder if such default is the result of war, hostilities, terrorist activity, revolution, civil commotion, strike, and epidemic or because of any other cause beyond the reasonable control of the Party affected. The Party affected by such circumstances shall promptly notify the other Parties in writing when such circumstances cause a delay or failure in performance and where they cease to do so.

1. **MISCELLANEOUS** 
   1. No Party may assign its rights under this Agreement or any part thereof without the prior written consent of the other Parties, such consent not to be unreasonably withheld or delayed, and no Party may sub-contract the performance of all or any of its obligations under this Agreement without the prior written consent of the other Parties, such consent not to be unreasonably withheld or delayed. Any Party who so sub-contracts shall be responsible for the acts and omissions of its sub-contractors as though they were its own.
   2. UMC Utrecht shall have the power of attorney to amend this Agreement with the aim to add new parties to this Agreement.
   3. Nothing in this agreement shall be construed as creating a joint venture, partnership or contract of employment between the Parties.
   4. Should there be a conflict between the terms and conditions of the Protocol and the Agreement concerning clinical, ethical or medical matters, the Protocol shall prevail; in all other matters, the Agreement shall prevail.
   5. The clauses 4 (Liabilities, Indemnification and Insurance); 6 (Quality Assurance and Control); 7 (Confidentiality).; 8 (Intellectual Property); 9 (Publicity); 10 (Publication and Authorship); 11.4 (Term and Termination); 12 (Financial Provisions); this clause 14.5 (Surviving Clauses), 14.6 (Governing Law), or other clauses contemplating performance after termination, shall survive termination or expiry of this Agreement. The provisions of clause 7.9 and 7.10 (Confidential Information) shall remain in force for a period of five (5) years.
   6. This Agreement shall be governed by, and construed in all respects in accordance with the laws of The Netherlands without regard to its conflicts of laws rules. Any claims, controversies or disputes arising out of or in connection with this Agreement which cannot be settled amicably between the Parties, shall be subject to the exclusive jurisdiction of the competent court in The Netherlands.

Annexes

Annex 1: Protocol

Annex 2: List of variables to be provided in the eCRF-UNITS

Annex 3: List of variables to be provided in the eCRF-PATIENTS

Signed on behalf of the **Sponsor**

Signature: …………………………………………

Name: Drs. S. Vernie

Title: Division Manager

Date: …………………………………………

Signature: …………………………………………

Name: Prof. dr. A.M.G.A. de Smet

Title: Medical Scientific Manager

Date: …………………………………………

Signed on behalf of the **Study Site**

Signature: …………………………………………

Name: ……………………………

Title: ……………………………

Date: …………………………………………

*The undersigned Site Investigator hereby declares that he/she has read the above Agreement between the Parties and that he/she agrees with the provisions of the Agreement relative to his/her role, responsibilities and duties concerning the Non-interventional Study;*

Signed by the **Site Investigator:**

Signature: …………………………………………

Name:

Title: ……………………………

Date: …………………………………………

ANNEX 1

**PROTOCOL TITLE: INTOXICated pAtients ouTcome in Europe and other continents (INTOXICATE study)**

|  |  |
| --- | --- |
| **Short title** | **INTOXICATE** |
| **Version** | **3.8** |
| **Date** | **9-9-2021** |
| **Coordinating investigator/project leader** | **Prof. Dylan de Lange, MD, PhD, Toxicologist (ERT)**  **UMCU, Dept. of Intensive Care Medicine & Dutch Poisons Information Center (DPIC)**  **Phone: 088-755 8561**  **E-mail: D.W.deLange@umcutrecht.nl** |
| **Principal investigator (in Dutch: hoofdonderzoeker/ uitvoerder)** | **Claudine C Hunault, MD, PhD, Clinical Epidemiologist, UMCU, Dutch Poisons Information Center (DPIC)**  **Phone: 088-755 8561**  **E-mail:** [C.Hunault@umcutrecht.nl](mailto:C.Hunault@umcutrecht.nl) |
| **Contact person:** | **Samanta M Zwaag, PhD student**  **DPIC**  **Email: S.M.Zwaag@umcutrecht.nl** |
| **Executive Committee:** | * **Prof. Dylan de Lange** * **Dr. Claudine C. Hunault** * **Samanta M Zwaag, PhD student** * **Irma van den Hengel-Koot, Research Nurse** |
| **Multicentre research:**  **Other investigators** | **See Appendix A** |
| **Steering Committee (alphabetic order):** | * **Barbara Borgatta, MD, PhD: Liverpool, UK** [barbarabo@gmail.com](mailto:barbarabo@gmail.com) * **Prof. Maurizio Cecconi, MD PhD: Milan, Italy**   [maurizio.cecconi@hunimed.eu](mailto:maurizio.cecconi@hunimed.eu)   * **Prof. Paul Dargan, MB ChB: London, UK**   **Paul.Dargan@gstt.nhs.uk**   * **Prof. Ana Ferrer Dufol, MD PhD: Zaragoza, Spain**   [aferrerd@salud.aragon.es](mailto:aferrerd@salud.aragon.es)   * **Prof. Hans Flaatten, MD PhD: Bergen, Norway Hans.Flaatten@uib.no** * **Prof. Bertrand Guidet, MD PhD: Paris, France**   **bertrand.guidet@aphp.fr**   * **Prof. Christian Jung, MD PhD: Düsseldorf, Germany**   **Christian.Jung@med.uni-duesseldorf.de**   * **Prof. Bruno Mégarbane, MD PhD: Paris, France** [bruno.megarbane@aphp.fr](mailto:bruno.megarbane@aphp.fr) * **Prof. Rui P. Moreno, MD PhD: Lisbon, Portugal**   [**moreno.rui@gmail.com**](mailto:moreno.rui@gmail.com)   * **Prof. Andrew Rhodes, MD PhD: St. Georges Hospital, London, UK**   [andrewrhodes@nhs.net](mailto:andrewrhodes@nhs.net)   * **Prof. Sigal Sviri, MD PhD: Hadassah Medical Center, Hadassah, Israel**   [sigal.sviri@gmail.com](mailto:sigal.sviri@gmail.com)   * **Dr David Wood, MD: London, UK**   [David](mailto:sigal.sviri@gmail.com)**.Wood@gstt.nhs.uk** |
| **Sponsor (in Dutch: verrichter/opdrachtgever)** | **UMCU, Dutch Poisons Information Center (DPIC)**  **Head of Department: prof. Dylan de Lange, MD, PhD, Intensivist.**  **Phone: 088-755 8561**  **E-mail: D.W.deLange@umcutrecht.nl** |

**PROTOCOL SIGNATURE**

|  |  |  |
| --- | --- | --- |
| **Name** | **Signature** | **Date** |
| **Sponsor or legal representative:**  **Head of Department DPIC:**  ***Dylan de Lange, MD, PhD, Intensivist*** |  |  |
| **Project leader/Principal Investigator:**  ***Claudine C Hunault, MD, PhD, Clinical Epidemiologist*** |  |  |

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**ABBREVIATIONS used in the protocol**

|  |  |  |  |
| --- | --- | --- | --- |
| APACHE | Acute Physiologic Assessment and Chronic Health Evaluation | Lab | Laboratory |
| AUC | area under the receiver operating characteristic curve | LASSO | Least Absolute Selection and Shrinkage Operator |
| CPR | Cardiopulmonary resuscitation | LOS | Length of Stay |
| DPIC | Dutch Poison Information Center | MREC | MedicalResearch Ethics Committee |
| DTA / DSA | Data Transfer Agreement / Data Sharing Agreement | PIC | Poisons Information Centre |
| EAPCCT | European Association of Poison Control Centres and Clinical Toxicologists | SAPS | Simplified Acute Physiology Score |
| ECG | Electrocardiogram | SBP | Systolic Blood Pressure |
| eCRF | Electronic Case Report Form | SOFA | Sequential Organ Failure Assessment |
| ED | Emergency Department | TRIPOD | Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis |
| ESICM | European Society of Intensive Care Medicine | UMCU | University Medical Center Utrecht |
| FiO2 | Fraction of Inspired Oxygen | WMO | Medical Research Involving Human Subjects Act (in Dutch: “Wet medisch-wetenschappelijk onderzoek met mensen”) |
| GCS | Glasgow Coma Scale |  |  |
| GDPR | European General Data Protection Regulation |  |  |
| HCU | High-care unit |  |  |
| HDU | High Dependency Unit |  |  |
| HR | Heart rate |  |  |
| ICMJE | Recommendations for the Conduct, Reporting, Editing, and  Publication of Scholarly Work in Medical Journals |  |  |
| ICU | Intensive Care Unit |  |  |

**SUMMARY**

**Rationale:**

Many patients are admitted to Intensive Care Units (ICUs) but only a few actually need an ICU treatment. Observation is the main reason for their admission. Identifying patients that really need ICU treatment is necessary. There is no database on acute intoxications available in Europe and other continents.

**Objective**:

Firstly, to determine the proportion of patients with an eventful admission among acutely intoxicated adult ICU patients; secondly, to develop a prediction model for predicting an eventful admission in this group.

**Study design:**

An international, prospective, observational, multicentre cohort study.

**Study population:**

Acutely intoxicated adult ICU patients admitted to an ICU in Europe and other continents.

**Main study parameters/endpoints:**

The primary endpoint, “eventful admission”, is a composite outcome defined as “receiving an ICU treatment” i.e. any of the following treatments in the first 24 h of the ICU admission: oxygen supplementation with a FiO2 > 40%, mechanical ventilation, vasopressors, renal replacement therapy, cardiopulmonary resuscitation, antidote, targeted temperature management / active cooling, fluid resuscitation (>1.5 litre of intravenous fluids of any kind), sedation or in-hospital death.

**Nature and extent of the burden associated with participation, benefit and group relatedness:**

The study is purely observational in nature; no interventions are planned. No extra burden or risks are associated with participation.

# INTRODUCTION AND RATIONALE

Intoxications can be accidental or intentional (suicide attempt, homicide) and pose a huge burden on intensive care units (ICUs). Although the admission rate of poisoned patients onto the ICU differs per country, region and type of ICU the majority of ICUs treats poisoned patients. Depending on the setting and the type of ICU 3-18% of the population consists of patients with an acute intoxication. Brandenburg 2014, Clark 2014

However, the mortality of intoxicated patients at the ICU and in-hospital is generally low and below that of the general Western ICU population (0.2–7.0% Brandenburg 2014, Banderas-Bravo 2017, Lindqvist 2017, Athavale 2017, Fernando 2018, Mühlberg 2005 vs 7–18% Weigl 2017).

Apparently, in developed countries, the predominant reason to admit intoxicated patients to the ICU is for observation purposes only and not for immediate treatment. Indeed, severe symptoms might arise if the time to maximum concentration of these xenobiotic substances has not yet been reached.

Clearly, for many patients with severe sequelae of their intoxication the only place to be treated is the ICU. For example, if a patient is mechanically ventilated on the Emergency Department or has received cardiopulmonary resuscitation (CPR) then the only place a patient can be treated is the ICU. However, it is necessary to await such symptoms in majority of patients who are not present with these serious sequelae and observations. Since prediction of these adverse symptoms is difficult, many intoxicated patients have to be admitted to the ICU to detect only very few with serious symptoms. Although these ICU admissions are justifiable from a safety perspective, it has an economic disadvantage. van Beusekom 2019 In most countries a formal cost analysis is lacking, but Irish ICUs estimated the costs at €7717 per intoxicated patient per ICU admission. McLaughlin 2009

A better allocation of intoxicated patients will prevent unnecessary admissions to the ICU, increase the availability of ICU care for those patients that rely on it, and it will reduce costs. However, to create a better allocation of resources it is necessary to identify, from readily available parameters, patients that really need ICU treatment.

Studies have been published about the prognosis of acutely intoxicated patients. Several algorithms have been developed for patients at the Emergency Department (ED) to identify those patients needing an hospital admission or an admission at the ICU. Brett 1987; Ambrosius 2012; Meulendijks 2013; van den Oever H 2017 However these algorithms cannot quantify the relationship between the different variables and none of them has further been externally validated. General scores like the APACHE or the SAPS scores developed to predict the prognosis of ICU patients in general have also been applied to acutely intoxicated patients. Banderas-Bravo B 2017; Jiang M 2018 Among these general scores, the APACHE-II score appeared to be useful for predicting prognosis of ICU patients with acute severe poisoning, contrarily to the SAPS score. Banderas-Bravo B 2017; Jiang M 2018 One of the major objections to the APACHE model is that predictions can only be done after 24 hours of ICU admission. In addition, the APACHE-II score is not well calibrated for drugs intoxications. For instance, in situations of altered level of consciousness, the APACHE-II score attributes the same number of points to a patient with a structural pathology, like a severe brain haemorrhage, as to an intoxicated patient whereas the clinical course differs substantially between these pathologies. The mechanical ventilation can usually be withdrawn early in the intoxicated patient. Finally, the performance of the APACHE-II score appears to depend on the different profiles and severity of poisoning that can vary by country. As an example. an Iranian and a Chinese study reported an intra-ICU mortality of 21.5% and 26% in patients admitted for acute poisoning. Alizadeh A 2014; Jiang M 2018 while mortality in European ICUs is much lower, 4-6%. Brandenburg R 2016; Banderas-Bravo B 2017

A retrospective study based on a large Finnish database identified risk factors on admission for prolonged ICU stay and hospital mortality. Liisanantti J 2011 However, no formal prognostic model was developed in this study in order to calculate these endpoints for individual patients. A case-control study aimed at predicting hospital mortality among emergency department patients with acute poisoning but focused only on triage vital signs. Yu J 2012 In another study, Lionte C 2017 a prediction model was developed (and validated) to estimate the in-hospital mortality in adults poisoned with drugs and non-pharmaceutical agents. However, this study was conducted at the Emergency Department and included relatively few patients.

We have previously developed a model that can predict whether a patient really needs organ support on the ICU. Brandenburg 2017 That study emphasized the important influence of chronic co-morbidities on the probability for the need of ICU treatment. This model has been successfully externally validated in a German population of poisoned patients on the Emergency department or specialised Toxicology Ward. Böll R 2017 However, one of the major shortcomings of this model was that many of the variables available on the Emergency Department were not considered. For example, arrhythmias and cardiac conduction abnormalities on the electrocardiogram were not incorporated. We know that many patients are admitted to high care units, like the ICU, for the observation of potential rhythm abnormalities. Second, the intoxications were only grouped in broad and general groups (e.g. “drugs of abuse”, “benzodiazepines”) although we know that the severity of intoxication differs from substance to substance, even within the same class of medications/chemicals. Finally, the dose and timing of the intoxication were not recorded.

In clinical medicine, the term “prognosis” is the forecast of future health outcomes of patients with a particular disease or health condition. Riley 2019 The INTOXICATE study aims at understanding and improving the prognosis of acutely intoxicated adult ICU patients in Europe and other continents.

# OBJECTIVES

## Primary objective

The primary objective is to determine the rate of “eventful admissions” among acutely intoxicated adult ICU patients in Europe and other continents, and to collect data on possible predictors of eventful admissions.

* The primary outcome is an “eventful admission” *i.e.* a composite outcome defined as “**ICU treatment necessary** or **in-hospital death**”. The need for ICU treatment is defined as:
  + - receiving oxygen supplementation with a FiO2 > 40%,
    - mechanical ventilation, vasopressors,
    - renal replacement therapy,
    - cardiopulmonary resuscitation,
    - antidote,
    - active cooling,
    - fluid resuscitation (> 1.5 litre of intravenous fluids of any kind) or
    - sedation in the first 24 h after ICU admission.

The definition of “eventful admission” in the present study is broader than the definition used in our previous study. Brandenburg 2017 (more ICU treatment are included in the definition).

* The descriptive data will include patient and exposure characteristics; variables obtained during clinical examination and diagnostic procedures (lab, ECG etc.), applied treatment(s) and (hospital) setting characteristics (see Appendix B and Appendix C for a list of variables). Differences in outcomes and prognostic factors between countries within Europe and other continents will be investigated.

## Secondary objectives

* Subsequently, we will develop a new prognosis model for predicting an eventful admission in acutely intoxicated adult ICU patients in Europe and other continents. In addition to the predictors already identified in our previous study Brandenburg 2017 and in the literature (e.g. age or systolic blood pressure), predictors like vital signs measured at the ER and ECG characteristics will be investigated (see Appendix C for a list of variables).
* The proportion of patients with other (secondary) outcomes will also be determined, these being: length of ICU stay, ICU mortality and 30-day mortality, and complications during the ICU stay. Specifically, the prognosis value of ECG characteristics, including the QT nomogram Chan 2007 will be investigated in patients intoxicated with drugs that can cause cardiovascular toxicity.
* We will assess the predictive ability of the predictors included in our previous prediction model. Brandenburg 2017

## Exploratory objectives

Our study population will be heterogeneous as it will reflect the broad scope of clinical toxicology. Exploration of this heterogeneity may induce explorative subgroup analyses. The list of pre-defined subgroup analyses or exploratory analyses that can be performed is as follows:

* the influence of age on outcome in intoxicated patients (subgroups <30 versus >80 years),
* 30-day survival curves for various intoxication subgroups,
* withdrawal of life sustaining treatments in intoxicated patients,
* variability of practices (treatment, admission) across countries,
* the effect of informed consent procedures on the external validity of observational studies in toxicology,
* comparison of treatments in propensity matched patients and outcome (e.g. TCA and sodium bicarbonate on rhythm disturbances),
* the variation in treatment in subgroups of intoxicated patients in Europe and other continents (e.g. yes/no silibinin in mushroom poisoning),
* the use of existing kinetic and/or statistic models as tool for the ICU physician,
* machine learning and modelling in intoxication.

# STUDY DESIGN, DURATION AND SETTING

## Study design

The INTOXICATE study is an international, prospective, observational, multicentre cohort study using medical data that is stored in Electronic Health Records (EHR). We aim to recruit ≥ 2000 intoxicated patients from a minimum of 100 ICUs within at least 20 countries in Europe and other continents. We will focus, preferably, but not exclusively, on European ICUs.

## Setting of the study

This research will be conducted in ICUs at university affiliated-, community teaching-, and community non-teaching hospitals in Europe and other continents. The ICU can be medical, surgical, specialised in toxicology or any other specialty (cardiac/coronary, transplantation, respiratory/pulmonary, burns, neurological etc…) or mixed. In the INTOXICATE study, an ICU is defined as a unit where a patient can be endotracheally intubated and mechanically ventilated. Therefore, high-dependency units (HDUs) or high-care units (HCUs) that can mechanically ventilate patients, if necessary, are considered an ICU in the INTOXICATE study.

## Executive Committee and Coordinating Centre

The Coordinating Centre will be located at the University Medical Center Utrecht, The Netherlands (Dutch Poisons Information Center).

The members of the Executive Committee are from the Coordinating Centre. Their names are mentioned at the beginning of this protocol.

Members of the Executive Committee (EC) will (see Figure 1):

* design the study;
* form the Steering Committee by contacting their current network of researchers and participants in other studies;
* advertise the study and identify participating countries and National Coordinators in agreement with the Steering committee;
* ensure that GDPR (General Data Protection Regulation) requirements are met;
* communicate with sites and serve as a resource for site recruitment, data entry, queries, and any questions that arise about the study;
* encourage optimal recruitment and follow-up during the study period, together with the National Coordinators;
* coordinate and monitor the study; send data queries if data are inaccurate
* ensure that the study is conducted in accordance with the protocol, together with the Steering Committee;
* take responsibility for the collected data and statistical analyses;
* take responsibilities for communication of the results and publications, according to the Steering Committee’s advice.



**Figure 1. Responsibilities of the different research partners.**

Numbers indicate the order in which tasks should be performed.

## Steering Committee

The members of the Steering Committee are indicated at the beginning of this protocol.

Members of the steering committee will:

* advise the Executive Committee with the fine-tuning of the protocol;
* advertise the study, and identify participating countries and National Coordinators, together with the Executive Committee;
* ensure that the study is conducted in accordance with the protocol;
* advise the Executive Committee regarding the publications.

## National Coordinators and Network Development

A National Coordinator in each country will be chosen to assist with identification of eligible ICUs and to serve as a national resource for ethics applications and logistical support.

The role of the national coordinators is:

* To advertise the study in the individual countries;
* To identify eligible ICUs and site investigators in their country;
* To include as many hospitals willing to participate as possible;
* To apply for regulatory approval at a national level where applicable and ensure that ethical committee approvals, or waivers of approvals, are obtained for all the participating hospitals in their country prior to the initiation of the study;
* To apply for regulatory approval from a local Data Protection Authority (DPA) where applicable in order to ensure that GDPR requirements are met;
* To assist with the translation of the study documents according to local regulations, if necessary;
* To assist the Executive Committee in communicating with the participating sites regarding data queries;
* To be a co-author of article(s) if the ICMJE criteria are fulfilled AND if enrolment of > 20 patients with complete data collection is achieved in their country.

## Participating Centres

To maximise the recruitment of centres, different approaches to invite ICUs for participation will be used:

* endorsement of the European Society of Intensive Care Medicine (ESICM), will be pursued. The ESICM facilitates spread of their projects through blast mails to all their members. In the past, we succeeded in gaining endorsement from the ESICM for several of our research projects;
* email of National Coordinators to their national ICU network;
* development of a dedicated informative website including an extensive Frequently Asked Questions (FAQs) section. In all recruitment initiatives the website will be mentioned;
* advertisement on websites of critical care societies such as the ESICM and/or the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT);
* flyers will be distributed at national and international critical care symposia and congresses.

To obtain a broad representation, we will recruit participating sites with a spread geographical distribution in Europe and other continents. We anticipate participation of at least 20 countries in Europe and other continents. The study is focused preferably but not exclusively on European ICUs. Participating sites should represent different hospital types (university affiliated, community teaching hospitals, and community non-teaching hospitals). Different ICUs from the same hospital will be considered as separate centres.

## Site Coordinators

For each participating ICU, one local site coordinator will be identified. Recruitment of participating ICUs will be achieved by personal invitation to physicians eligible as site coordinators by the National Coordinators and the Executive committee.

Site coordinators will have the following responsibilities:

* To provide leadership for the project in their institution;
* To apply for research ethics board approval and/or local site approvals in collaboration with the National Coordinator;
* To ensure that local approvals are in place prior to the initiation of the study;
* To notify and send verification of local site approval to the National Coordinator;
* To ensure adequate and timely data collection and entry in the eCRF;
* To reply promptly to data queries from the Executive Committee;
* To maintain effective communication with the National Coordinator and Coordinating Center;
* To store the decryption key in a separate folder to be able a) to collect data on mortality at 30 days; and b) to remove patients requesting to stop their participation to the INTOXICATE study, for any reason. The decryption key is the key which brings together a person’s code and his/her personal information, used during the process of pseudonymisation of the data.

## Time frame / study duration

We will permit staggered start times within a 6-month period to accommodate site-specific processes including research ethics board approval, completion of data sharing agreements, and personnel needs. The time frame will depend on the size of the ICU and the number of intoxicated patients that are referred to it, but is planned to be 1 year. If the recruitment is slower than forecasted, the Executive and Steering Committees will discuss the possibility to amend the data collection period and concede longer recruitment time to centres who will make the case for this.

# STUDY POPULATION

## Population (base)

The source population is adult ICU patients admitted for acute intoxications. An intoxication is defined as the occurrence of any toxic effect to humans following a single or repeated exposure to a mixture, natural or synthetic substance, available on the market or present in the environment.

In a previous study conducted in The Netherlands, the yearly average number of adult acutely intoxicated patients was 22 per ICU (9679 patients in 86 ICUs in 5 years), accounting for 3.7% of the total ICU population.The rate of “poor outcome” (in-hospital mortality or requiring ICU treatment) among these acutely intoxicated ICU adult patients was 6.5% but the definition of an “eventful admission” was stricter in this previous study (fewer ICU treatments were included in the definition of “eventful admission”; e.g. “active cooling” or “administration of an antidote” were previously not included in Brandenburg 2017).

## Inclusion criteria

To be eligible to participate in this study, a subject must meet all of the following criteria:

* + admitted to the ICU/HCU from ER or ambulance or ward
  + intoxication as primary reason for ICU admission
  + stayed at the ICU/HDU during 4 hours or longer
  + adult (≥18 years of age)

## Exclusion criteria

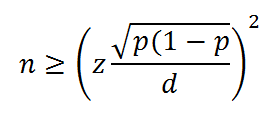
A potential subject who meets any of the following criteria will be excluded from participation in this study:

* + admitted to the ICU for another severe, concomitant condition (e.g. trauma due to car accident while intoxicated)
  + admitted at the ICU for < 4 hours

## Sample size calculation

Descriptive study estimating the rate of an “eventulf admission”

When the statistical parameter of interest is a percentage (here the percentage of “eventful admissions” among acutely intoxicated ICU patients), the usual formula is:



with *n* being the sample size, *z* the z statistic quantifying the chosen level of confidence, *p* the a-priori rate of an “eventful admission”, and *d* the allowable error, which is a surrogate measure of precision. In our case, p is quite rare (p < 0.1) so we used *d* = *p*/2. Further, in case of cluster sampling method, the design effect has to be taken into account.

We assume that the proportion of “eventful admissions” is at least *p*=6.5%, based on our previous study (Brandenburg 2017) that included N=9679 patients, among which n=632 patients had a “poor outcome” (in-hospital mortality or requiring ICU treatment); which gives, for *p*, a narrow 95% CI equal to [6%; 7%].

Taking the values *p*=6.5%, *z*=1.96 because we wish to have 95% confidence intervals for our sample size estimation; *d*=(0.065/2), a correction factor *DE* = 7.65 for 20 clusters (the 20 countries in Europe and other continents where the INTOXICATE study will be conducted), we get *n* = 1691. If we further apply a non-response rate of 10%, a sample size of 1879 patients is required.

Prognosis and prediction model study

There is currently no consensus on sample size considerations for binary logistic regression analysis. In the 90’s, simulation studies examining predictor variables for inclusion in logistic regression models suggested at least 10 events per candidate predictor to avoid over-fitting. Peduzzi 1996 More recently, others have suggested this figure could be as low as 5 Vittinghoff 2007 or even that no rationale exists for this “1 variable per 10 events criterion”. van Smeden 2006

In a sample of 2000 ICU acutely intoxicated adult patients with an *a priori* rate of eventful admissions equal to 6.5%, the expected number of patients with an eventful admission is about 130. The number of predictors for testing and/or inclusion into the multivariable modelling will be reduced as much as possible by reviewing the literature and by examining whether predictors can be combined. Predictors will also be considered for omission if the measurement is complex or if the distribution of the predictor is narrow, thereby unlikely to contain sufficient predictive information.

All in all, our plan is to recruit as many centres as possible, aiming at a minimum sample size of at least 2000 patients. There will be no upper limit to the number of patients or recruiting centres. This should include an adequate number of ICUs from each geographic location in Europe and other continents, as well as patients, to make the results generalizable.

# METHODS

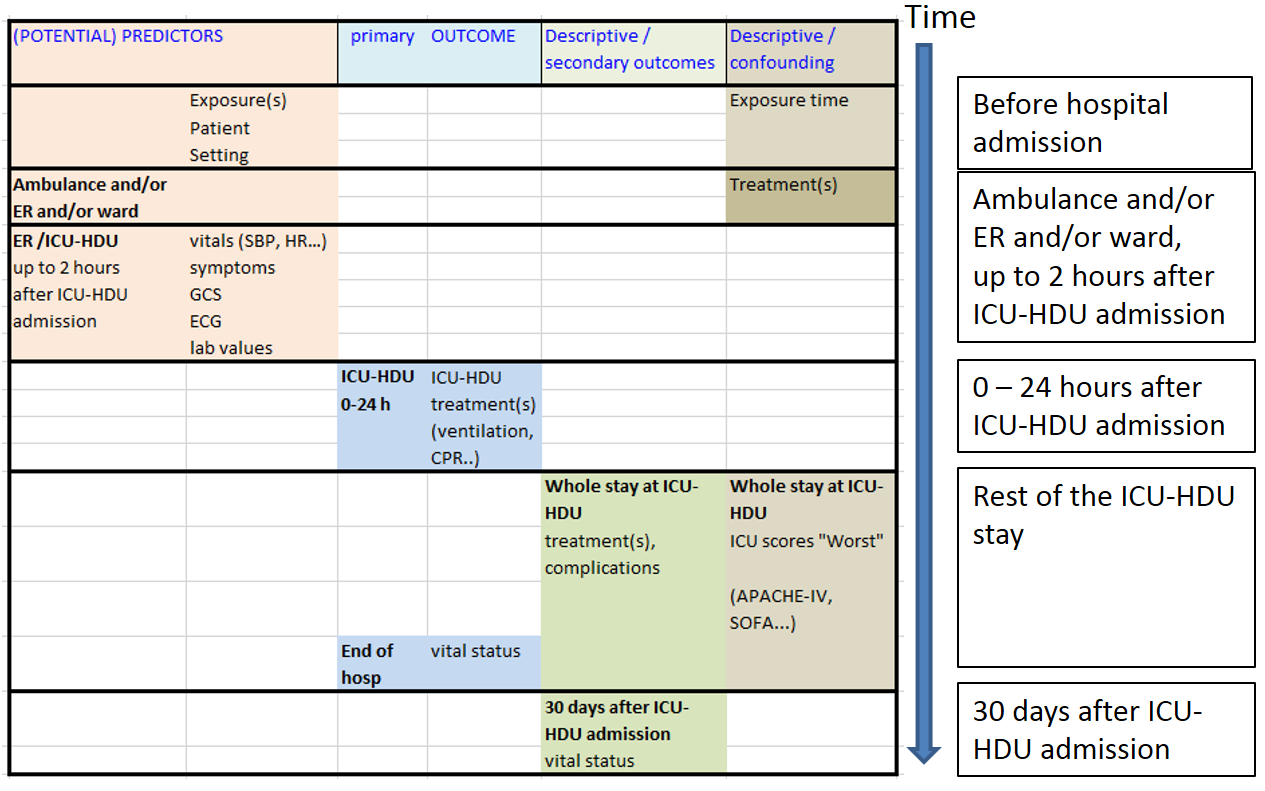
## Study parameters/endpoints (see Figure 2 & Appendix C)

### Main study parameter/endpoint

The main study endpoint is a composite outcome, called “eventful admission” defined as described in paragraph 2.1.

### Secondary study parameters/endpoints

* Mortality:
  + ICU mortality
  + 30-day mortality (after ICU admission)
* Length of stay (LOS):
  + ICU length of stay: ICU duration of stay at the ICU in hours.
  + in-hospital length of stay: duration of stay at the hospital in hours, at any somatic hospital ward. Psychiatric departments are excluded.
* Complications like, for instance, acute renal failure, acute respiratory distress syndrome, compartment syndrome, hemodynamic instability, severe rhythm or conduction disorder etc… (complete list in Appendix C).



**Figure 2**: study variables for the primary and secondary objectives. CPR: cardiopulmonary resuscitation, GCS: Glasgow Coma Scale, HR: heart rate, SBP: systolic blood pressure.

### Other study parameters

The other study parameters are the potential predictors and confounders of the different outcomes:

Predictors:

* intoxication-specific (“exposure”),
* patient-specific (demographics, comorbidities...),
* setting-specific (type of unit, size of unit…),
* vital signs, symptoms, GCS, lab. and ECG variables (either in the ambulance, at the ER or at ICU-HDU up to 2 hours after ICU-HDU admission),

Confounders / variables used for stratification:

* time elapsed since exposure. This variable is important because there is a negative correlation between the time spent at the Emergency Room and outcome. Groenland 2019
* treatment(s) in the ambulance and at the ER,
* Worst ICU scores:
  + sequential organ failure assessment (SOFA),
  + APACHE IV score (or II or III, eventually),
  + SAPS 3 score (or 2, eventually).

## Study procedures

The study is purely observational in nature; no interventions are planned.

## Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

## Follow-up of subjects withdrawn from treatment

Not applicable.

# DATA MANAGEMENT

## Data entry

Data will be recorded using electronic case report forms (eCRF) by the site investigators in a digital database (Castor®). All site investigators will be provided with Manuals of operations which provides information about completion of the electronic case report forms (eCRF) and includes relevant contact information of the members from the Coordinating Centre. There will be two eCRFs in Castor®, one for units’ data registration and one for patients’ data registration.

The data management will be carried out by the data manager of the Division of Anesthesiology, Intensive Care and Emergency Medicine of the UMC Utrecht.

## Statistical analyses

Data extraction from Castor, data consistency check and statistical analyses will be performed by S. Zwaag and C. Hunault. A single final analysis is planned at the end of the study; no interim analyses are planned except for the number of inclusions per center over time.

This study will follow the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline for prognosis studies. Collins 2015

Study cohort characteristics will be described as proportions for categorical variables; and for continuous variables as mean and standard deviation if normally distributed, or median and inter-quartile range if not normally distributed.

Multiple imputation techniques will be used to replace missing values Van Buuren 2018 except if the amount of missing data is very low (≤ 3%). If multiple imputation techniques are used, pooling across imputation datasets will be performed using Rubin’s rules or Rubin and Meng’s pooling for the appropriate test statistic. Rubin 1976; Meng X-L & Rubin 1992

Proportion of patients with an eventful admission among acutely intoxicated ICU patients

The rate of eventful admissions will be calculated as the number of patients with an eventful admission (as defined in paragraph 2.1) divided by all included patients (with a 95% confidence interval). If of value, the rate of eventful admissions will be provided for geographic regions (e.g. Northern Europe, Southern Europe, etc…).

Prognosis model for predicting an eventful admission among acutely intoxicated ICU patients

Firstly, the prognosis ability of the predictors included in our previous prediction model will be assessed, Brandenburg 2017 but for a different definition of “eventful admission” (more treatments are now considered as being a “required ICU treatment”). As the outcome is differently defined, we will have to develop a new prediction model.

To develop a new prediction model, we will use a generalised linear mixed-effects model with a logistic link function and a random intercept per ICU. We will initially include all candidate predictors and analyse continuous variables as linear terms. We will assess departure from linearity graphically and eventually adding quadratic and cubic terms into the model. We will explore interactions and check multicollinearity between variables. Faraway, 2002 Possible differences between geographic regions within Europe and other continents will be included in the model as fixed effects, if necessary.

Next, the model will be fitted to the data to estimate regression coefficients using shrinkage techniques (for instance Lasso or Ridge procedures, or an Elastic Net regularisation). Shrinkage will therefore be incorporated as part of the model fitting to avoid model over-fitting as recommended in situations where the events per variable ratio is low. Pavlou 2015 Common approaches such as stepwise selection or univariable screening are problematic and should be avoided when the number of events is low relative to the number of predictors in the prediction model. Pavlou 2016 Results of the final multivariable logistic regression model will be reported as adjusted odds ratios with 95% confidence intervals. If needed, machine learning will also be considered.

The performance of the final prediction model will be assessed by measures of discrimination, prospective prediction results, calibration, and accuracy. The discrimination will be expressed as the area under the receiver operating characteristic curve (AUC). The prospective prediction results include the sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios. The calibration will be analysed by inspecting the calibration plots. Finazzi 2011 The accuracy of the model will be assessed by the Brier score. Steyerberg 2003 A decision curve analysis approach may also be used to evaluate the final prediction model. Baker 2014; Vickers 2019

If the performance of the final prediction model is satisfactory, we will develop a simple point system (a so-called “chart”) so as to facilitate its use. Categories will be made by considering clinical and statistical criteria. Cut-offs will be decided by considering feedback from the potential users of the prognostic model and by looking at previous publications. The chart will be based on the variables included in the final generalised linear mixed-effects model. Sullivan 2004

The proportion of patients with secondary outcomes (ICU mortality and 30-day mortality) will be calculated in the same way as for the primary outcome parameter. Country and regional differences in severity of intoxications and outcome will be studied. For the prognostic factor research concerning the outcome “30-day mortality”, unadjusted and adjusted survival curves will be used (Time-to-event analyses). Mean LOS will be calculated after adjustment for confounders (severity scores, treatments, patients’ co-morbidities and age).

Exploratory objectives

Variables will be presented as mean (with standard deviation [SD]), median ((with the first and third quartiles (Q1;Q3)),) or number (proportion), where appropriate. Regression techniques will be used to study the prognostic value of specific predictors; a generalised mixed model with a logistic link function will be used when the outcome is binary, and Kaplan Meier and/or Cox models with mixed effects in cases of survival data. For statistical analysis concerning machine learning and modelling in intoxication, the principal investigator will be assisted by expert statisticians.

Statistical analyses will be carried out using R (version 3.6.0) with RStudio (version 1.2.1335) or SPSS for Windows (version 25.0.0.2).

## Documentation of the study and access

The documentation of the study will be organized according to a "Research Folder Structure (RFS)" in the network of the UMC Utrecht that will be created by the data manager of the Division of Anesthesiology, Intensive Care and Emergency Medicine of the UMC Utrecht. Database containing “pseudoanonymous” data and files will be stored in this directory. “Pseudoanonymous” means that data are made unidentifyable but are locally still traceable. The data manager will also ensure that only people from the Executing Committee can have access to this directory.

# ETHICAL CONSIDERATIONS

## Regulation statement

The INTOXICATE study will be conducted according to the principles of the Declaration of Helsinki (October 2013), the European General Data Protection Regulation (GDPR) (Regulation (EU) 2018/1725), and other local applicable regulations.

## Recruitment and consent

The research study conducted by the academic institutions is necessary for the performance of a task carried out in the public interest pursuant to Article 6(1)(e) GDPR. Therefore, patients will not be asked for consent for this secondary use of personal data.

The objective(s) of the study cannot be reached without the use of the personal data that is stored in Electronic Health Records (EHR). Considering the nature and purpose of the research, and the need for a sample that is representative for the population under study, asking for permission cannot reasonably be required.

The need for consent might hinder that all intoxicated patients admitted to ICU contribute their data, leading to potentially selection bias de Lange 2019 , as a result of which this research cannot give valid and useful results and therefore undermines the purpose of the study. If the results are based on a non-representative part of the population of interest, there is a possibility that treatment may even deteriorate. Therefore we conclude that asking for permission is also reasonably not possible. To prevent this possible bias as much as possible, local investigators should maintain a “screening log”. This screening log will allow them to count the total number of intoxicated patients admitted to their unit and the number of patients included in the INTOXICATE study; these two numbers will be sent monthly to the coordinating center as aggregated (anonymous) data.

Assurances that the privacy of the data subject will not be disproportionately harmed are in place. The participating institutions will handle the research data in accordance with applicable regulations and local institutional policies. Privacy of the research subjects is protected to the highest possible degree. Privacy enhancing techniques among which pseudonymization, a certified electronic data capturing tool (Castor EDC) will be used and network folders with differentiated access rights for different users shall be applied. Researchers are not able to re-identify the research subjects. Only the site investigator has direct access to the key document and is able to re-identify the research subjects of their own institution.

While waived consent will be our preferred approach, rules and regulations may however differ from country to country. de Lange 2019 Each centre will obtain authorisation to perform the study according to their national regulations. Centres will abide by regulations within their country.

If participating ICUs or hospitals require additional agreements to be compliant with the GDPR in data sharing, the Executive Committee will provide those centres with a data transfer agreement (DTA). This study will be suggested to institutional research committees of ICUs only if the national ethics committee agrees with the research. If needed, Patient Information Sheet templates will be provided to National Coordinators and/or local investigators on request (see Appendix D).

The data will not be shared with countries outside the EU.

# HANDLING OF DATA, STORAGE AND PUBLICATION

## Handling of data

Data of patients who meet the inclusion criteria will be entered by the site investigators in electronic case report forms (eCRFs) in a digital database (Castor®). There will be two eCRFs: one for unit registration and one for patients’ data registration. The location (country, city, hospital name…) where the patients were admitted will therefore not be registered in the same Castor® database than the rest of the patient’s data. The two databases cannot be directly linked within Castor®. No patient identifying information will be collected, no personal data such as name or date of birth will be recorded in the eCRFs. Data encryption will be used for pseudonymisation of the data. Each unit will be assigned a sequential number (e.g. 001, 002, 003, etc.), and patients will be assigned consecutive unique identifiers, so that patients will be labelled as: Unit number - Patient number (e.g. 001-0001, 001-0002, etc.).

The decryption key i.e. the key to identification until a person will be stored in a separate folder by the site investigators who will be the only people with access to the decryption key. The researchers from the executive committee will have access only to the pseudonymous data, and will analyse them in order to answer the specific research questions.

According to the GDPR regulation, patients requesting to be removed from the database should be removed by the site investigators.

## Data storage

Patients’ medical data will be stored for 20 years, according to institutional policy of the UMC Utrecht. Data will be stored in the digital database (Castor®) for 20 years, according to the national law or regulations of the member states involved, after the study is closed and can be exported at any time if necessary.

## Publication and Authorship

Results will be made available to ESICM and/or EAPCCT members and to the scientific community by means of abstracts submitted to annual conferences and by scientific papers submitted to peer-reviewed journals.

Authorship of the manuscripts will follow the International Committee of Medical Journal Editors (ICMJE) recommendations ICMJE that base authorship on the following 4 criteria:

* Substantial contributions to the conception or design of the work; or the acquisition, analysis, or

interpretation of data for the work; AND

* Drafting the work or revising it critically for important intellectual content; AND
* Final approval of the version to be published; AND
* Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A writing committee, comprised by the Executive Committee and selected members of the Steering Committee, will draft the work and the writing committee members will be authors of the manuscripts. As more than one manuscript is planned, the composition of the writing committee as well as the order of the co-authors will change per manuscript. National coordinators will be authors if they meet the ICMJE criteria AND if they promote the enrolment of a significant number of units in their country, with complete data collection of at least 20 patients per unit.

All national coordinators will be listed in the acknowledgment section. ESICM and/or EAPCCT support and endorsement will be acknowledged on all INTOXICATE publications.

The primary analysis of the study will be submitted preferentially to a journal that allows all site investigators to be added as author or collaborator if the former is not possible, albeit that a minimum of 10 patients with complete data collection should have been included in the study. All investigators will be credited in the “INTOXICATE Investigators” group authorship. In each manuscript, the corresponding author will specify the group name and will clearly identify the group members who can take credit and responsibility for the work as collaborators. Centers can have 2 collaborators listed for the group authorship. The names and affiliations of the collaborators need to be entered in the digital database (Castor®).

All investigators have the right to submit study questions after the analyses described in the protocol have been completed. Any requests will be submitted in writing to the INTOXICATE Executive Committee and Steering Committee who will decide whether the proposed analysis can be performed and only if there is no conflict with other ongoing or completed analysis.

Data in the database will not be distributed to third parties without explicit and written agreement of the local investigator.

## Amendments

Amendments are changes made to the research after the accredited Medical Research Ethic Committee (MREC) judged that the Medical Research Involving Human Subject Act was not applicable. Any amendments to the protocol will require review and approval by the Steering Committee, and eventually by the accredited MREC(s), before the changes are implemented to the study. For instance, if the recruitment is slower than forecasted, the Steering Committee will discuss the possibility to amend the data collection period. Specifically, any change that may cause the research to fall within the scope of a WMO study will be submitted to the accredited MREC(s).

# BUDGET

The UMCU, Dutch Poisons Information Center (DPIC) is the sponsor of the study. Costs related to Castor (Electronic Data Capture) or Wordpress (for the making of a website) will be borne by the UMCU-DPIC. There is no financial compensation for participation(s) and/or inclusion(s). Participation in the study is completely voluntary.

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**APPENDIX A – List of National Coordinators and list of Local Investigators**

**APPENDIX B – variables in the eCRF - UNITS**

**APPENDIX C – variables in the eCRF - PATIENTS**

**APPENDIX A**

**List of National Coordinators** (on the website, regularly updated).

|  |  |  |
| --- | --- | --- |
| **Country** | **Name** | **Contact** |
| **Armenia** |  |  |
| **Australia** | Rukhshad Mehta | [Rukhshad.Mehta@act.gov.au](mailto:Rukhshad.Mehta@act.gov.au) |
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| **Bulgaria** |  |  |
| **Croatia** |  |  |
| **Czech Republic** |  |  |
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| **Iceland** |  |  |
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| **Lithuania** | Gabija Laubner | [gabija.laubner@rvul.lt](mailto:gabija.laubner@rvul.lt) |
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| **Sweden** | Elin Lindqvist | [elin.lindqvist@ki.se](mailto:elin.lindqvist@ki.se) |
| **Switzerland** |  |  |
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| **Ukraine** | Yuriy Nalapko | [nalapko@ukr.net](mailto:nalapko@ukr.net) |
| **United Kingdom** | David Wood | David.Wood@gstt.nhs.uk |

**Form to complete by Local Investigators** (internal use, regularly updated).

This is intended for **internal use;** contact information will stay at the Coordinating Center.

**INTOXICATE study - Contact Information**

1.1 Name of the Intensive Care Unit

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1.2 Address of the unit

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1.3 Name and title (position and/or academic) of the primary collaborator

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1.4 Email address of the primary collaborator

This email address is the primary address to communicate with the INTOXICATE coordinating committee. For all questions about patient's registration, data entry and patient's follow up, we will use this email. Please make sure that this email address belongs to the person that will actively participate in the INTOXICATE study.

If you need to change the email of the primary collaborator after you have entered data, please email the new address to: [contact@toxicstudy.org](mailto:contact@toxicstudy.org)

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1.5 Is the primary collaborator the head of the unit?

 Yes

 No

1.6 If “No” , Name and title (position and/or academic) of the head of the unit

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1.7 Email address of the head of the unit

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1.8 Do you have a second collaborator?

The secondary collaborator is the second person who handles data entry at your unit.

 Yes

 No

1.9 If “ Yes” , Name and title (position and/or academic) of the second collaborator?

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1.10 Email address of the second collaborator?

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**APPENDIX B – variables in the eCRF - UNITS**

Hospital

-Name of the hospital or institution

-Type (University / Community teaching / Community non-teaching / Other: specify)

-Country

-City

-Is informed consent required at your unit to collect data for INTOXICATE?

Unit

-Name of the unit

-Address of the unit

-Type of unit (ICU / HDU or HCU)

-At this unit may non-IC doctors write orders?

-What are the unit specialties? (Medical / Toxicological / Respiratory / Surgical / Trauma / -Cardiothoracic surgery / Cardiac or coronary / Transplantation / Burns / Neurological or Neurosurgical / Other: specify

-Number of beds at the unit (<10 / 10-15 / 15-30 / >30

-Number of admissions to your ICU/HCU in the last year (<500 / 500-1000 / 1000-2000 / 2000-3000 / >3000<)

-Number of admissions to your ICU/HCU in the last year for an acute intoxication (<30 / 30-60 / 60-120 / 120-180 / >180

**APPENDIX C – variables in the eCRF - PATIENTS**

Location prior to ICU/HDU admission

-Was the patient directly admitted from the Emergency Room or an ambulance OR was the patient transferred from a ward?

-Where did the intoxication take place?

Dates and Times of Admission and Discharge

*if the patient passed through the emergency department after exposure:*

-Date and Time of ER presentation

-Date and Time of ER discharge

*if the patient was transferred from a ward to ICU/HDU:*

-Date and time of ward admission

-Date and Time of ward discharge

-Date and Time of ICU/HDU admission

-Date and Time of ICU/HDU discharge

-Date and Time of Hospital discharge

-Date of record creation

-If the duration of stay at the ICU/HDU is shorter than 24 hours, was the patient transferred to another ICU/HDU?

Contact with a Poisons Information Center (PIC)

-Was a Poisons Information Center contacted?

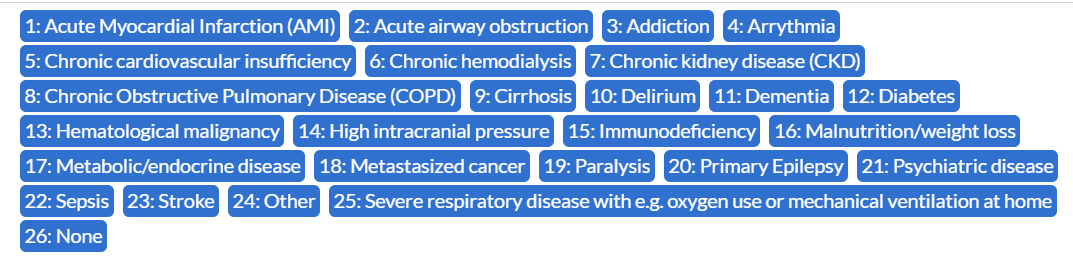
-*Optional: if yes, what was the estimated severity by the PIC?*

-*Optional: if yes, Hospital admission advice by the PIC*

Patient characteristics

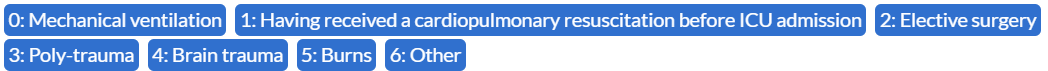
-Age, gender, weight, height

-comorbidities: choose from the following list (specify if “Other” is selected):



-is there a second reason for ICU/HDU admission?

-If yes, what is the second reason? Choose from the following list (specify if “Other” is selected):



Exposure

-Number of exposures

-Reason of exposures (Intentional / Unintentional)

-If “intentional” choose from the following list:



-If “unintentional” choose from the following list:



-Is time of exposure known, unknown or estimated?

-How much time has elapsed between exposure and hospital presentation?

-Table of exposures:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Name exposure | Exposure category | Route of exposure | Dose of exposure | Unit dose | Was the exposure a slow release medication? | Animal (if relevant…) |
| … | … | … | … | … | … | … |

Clinical assessment between the start of intoxication and up to 2 hours after ICU/HDU admission

* Symptoms

-Choose from different lists of symptoms (Gastrointestinal symptoms list / Respiratory symptoms list / Cardiovascular symptoms list / Neurological symptoms list / Dermatological symptoms list / various symptoms list)

-Table indicating at which location(s) the symptoms were observed:



* Vital functions

|  |
| --- |
| Indicate the most deviant value. If values stay within normal range, please give the first values measured at ICU/HDU admission (within 2 hours after ICU/HDU admission): |

- Heart Rate / Systolic Blood Pressure / Diastolic Blood Pressure / Mean Arterial Pressure / Respiratory Rate / Body temperature

* Glasgow Coma Scale (GCS)

-Was a GCS assessed between the start of intoxication and up to 2 hours after ICU/HDU admission?

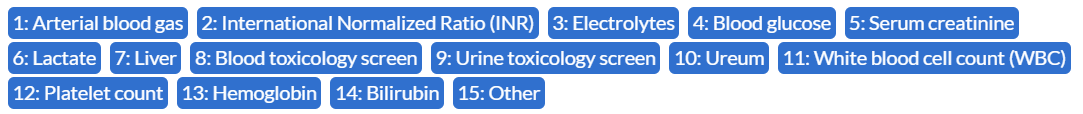
-If yes, give the GCS sub-scores of the lowest GCS score (Eye Opening / Motor Response / Verbal Response)

-If yes but no sub-scores are available, give the total score of the lowest GCS

* Lab

-Was lab performed between the start of intoxication and up to 2 hours after ICU/HDU admission?

-If yes, choose from a list of tests which lab tests were performed



-Depending of the tests performed, results of the tests

* ECG

-Was an ECG performed between the start of intoxication and up to 2 hours after ICU/HDU admission?

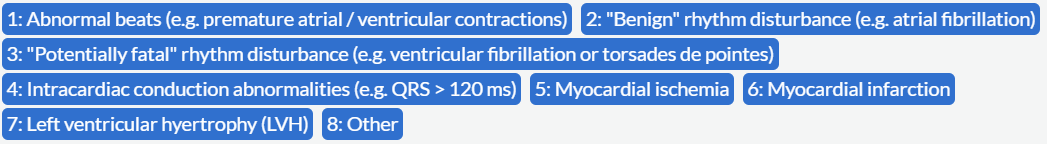
-If yes:

-what were the date and time of the ECG?

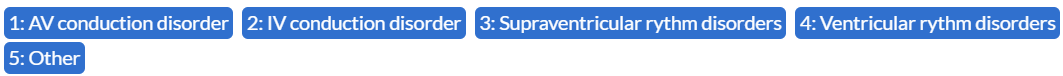
-what were the Heart Rate / QRS duration / QT time on the ECG?

-were there any abnormalities on the ECG?

-if abnormalities, what were these abnormalities? Choose from a list:



-if intra-cardiac conduction abnormalities, which types? Choose from a list:



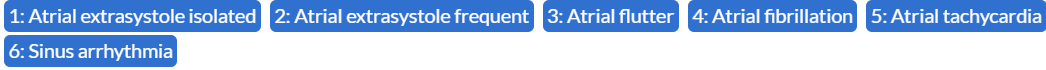
-if atrioventricular conduction disorder, which type? Choose from a list (specify if “Other” is selected):



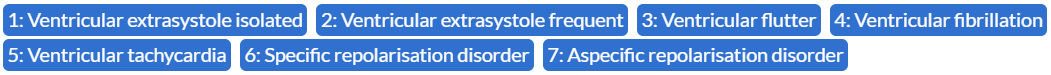
-if intraventricular conduction disorder, which type? Choose from a list:



-if supraventricular rhythm disorder, which type? Choose from a list:



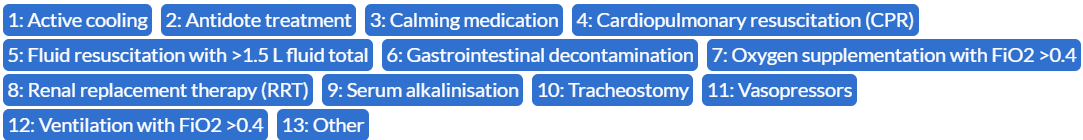
-if ventricular rhythm disorder, which type? Choose from a list:



*-Optional: if ventricular rhythm disorder, specify the repolarization disorder observed*

Treatment - Treatment before ICU/HDU admission

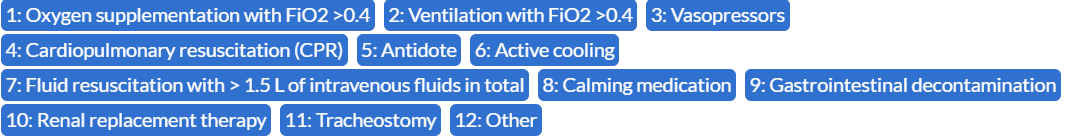
-Which treatments were given between exposure and ICU/HDU admission? Choose from a list (specify if “Other” is selected):



-Table to enter the locations where treatments were administered.

Treatment - Treatment given within 0-24 hours of ICU/HDUstay

-Which treatments were initiated within the first 24 hours at the IC/HDU? Choose from a list (specify if “Other” is selected):

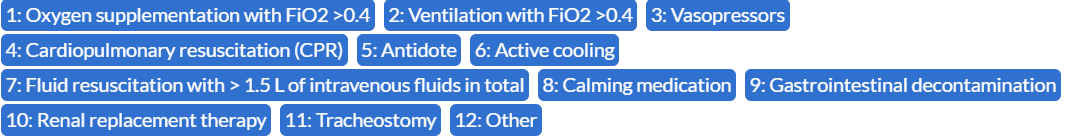


-Table to collect information of all ICU/HDU treatments given to the patient in the first day of ICU/HDU stay (<24h):

|  |  |  |  |
| --- | --- | --- | --- |
| Treatment | Where did the treatment start? | Unit of duration of treatment | Duration of treatment |
| … | … | … | … |

Treatment - Treatment given later than 24 hours after ICU/HDU admission, during the rest of the ICU/HDU stay

-Which treatment(s) did the patient receive after the first 24 hours of ICU/HDU stay? Choose from a list (specify if “Other” is selected):



-Table to collect information on ICU/HDU treatments given to the patient after the first 24 hours of ICU/HDU stay:

|  |  |  |  |
| --- | --- | --- | --- |
| Treatment | Where did the treatment start? | Unit of duration of treatment | Duration of treatment |
| … | … | … | … |

Intensive Care or High Dependency Unit (ICU/HDU) stay -APACHE score during ICU/HDU stay

-Is an APACHE score available?

-If yes, which version of the APACHE score is available?

-If yes, value of the APACHE score at ICU/HDU

Intensive Care or High Dependency Unit (ICU/HDU) stay -SOFA score during ICU/HDU stay

-Is there a SOFA score available?

-If yes, score the sub-scores if possible; otherwise, enter the total SOFA score if sub-scores cannot be scored

Intensive Care or High Dependency Unit (ICU/HDU) stay -SAPS score during ICU/HDU stay

-Is a SAPS score available?

-If yes, which version of the SAPS score is available?

-What was the value of the SAPS score?

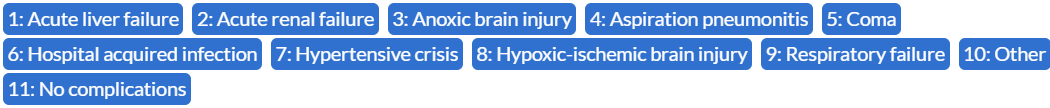
Intensive Care or High Dependency Unit (ICU/HDU) stay -Optional: Other scores

*-Optional: are other scores available? (e.g. Toxscore or Poisoning Severity Score (PSS)?*

*-Optional: if yes, please indicate the name of the other score available and its value.*

Intensive Care or High Dependency Unit (ICU/HDU) stay -Complications during ICU/HDU stay

-Select the complication(s) that occurred during the whole ICU/HDU stay or select “no complication”. Choose from a list (specify if “Other” is selected):



Vital status - Vital status at hospital discharge

-What was the patient’s vital status at hospital discharge?

-If “Alive patient” where did the patient go after leaving the ICU/HDU?

-If “Not alive”, how much time elapsed between ICU/HDU admission and death? + unit of time

-If “Not alive”, what was the cause of death?

-If “Not alive”, was life sustaining care withheld? If yes, how much time elapsed between ICU/HDU admission and withdrawal of life sustaining care + unit of time

-If “Life sustaining care withheld” is selected, which treatments were withheld? Choose from a list (or specify if “Other” is selected):



Vital status - Vital status 30 days after ICU/HDU admission

-What was the patient’s vital status 30 days after ICU/HDU admission?