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Acutelines: a large de novo data,- image,- and biobank aiming to improve early recognition and outcomes of acute diseases.

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Cohort profile of Acutelines: a Large Data-/Biobank of Acute and Emergency Medicine.

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Abstract

Purpose: research in acute care faces many challenges, including enrollment challenges, legal limitations in data sharing, limited funding, and lack of singular ownership of the domain of acute care. To overcome these challenges, the Center of Acute Care of the University Medical Center Groningen in the Netherlands, has established a de novo data-, image- and biobank named "Acutelines".

Participants: clinical data, imaging data and biomaterials (*i.e.* blood, urine, feces, hair) are collected from patients presenting to the Emergency Department (ED) with a broad range of acute disease presentations. A deferred consent procedure (by proxy), is in place to allow collecting data and biomaterials prior to obtaining written consent. The digital infrastructure used ensures automated capturing of all bed-side monitoring data (*i.e.* vital parameters, electrophysiological waveforms), and securely importing data from other sources, such as the electronic health records of the hospital, ambulance and general practitioner, municipal registration and pharmacy. Data are collected from all included participants during the first 72-hours of their hospitalization, while follow-up data is collected at 3-months, 1-year, 2-years and 5 years after their ED visit.

Findings to date: enrollment of the first participant occurred on September 1st 2020. During the first month, 653 participants were screened for eligibility, of which 180 were approached as potential participants. In total 151 (84%) provided consent for participation of which 89 participants fulfilled criteria for collection of biomaterials.

Future plans: the main aim of Acutelines is to facilitate research in acute medicine by providing the framework for novel studies and issuing data, images and biomaterials for future research. The protocol will be extended by connecting with central registries to obtain long-term follow-up data, for which we already request permission from the participant.

Registration: the Acutelines biobank is registered under trial registration number NCT04615065 at ClinicalTrials.gov.

Introduction

Research in Acute Care is important to prevent diseases, and to establish best practices for treatments of many acute conditions. Over the past 50 years, medical knowledge has grown exponentially, and specialties as Emergency Medicine and Acute Internal medicine have developed rapidly.[1] Despite this, knowledge gaps still exist. Amongst these are logistics of care (optimal patient disposition, triage, and prevention of crowding), the development of tools for early recognition of acutely sick patients (including risk prediction models, biomarkers and/or artificial intelligence), and the development of more patient centered and personalized care for specific subgroups presenting in the emergency department (ED), such as the frail elderly population, patients with psychiatric illnesses and patients with (early) sepsis. [2-4]

However, conducting research in acute care may prove difficult for various reasons. First, enrollment challenges often limit the number of participants eligible to participate in clinical studies [5,6]. As many acute conditions are time sensitive and expedited diagnostic evaluation and/or initiation of treatment is warranted, this is normally prioritized over study enrollment. Further, obtaining consent from acutely ill patients to participate in clinical studies can be challenging or even impossible, especially when a proxy or legal representative is not available to emergency medical services (EMS) or emergency department (ED) personnel to discuss study aims- and risks within the enrollment window [7,8]. Finally, availability of staff for enrollment of participants can be an issue with increasing pressure on healthcare systems and the resultant crowding of Emergency departments (ED's) in many countries. [9]

Second, in order to gain more insight into the natural course of acute diseases, and to be able to investigate which patients will deteriorate rapidly during the course of their disease, it is important

to collect data from the start of their disease onwards until they are fully recovered or died. However, this is often difficult to achieve due to legal limitations in data sharing. Data transfer for clinical research between various organization involved in the care for a particular patient and the secondary research use of data- and or biomaterials can only occur with explicit permission of the patient. [10]. As with consent, timely permission is often not possible to obtain. Further, no single specialism is the "owner" of acute care. Although the organization of healthcare systems may vary from one country to the other, acute care is multidisciplinary by nature. Research interests and priorities may vary between specialties involved, which may complicate conduct of clinical studies. Finally, it can be a challenge to obtain funding for acute care research. Although researchers may apply for government sponsored grants of organizations as the National Institute of Health (NIH) or the Dutch research Council (NWO), the number of grants funded by these institutions related to acute care are low [11], and additional funding is often required.

In an attempt to overcome some of these aforementioned challenges, the Center of Acute Care of the University hospital Groningen in the Netherlands, has established a de novo data, image- and biobank named "Acutelines". AcuteLines is unique, as it is not aimed at one specific disease or condition as other critical care biobanks [12,13], but instead collects data, imaging and biomaterials from as many patients presenting with acute conditions as possible, aiming to explore the association between pre-existing health, acute illness and (long term) outcome. (Figure 1) The objective of this manuscript is to describe the process by which we established Acutelines, and how we integrated operations into ED clinical workflow allowing Acutelines to operate 24 hours a day, seven days a week (24/7).

Cohort description

Study design

Acutelines is a prospective data-, image- and biobank including patients with a broad spectrum of acute conditions. Its aim is to facilitate interdisciplinary research on the etiology and development of acute diseases with the aid of systematically collected biomaterials and medical data over various time points, both during the course of the patient's disease and after recovery. Acutelines is initiated by the departments of Emergency Medicine and Internal Medicine of the University Medical Center Groningen, the Netherlands, and registered in ClinicalTrials.gov (see table 1 for WHO trial registration dataset) and in the Groningen data catalogue. The latest biobank protocol and regulations are accessible via http://acutelines.umcg.nl. The biobank is governed by a three-person scientific committee (HB, JtM and EtA) with oversight of a trustee (BvM), and supported by two data managers (RvW and ST) and a team of research assistants, led by team captains (StH, TTH, LvH FvB, FvdV).

Setting

All patients admitted to the ED of the UMCG, a large tertiary care center with approximately 26,000 ED visits per year, for specialties participating in Acutelines are screened for eligibility. Participating specialties during the (current) initiation phase of the biobank are: emergency medicine, internal medicine (including sub-specializations as allergology, acute medicine, oncology, hematology, infectiology, nephrology, vascular medicine, geriatric medicine), pulmonology, gastro-enterology and rheumatology. The scientific board of Acutelines aims to allow participation of other specialties as well in the near future after the initiation phase. The ultimate goal of Acutelines is to generate a biobank for acute diseases with a high scientific merit, that is logistically efficient and financially sustainable, and can become a resource to both academic and industry partners. The sample size of

the biobank is directly related to available funding, which allows us to include approximately 3,500 participants/year in the initiation phase. This number is likely to expand once more specialties will participate, and/or when external parties will apply for the use of data and samples from the bank. The first participant was enrolled on September 1st, 2020. Acutelines does not have a fixed end date or sample size.

Eligibility criteria

To be eligible for inclusion, according to the latest version of the Acutelines protocol participants have to meet at least one of the following criteria (Figure 2):

- Patients with the highest- and second highest urgency triage categories (red or orange) of the Emergency Severity Index (ESI) [14].
- Patients with the third highest category urgency triage category (yellow) of the ESI when arriving by (Helicopter) Emergency Medical Service
- Patients with several specific conditions regardless their triage category are included: sepsis, shock, syncope, anaphylaxis, acute renal failure, electrolyte disturbances intoxications, COPD and asthma exacerbations, (suspicion of) deep venous thrombosis or pulmonary embolism, gastrointestinal bleeding and patients who are bleeding (any source) whilst using vitamin-K antagonists or DOAC.

While data- and imaging will be collected from all included participants, biomaterials will only be collected from participants fulfilling the first criterion and from participants with shock or a suspicion of sepsis (irrespective of their triage category, figure 1). Criteria to define sepsis and shock are intentionally left broad in order to recruit participants who might present with aspecific complaints and in addition include cases to serve as controls in future studies as well. Sepsis is defined based on either the physician's gestalt [15] , or when sepsis-2 or sepsis-3 criteria are met [16]. Shock is defined

as hypotension (systolic blood pressure < 90 mmHg or a decrease of > 40 mmHg compared to pre-existent) in combination with tachycardia (heart rate > 100 beats/minute). Inclusion criteria will be adapted and broadened with each new specialty participating in the biobank.

Participant recruitment

In order to allow biomaterial collection when applicable upon first contact, primary screening of patients for eligibility upon arrival in the ED is performed 24/7 by the ED-(triage)nurse together with a trained dedicated research team (*i.e.* research assistants). After identification of potentially eligible participants, the ED nurse will briefly inform participants about Acutelines. If the potential participant or his/her proxy does not refuse potential participation at that stage, blood specimens for Acutelines are collected during venipuncture for regular care. Subsequently, the research assistant informs participants and their relatives, obtains consent (by proxy), and collects and processes data and biomaterials in the ED.

Data collection

In total four team captains perform quality control by verifying all entered data according to a data verification protocol, while data managers periodically perform quality assurance of entered and imported data. Most data are captured automatically either from the hospital electronic health record (EHR; EPIC) or directly from bed-side monitors (electrophysiological waveforms and vital parameters). Surveys are used to obtain information regarding health status, frailty (if age >70), mood and depression, cognitive function (if age >70 years) and physical activities [17-23]. Surveys are filled in by participants (whenever possible) or their relatives using a tablet device at the time of presentation in the ED, their smartphone (after scanning a QR-code) or using pen/paper. Digital responses are entered directly into the research database, whilst paper responses will be entered by

the research assistant and verified by the team captain. In order to obtain information about co-morbidity and medication use at the moment of presentation, data are imported from other health care providers and from central registries when corresponding consent is given.

Study data are collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at UMCG, either by direct entry by research assistant, participant or next of kin; or by importing data from EPIC [24,25]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages and procedures for data integration and interoperability with external sources. Traffic between REDCap and the web browser is encrypted, and data are directly stored on a database server located in the UMCG and protected by a firewall. These systems are compliant with Good Clinical practice (GCP) and are ISO 27001 certified. All participants are registered under a study number, which is used during both data collection and data processing. Table 2 and supplementary figures 1 and 2 provide an overview of data collection at various time points. Acutelines' complete protocol and the actual, full data dictionary is available via https://acutelines.umcg.nl, while a summarized version of the data dictionary is shown in supplementary Table 1.

Vital parameters and cardiorespiratory waveforms

Vital parameters (Respiration rate (RR), Oxygen saturation (SaO_2) Blood pressure (BP), Heart rate (HR), Glasgow Coma Scale (GCS) and temperature are collected from prehospital data provided at handover, and the first set of observations at triage in the ED is registered. In addition, high frequency (100-500 Hertz) cardiorespiratory waveforms (electrocardiogram, arterial blood pressure,

photoplethysmogram, transthoracic impedance and airway flow and pressure) are recorded continuously for all participants from the moment of arrival-until discharge from the ED. Availability of waveforms is dependent on necessity for standard care. Waveform data are transferred from the monitoring equipment (Philip IntelliVue MX550, Koninklijke Philips N.V., Eindhoven, the Netherlands) and ventilators (Dräger Primus, Dräger, Lubeck, Germany), to a waveform platform using a hub (Capsule Neuron, CapsuleTech) with dedicated drivers (Enovation) and automatically uploaded in the bank database. Waveform data are highly valuable for development of outcome prediction models and to monitor effects of ED interventions in future studies.

Biomaterials

During the initiation phase, we will collect four types of biomaterials from participants: blood, urine, feces and hair. Once inclusion criteria are met, the following blood samples for Acutelines are drawn combined with regular blood sampling as part of standard clinical care (to streamline research efforts with clinical workflow and to avoid extra vena punctures): Plasma (citrate, EDTA, Li-heparin), Buffy coat (collected from EDTA), Serum (clot tube) and Whole blood (PAXgene RNA). In addition, the participant is asked to donate urine and feces (at the time of or within 24 hours of ED visit) and hair. The collected materials are processed in the ED and stored by trained research assistants, in accordance with Acutelines standard operating procedures (SOPs) and applicable hospital regulations: samples are logged into the REDCap database where the link between participant identity and sample barcodes is stored. Pseudonymised samples are then aliquoted into 2.0 mL QR-coded screwcap microtubes (Sarstedt, Nümbrecht, Germany) and subsequently stored in the UMCG Central Freezer Facility at -80°C. The location of samples will be registered in the biobank information management system (BIMS), which is only accessible to researchers associated with the project.

Imaging data

Indication, type of imaging performed and conclusion arising from imaging studies performed during the ED visit (including Point of care Ultrasound [POCUS] carried out for clinical- and research purposes, X-rays and CT-scans) are read from the reports by research assistants and entered in the databank. Related images are stored on the hospital Picture Archiving and Communication System (PACS) system, and linked to the Acutelines database via a unique accession number. Additionally, to be able to unravel the factors that contribute to the phycisians' clinical impression and develop a computer-driven clinical impression using artificial intelligence (AI), we will ask participants for their permission to capture a photograph and short movie (10 seconds) of the face of the participant. These photographs data will be stored on a secured server within the UMCG network, coded by an image ID and separate from other research data. The image ID can be used to look up the subject ID and in turn, using the EHR, identify the patient. This method precludes the ability to directly related image information to other personal data of the participant.

Follow-up data

At 3-months and 1-year after their ED visit patients are asked to fill in follow-up surveys about their health status and functioning, which will be send by email or regular mail. In addition, at 3-months, 1 year , 2-years and 5 years after the initial visit to the ER, laboratory results are retrieved from the hospital information system (when performed for routine patient care), and demographic data (including mortality), co-morbidities, hospitalizations and medication use can be linked with data from the general practitioner, pharmacy, municipal registry, Dutch Statistics' Office and other registries.

External data sources

To facilitate (large scale) data importation from sources outside the hospital, we aim to make use of existing connections between health care databases, such as the national support center for pharmacy (in Dutch: Landelijk Schakelpunt, LSP) the drug interaction database (IADB/Lareb) and health insurance companies (Vektis), the integral cancer center of the Netherlands (IKNL), the Pathological-Anatomical National Automated Archive (PALGA), and the Dutch institute for health care research (NIVEL) as much as possible. To obtain information about the potential date and cause-of-death, consent is sought to import data from the Municipal registry (in Dutch: basisregistratie personen, BRP) and the Dutch Statistics' office (in Dutch: Centraal Bureau Statistiek, CBS) containing up-to-date mortality data of all Dutch citizens. Linking these registries to the Acutelines database will be performed using pseudonymization and encryption, preferably via a Trusted Third Party (TTP).

Findings to date

Enrollment of the first patient occurred on September 1st 2020. During the first month, 653 patients were screened for eligibility, of which 180 were approached as potential participants. In total 151 (84%) provided consent for participation of which 89 patients fulfilled criteria for collection of biomaterials.

Strengths and limitations

- Presence of a dedicated research team to screen and include patients in the emergency department and perform data entry, quality control and quality assurance.

- Deferred consent procedure, when applicable by proxy, to allow collecting data and biomaterials prior to obtaining consent.
- Digital infrastructure to automatically capture all bed-side monitor data (*i.e.* electrophysiological waveforms, vital parameters) from every patient in the emergency department.
- Software to securely import data from other sources, such as the electronic health records of the hospital-, ambulance- and general practitioner, municipal registration, health insurance companies and pharmacy.
- A potential limitation is the relative inefficiency as patients are included based on broad inclusion criteria (*i.e.* transport, urgency, complaints), while data and biomaterials will mostly be used for subsequent studies based on specific discharge diagnosis.

Collaboration

Patient and public involvement

Acutelines was initiated based on input provided by patients who expressed a specific interest in optimization of early recognition- and treatment of acute diseases, and into long-term patient centered outcomes (such as quality of life) of acute diseases. The Acutelines protocol and regulations were written in accordance with this interest and in line with templates provided by the institutional review board, wherein the public is represented.

Data sharing

Data and biomaterials of Acutelines can be used for future studies nested within the scope of the scientific aim of Acutelines, to facilitate interdisciplinary research on the etiology and development

of acute diseases. The data management plan is in line with current best practices, including the FAIR principles for optimal reusability of data (i.e. Findable, Accessible, Interoperable and Reusable), and the GDPR regulations. The data management plan covers aspects of data standardization, harmonization, security and privacy protection, ICT infrastructure, measures to ensure data preservation and reuse. To make the data findable for others, a description of the data is included in the Groningen Data Catalog (https://groningendatacatalogus.nl/) and data is findable via Google Dataset Search (https://datasetsearch.research.google.com/). A detailed data dictionary is available upon request via acutelines@umcg.nl.

Data and/or biomaterials can be made available after filing a data access request form explaining the purpose of use, for researchers inside and outside the institute. To obtain data and/or biomaterials, researchers can submit a study proposal to the scientific board, wherein the research question is described together with type and number of biomaterials requested from the bank and a data management plan (see http://acutelines.umcg.nl/ for instructions). The board can seek epidemiological, statistical, legal or ethical advice when they evaluate the proposal based on scientific merit and solidity. If a study proposal is approved by the scientific board, subsequent medical ethical approval will have to be sought from the central review board (in Dutch: centrale toetsingscommissie: CTc) in case of non-WMO-compliant research or the medical ethical committee (in Dutch: METc) in case of WMO-compliant research. When data and/or biomaterials will be sent to external parties for processing or analysis the proper contracts (o.a. Material and Data Transfer Agreement [MDTA]) will have to be drawn up and signed in coordination with the UMCG Contract Research Office. Thereafter, data and/or biomaterials can be transferred anonymized or coded to another institute. Biometry data in the form of a photograph and small movie (10 seconds) cannot be shared with third parties.

Dissemination plan

Results of studies performed with Acutelines data will be presented on (inter)national conferences, published in (inter)national peer-reviewed journals, and will also be made available to a broader (lay) public and Acutelines participants through the dedicated website (http://acutelines.umcg/) and via social media (twitter: @Acutelines; LinkedIn: https://www.linkedin.com/company/acutelines). To facilitate outreach to general public and health care professionals, we request every researcher using data and/or biomaterials to submit a lay person summary for social media and the website, when publishing a scientific paper.

Further details

Ethical considerations

The Medical Ethics Board (in Dutch: Medisch-Ethische Toetsingscommissie, METc) and the Central Review Board (in Dutch: Centrale Toetsingscommissie, CTc) of the University Medical Center Groningen have evaluated the protocol of Acutelines and subsequent amendments and determined it is outside the scope of the Dutch Medical Research Involving Human Subjects Act (in Dutch: Wet medisch-wetenschappelijk onderzoek met mensen, WMO; registration number 2019/589). In general, biobanks in the Netherlands do not fall within the scope of the WMO. Any future amendments to the bank protocol that may potentially impact patient safety, data collection or data analysis will need to be approved by the Central Review Board of the University Medical Center Groningen.

The biobank is compliant with the Dutch Medical Treatment Agreement Act (in Dutch: Wet op de geneeskundige behandelingsovereenkomst, WGBO) and with general data protection regulations

(GDPR): a minimal amount of data from the specified population will be acquired and stored coded with a pseudonym, and data will only be made available on an individual level if required to answer the research question; in other cases aggregated data will be made available. The keylist that can be used to identify subjects and obtain personal data (*e.g.* name, address and other contact information, date of birth) can only be used by researchers employed by Acutelines who specifically need this information to fulfill their function. By exception and as allowed by the Data Protection Officer of the UMCG email address, country of origin and biometry data are stored in the research database. E-mail address is stored in a specific field labeled "identifier" to prevent it from being exported with data, while allowing us to send digital follow-up surveys. Country of the patient and his/her parents will be collected, since genetic background can be a risk factor and of influence on the presentation and course of certain diseases, which we explain to the patient when collecting these optional data.

Consent procedure: deferred consent (by proxy)

All potentially eligible patients arriving in the ED are requested to provide verbal consent first to collect data, images and biomaterials that cannot be collected at a later moment. If the patient has no capacity to consent at that moment, oral consent by a proxy will be sought. Written consent of the candidate-participant is subsequently obtained according to the principle of deferred consent: the patient is given a maximum of 30 days to read the information provided about the biobank, to ask questions (to the scientific board or to an independent expert), and to reflect on the decision to participate. If the candidate-participant is not able to give permission to participate, we will aim to obtain written permission from their legal representative according to the principle of deferred consent by proxy.

Consent is asked explicitly for collection and storage of data and biomaterials for research purposes, for obtaining data from other health care providers involved in patient care (general practitioner, EMS, pharmacist), for contacting the patient for follow-up purposes, and finally for making the (anonymized) data available to researchers allowing them to collaborate with commercial parties. Patients are informed explicitly that their genetic code may be read from the biomaterials they provided. Additional (optional) consent is sought for automated acquisition of data from health care registries, including the request to access communication data and identifying data. We request permission to contact the participant again in the future (e.g., for additional informed consent or data collection). Once patients decide to withdraw a previously given consent (possible at any moment), they will no longer be approached for follow-up, and they can in addition request to delete and destroy all collected data and biomaterials. Finally, patients are asked whether they would like to be informed about incidental findings that might arise.

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Authors' contributions

HRB drafted the first version of the biobank protocol, which was critically reviewed and edited by EtA, BCvM and JCtM. EtA drafted the manuscript of this paper, which was critically reviewed by all authors before submission.

Competing interests

The authors have not competing interests to disclose.

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References

[1] Densen P. Challenges and opportunities Facing medical education. *Trans Am Clin Climatl Assoc* 2011;122: 48-58.

[2] Smith J, Keating L, Flowerdew L et al. PSP Steering Group. An Emergency Medicine Research Priority Setting Partnership to establish the top 10 research priorities in emergency medicine. *Emerg Med J* 2017;34:454-456.

[3] van de Glind I, Berben S, Zeegers F et al. A national research agenda for pre-hospital emergency medical services in the Netherlands: a Delphi-study. *Scandinavian J Trauma, Resusc Emerg Med* 2016:24:2.

[4] NIV kennisagenda. Nederlandse internisten vereniging. Accessed on October 22th 2020 https://www.demedischspecialist.nl/sites/default/files/Kennisagenda-NIV.pdf

[5] Sole ML, Middleton A, Deaton L et al. Enrollment Challenges in Critical Care Nursing Research. *Am J Crit Care* 2017;26:395-400.

[6] Dahlber J, Eeriksen C, Robertsen A et al. Barriers and challenges in the process of including critically ill patients in clinical studies. *Scandinavian J Trauma, Resusc Emerg Med* 2020:28:6:51.

[7] Garde A, O'Hearn K, Nicholls S et al. reporting of consent rates in critoical care studies: room for improvement. *J Clin Epidemiol.* 2016;74:51-56.

[8] Appelbaum PS. Clinical practice. Assessment of patients'competence to consent to treatment. *N Engl J Med* 2007;357:1834-40.

[9] Morley C, Unwin M, Peterson GM et al. Emergency department crowding: A systematic review of causes, consequences and solutions. *PLoS One* 2018;13:e0203316

[10] Peloquin D, DiMaio M, Bierer B et al. Disruptive and avoidable: GDPR challenges to secondary research uses of data. *European Journal of Human Genetics* 2020;28:697-705.

[11] Coopersmith CM, Wunsch H, Fink MP et al. A comparison of critical care research funding and the financial burden of critical illness in the United states. *Crit care Med* 2012:40;1072-79.

[12] H Jalalzadeh, R Indrakusuma, JD Blankensteijn et al. Design and protocol of a comprehensive multicentre biobank for abdominal aortic aneurysms. *BMJ Open* 2019;9:e028858.

[13] CM Clements, JR Anderson, J Uhl et al. Biobanking in the emergency department: implementation of the Mayo Clinic Emergency Department Sepsis Biorepository. *Crit Care*. 2014; 18: P41.

[14] DR Eitel, DA Travers, AM Rosenau, N Gilboy, RC Wuerz. The emergency severity index triage algorithm version 2 is reliable and valid. *Acad Emerg Med* 2003;10:1070-80.

[15] Quinten VM, van Meurs M, Wolffensperger AE et al. Sepsis patients in the emergency department: Stratification using the clinical impression score, predisposition, infection, response and organ dysfunction score or quick sequential organ failure assessment score? *Eur J Emerg Med.* 2018;25:328-334.

[16] Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315:801-810.

[17] Perez Valdivieso JR, Bes-Rastrollo M et al. Karnofsky performance score in acute renal failure as a predictor of short-term survival. *Nephrology* 2007;12:533-538.

[18] Rabito EI, Marcadenti A, da Silva Fink J et al. Nutritional risk screening 2002, short nutritional assessment questionnaire, malnutrition screening tool, and malnutrition universal screening tool are good predictors of nutrition risk in an emergency service. *Nutr Clin Pract.* 2017;32:526-532.

[19] Laan W, Zuithoff NP, Drubbel I et al. Validity and reliability of the katz-15 scale to measure unfavorable health outcomes in community-dwelling older people. *J Nutr Health Aging*. 2014;18:848-854.

[20] Lakkis NA, Mahmassani DM. Screening instruments for depression in primary care: A concise review for clinicians. *Postgrad Med*. 2015;127:99-106.

[21] Reeve BB, Stover AM, Alfano CM et al. The piper fatigue scale-12 (pfs-12): Psychometric findings and item reduction in a cohort of breast cancer survivors. *Breast Cancer Res Treat*. 2012;136:9-20.

[22] Gierk B, Kohlmann S, Toussaint A et al. Assessing somatic symptom burden: A psychometric comparison of the patient health questionnaire-15 (phq-15) and the somatic symptom scale-8 (sss-8). *J Psychosom Res.* 2015;78:352-355.

[23] de Gelder J, Lucke JA, Blomaard LC et al. Optimization of the apop screener to predict functional decline or mortality in older emergency department patients: Cross-validation in four prospective cohorts. *Exp Gerontol.* 2018;110:253-259.

[24] PA Harris, R Taylor, R Thielk et al. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, *J Biomed Inform.* 2009;42:377-81.

[25] PA Harris, R Taylor, BL Minor et al. The REDCap consortium: Building an international community of software partners, *J Biomed Inform.* 2019;95:103208

Figure legends

Figure 1. Schematic overview of the Acutelines biobank. By collecting data from pre-hospital up to long after hospital discharge, Acutelines follows the complete acute patient journey. Specially trained research assistants screen potential participants in the ED (24/7). Waveform data and vital parameters from bed-side monitors are captured automatically, and biomaterials (i.e. blood, urine, feces) will be collected whilst awaiting deferred consent (by proxy). ED facilities allow rapid processing and storage of biomaterials (-80oC). Wearable devices are used to continue capturing waveforms and vital parameters during the first 72 hours of hospital admission. Connections with the electronic health record (EHR) and external databases (e.g. GP, pharmacy, health insurance companies) allow to collect relevant clinical data such as medication use and co-morbidity up to 5 years after presentation. Digital survey-based patient-reported outcomes will be collected on fixed intervals and survival will be monitored indefinitely using the municipal registration.

Figure 2. Inclusion criteria of patients for Acutelines in the initiation phase. Data (demographic- and medical data, waveforms) will be collected from all patients, but surveys and biomaterials will only be collected from patients with the highest- and second highest urgency triage categories (red or orange) of the Emergency Severity Index (ESI) or patients with a suspicion of sepsis or shock. Blood tube: biomaterials, pen/paper: survey, database: health data (i.e. from EHR and central registries), ECG: waveform data with vital parameters.

Supplementary figure 1. Overview of data collection in Acutelines. EHR: electronic health record; CCI: Charlson comorbidity index; LSP: national pharmacy database (in Dutch: Landelijk Schakelpunt Pharmacy); ECG: electrocardiogram; APOP: acute presenting elderly patient in the emergency room; VMS: safety management system (in Dutch: veiligheidsmanagementsysteem), Vektis: national health care insurance database; NIVEL: national database of general practitioners (GPs, in Dutch: nederlands instituut voor onderzoek van de gezondheidszorg), 4AT, 4 'A's delirium Test; 6-CIT, 6 item Cognitive Impairment Test; DOS, Delirium Observation Screening.

Supplementary figure 2. Overview of data collection using surveys in Acutelines. FHQ-6, Family History Screening Questionnaire; PSQ-18, patient satisfaction questionnaire-18; PHQ-2/9/15, Patient Health Questionnaire-2/9/15 ; GDS-15, Geriatric Depression Score-15; SNAQ, Patient-Generated Subjective Global Assessment (PS-SGA Short Form/Short Nutritional Assessment Questionnaire, SNAQ); MUST, Malnutrition Universal Screening Tool; EQ-5D-5L, 5-level EQ-5D test; Katz ADL-6, Katz activities of daily living-6; UAL, Utrecht activity list; SQUASH, Short Questionnaire to Assess Health-enhancing physical activity; OPT, outcome priorization tool.

TABLE 1.WHO trial registration dataset.

Primary registry and trial identifying number	ClinicalTrials.gov: NCT04615065
Date of registration in primary registry	October 18, 2020
Secondary identifying numbers	University Medical Center Groningen Research Registry Number 201900635
Sources of monetary of material support	University Medical Center Groningen, University of Groningen, The Netherlands
Primary sponsor	University Medical Center Groningen, University of Groningen, The Netherlands
Secondary sponsor	None
Contact for public queries	Acutelines steering group (acutelines@umcg.nl)
Contact for research queries	Acutelines steering group (acutelines@umcg.nl)
Public title	Acutelines
Scientific title	Acutelines de novo data-/biobank
Country of recruitment	Netherlands
Health conditions	Acute conditions
Interventions	None
Key inclusion-exclusion criteria (biobank protocol version 5, 09-2020)	Included are ED patients with the highest- and second highest urgency triage categories of the Manchester triage system, and patients with the third highest category when arriving by (Helicopter) Emergency Medical Service. In addition, patients with several specific conditions regardless their triage category are included: Sepsis, shock, syncope, anaphylaxis, acute renal failure, intoxications, COPD exacerbations, deep venous thrombosis or pulmonary embolism, gastrointestinal bleeding and patients who are bleeding (any source) whilst using warfarin-or DOAC.
Study Type	Observational, biobank
Date of first enrollment	September 1, 2020
Sample size	Anticipated at 3,500 per year
Recruitment status	Recruiting
Ethics approval	Status: approved Date of approval: April 8, 2020 Name and contact details of ethics committees: Institutional Review Board and Central Review Board University Medical Center Groningen Phone: +31503613564 Email: nwmoloket@umcg.nl Address: PO Box 30001 9700 RB Groningen The Netherlands
Completion Date	Not applicable (no end date defined)
Summary statement	No results yet
IPD sharing statement	Individual participant data (IPD) may be available to other researchers if needed for their specific research purposes, which amongst others must be in line with the study protocol, the informed consent form and the general data protection regulations (GDPR). Each request for re-use of data will be reviewed by Acutelines' steering group, manager and local review board (LRb), prior to establishing a material and data transfer agreement (MDTA). No IPD will be shared if not required to answer research question.

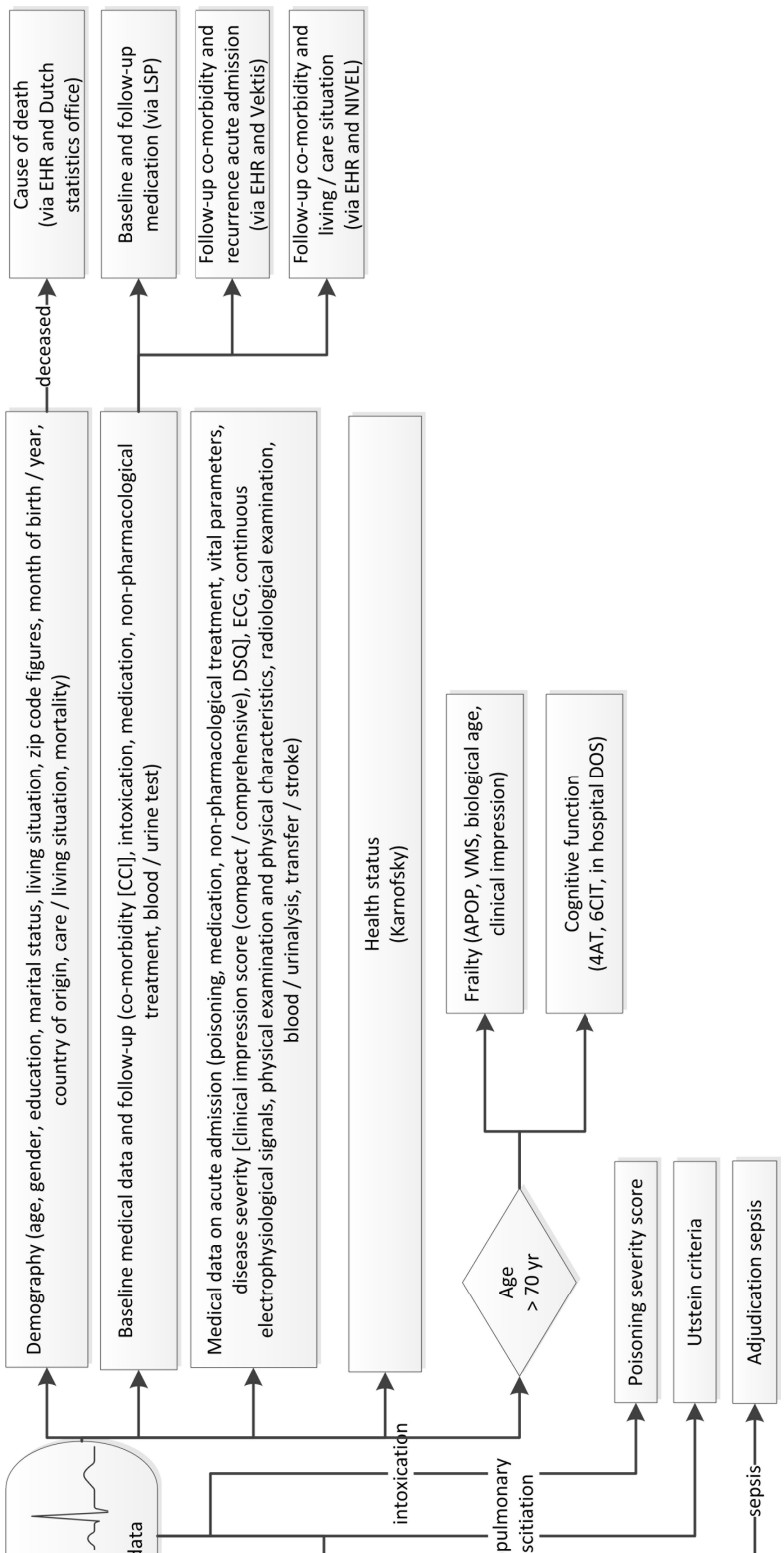
TABLE 2. Overview of data collection Acute Lines biobank

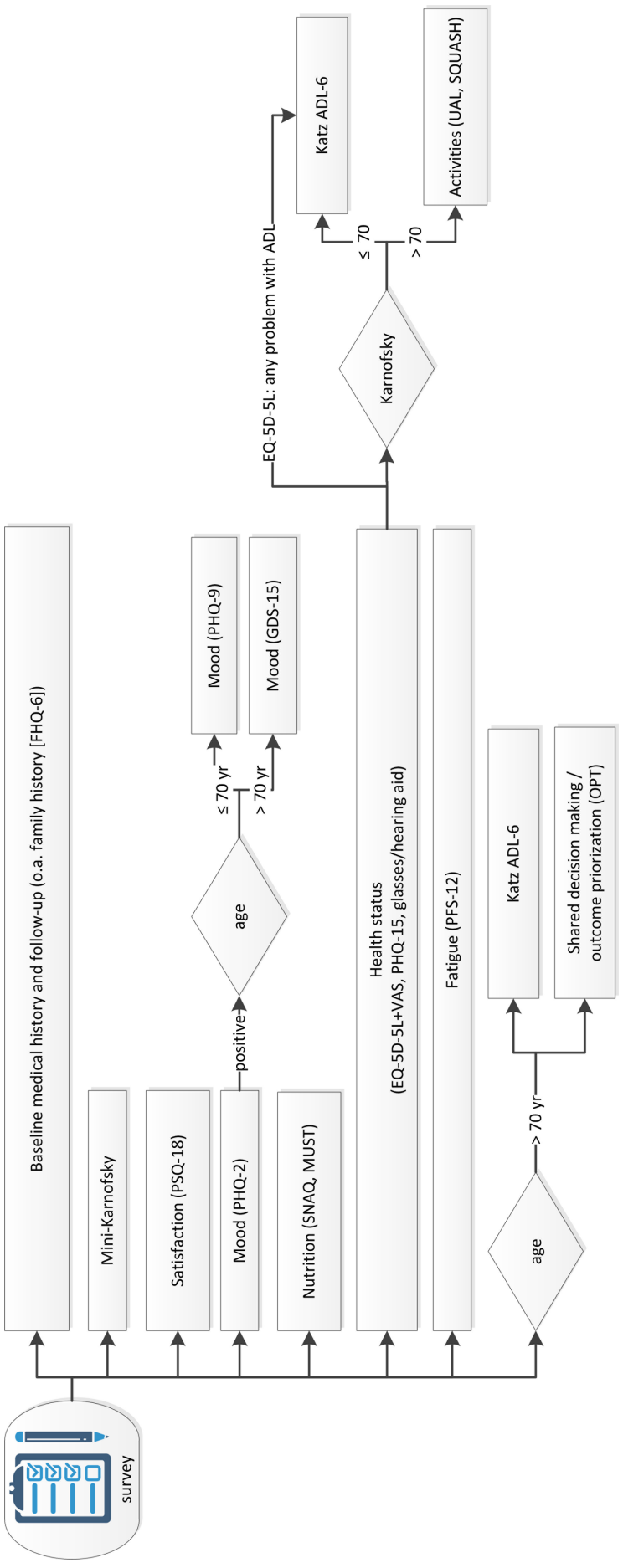
Data and biomaterials	<1yr – ED visit	Pre-hospital	**ED – 72h**	3 months	1 year	2 years	5 years	∞	
Contact info and deferred consent			**√**						Consent within 30 days
Meta data ED visit (i.e. referral, mode of transport, triage category, length of stay, decision making, final disposition)			**√**						
Presenting complaints		√	**√**						
Demographic data (i.e. gender, age, living situation, mortality, country of origin)		√	**√**	√	√	√	√	√	
Medical (family) history			**√**						
Medication use and intoxications		√	**√**	√	√	√	√		ATC level 1, 3 and 5 as defined daily dose (DDD)
Non-pharmacological treatment		√	**√**						
Vital parameters, physical examination and disease severity		√	**√**						
ECG		√	**√**						
Radiologic results			**√**						Including point-of-care ultrasound (POCUS)
Biometry			**√**						Photograph or movie (< 10 sec) of face to capture clinical impression
Laboratory results (full)		√	**√**						
Laboratory results (core set)	√	√	**√**	√	√	√	√		Kidney and liver function, lipid profile, albumin, cardiac markers, ESR and CRP
Health status			**√**	√	√				Nutrition, Karnofsky, EQ-5D-5L, PHQ-2, PHQ-15, Katz ADL-15 [if Karnofsky < 70]
Frailty screening *[if age > 65 years]*			**√**						APOP
Fatigue				√	√				Piper fatigue scale
Mood and depression *[if PHQ-2 positive]*			**√**	√	√				PHQ-9 [if age > 70 years: GDS-15]
Cognitive function *[if age > 65 years]*			**√**	√	√				4AT [in hospital], 6-CIT [in hospital], DOS [in hospital]
Physical activities *[if karnofsky > 70]*			**√**	√	√				Utrecht activity list, SQUASH
Biomaterials (plasma, serum, buffy coat, RNA, feces, urine, hair)			**√**						If triage color red or orange (hair only if COPD/asthma exacerbation)

Legend Table 2: ED, Emergency Department; ECG, Electrocardiogram; RNA, ribonucleic acid. ATC; Anatomical Therapeutic Chemical Classification system; EQ-5D-5L, 5-level EQ-5D test; PHQ-2/9/15, Patient Health Questionnaire-2/15; GDS-15, Geriatric Depression Score; 4AT, 4 'A's delirium Test; 6-CIT, 6 item Cognitive Impairment Test; DOS, Delirium Observation Screening; SQUASH, Short Questionnaire to Assess Health-enhancing physical activity. A visual overview of data to be collected is presented in supplementary figures 1 and 2.

Wireless monitoring
Patient-reported outcomes
Data transfer from the EHR
Connect with external sources to obtain long-term health data
Rapid biomaterial processing
Biometry capturing
in-patient
out-patient
Automated data capturing
24/7 screening and inclusion
Pre-hospital data connection
Acutelines

Adult patients visiting emergency room for: internal medicine (and subspecialities), gastro-enterology, pulmonology, rheumatology, emergency medicine (non-trauma)
Triage urgency
any
+
any
Complaints
any
Sepsis
Shock
any
Anaphylaxis
Intoxication
Syncope
Trombosis/embolism
GI-bleeding
Bleeding + anticoagulants
Electrolyte disturbance
Acute kidney injury
COPD exacerbation
Data / biomaterials


Cause of death
(via EHR and Dutch
statistics office)
Baseline and follow-up
medication (via LSP)
Follow-up co-morbidity and
recurrence acute admission
(via EHR and Vektis)
Follow-up co-morbidity and
living / care situation
(via EHR and NIVEL)
deceased
Demography (age, gender, education, marital status, living situation, zip code figures, month of birth / year,
country of origin, care / living situation, mortality)
Baseline medical data and follow-up (co-morbidity [CCI], intoxication, medication, non-pharmacological
treatment, blood / urine test)
Medical data on acute admission (poisoning, medication, non-pharmacological treatment, vital parameters,
disease severity [clinical impression score (compact / comprehensive), DSQ], ECG, continuous
electrophysiological signals, physical examination and physical characteristics, radiological examination,
blood / urinalysis, transfer / stroke)
Health status
(Karnofsky)
Frailty (APOP, VMS, biological age,
clinical impression)
Cognitive function
(4AT, 6CIT, in hospital DOS)
Age
> 70 yr
Poisoning severity score
Utstein criteria
Adjudication sepsis
data
intoxication
cardiopulmonary
resuscitation
sepsis


survey
Baseline medical history and follow-up (o.a. family history [FHQ-6])
Mini-Karnofsky
Satisfaction (PSQ-18)
Mood (PHQ-2)
positive
Nutrition (SNAQ, MUST)
Mood (PHQ-9)
≤ 70 yr
Mood (GDS-15)
> 70 yr
age
Health status
(EQ-5D-5L+VAS, PHQ-15, glasses/hearing aid)
Fatigue (PFS-12)
EQ-5D-5L: any problem with ADL
Karnofsky
≤ 70
Katz ADL-6
> 70
Activities (UAL, SQUASH)
Katz ADL-6
Shared decision making / outcome priorization (OPT)
> 70 yr
age

Supplementary table 1.

	<1jr-ER	Prehospital	ER-72h	3Mos	1Yr	2Yr	5Yr	∞	Explanation	Source
Communication data and consent										
Name, phone number, address, zip code, place of residence, e-mail address and the UMCG-number of participants			√						This data will not be stored in the research database, but will be kept in the electronic patient file	Participant and/or representative
Relationship with participant, name, phone number and e-mail address form first contact			√						This data will not be stored in the research database, but will be kept in the electronic patient file (except e-mail address, which will be stored in a hidden field in the research database to be able to send digital surveys)	Participant and/or representative
Consent			√						Consent from participant and/or representative, date	Participant and/or representative
Biometry: photograph/short movie of face			√[1]						Photograph and short movie (10 seconds) of face	Participant
Data regarding ER visit										
Logistics		√	√						Such as type of transport, time of notification, time of patient arrival, zip code (numbers), urgency (A1, A2, B), date and time of entering ER, time leaving ER, number of patients in ER (in treatment and waiting room), number of consultations	Electronic patient file, general practitioner, Ambulance Care/MMT Electronic File , observations and measurements
Triage			√						Such as triage time, triage urgency code	Electronic patient file
Practitioner			√						Such as department to which the patient is assigned, time of	Electronic patient file, interview with

									arrival of practitioner (first patient contact), practitioner type (resident, attending), years of work experience after completion of study/training, algorithm primary care	practitioner
Complaints			√						Main complaint (s) and findings at anamnesis, graded by severity and categorized by tract	Electronic patient file, general practitioner, Ambulance Care/MMT Electronic File , observations and measurements
Shared decision making			√[1]						- Patient satisfaction questionnaire (PSQ-18)(1) - Outcome Priorization Tool (OPT) (2)	Questionnaires
Demographic data										
Age when visiting ER			√							Electronic patient file
Gender			√							Electronic patient file
Highest completed education			√							Electronic patient file, (proxy) history, questionnaire
Marital status			√	√	√					Electronic patient file, (proxy) history, questionnaire
Living situation			√	√	√					Electronic patient file, (proxy)history, questionnaire
Zip code (only numbers)			√	√	√					Electronic patient file
Birth month and year			√							Electronic patient file
Country of origin (self and parents)			√							Electronic patient file, (proxy) history, questionnaire
Care/living situation			√	√	√	√	√		Such as use of home care, living independently, care/nursing home, recurrence acute	Electronic patient file, general practitioner, health insurance,

									admissions	questionnaire
Mortality			√	√	√	√	√	√	Date and cause of death	Electronic patient file, general practitioner, municipal registration, Dutch statistics' office
Medical and physical data										
Family history			√						Family History Screening Questionnaire (FHQ-6)	
Intoxication			√	√	√				Such as alcohol, tobacco, drugs (in case of intoxication as reason of visiting, supplemented with ingested agent, dose, route of exposure, intention)	(hetero)anamnesis , questionnaire
Comorbidity			√	√	√	√	√		Charlson Comorbidity Index , supplemented with pregnancy, transplant (year, type) and malignancy (type, curative/palliative treatment)	Electronic patient file, general practitioner, integral cancer center of the Netherlands (IKNL), Pathological-Anatomical National Automated Archive (PALGA), Dutch institute for health care research (NIVEL), (hetero)anamnesis
Medication		√	√	√	√	√	√		Anatomical Therapeutic Chemical Classification System (ATC) level 1, 3 and 5, defined daily dose (DDD)	Electronic patient file, general practitioner, pharmacy, Ambulance Care/MMT Electronic File , (hetero)anamnesis
Non-pharmacological treatment		√	√						Including treatment instructions, oxygen administration, intravenous line, resuscitation (Utstein criteria , use of AED), advanced treatment (such as intubation, transfusion, thoracostomy), decontamination (in	Electronic patient file, general practitioner, ambulance care/MMT, observations, (hetero)anamnesis

									case of CBRN)	
Vital parameters		√	√						Such as blood pressure, heart rate, respiratory rate, oxygen saturation, consciousness, temperature, diuresis, pain score	Electronic patient file, general practitioner, Ambulance Care/MMT Electronic File, observations and measurements
Disease severity			√						Such as clinical eye score , double surprise question (DSQ)	Interview practitioner at ER (estimation practitioner), (proxy) history (own estimation)
ECG		√	√						Such as rhythm, beats per minute, P-top, conduction times (PR, QRS, QT), type of AV block, ST depression/elevation	Electronic patient file
Continuous electrophysiological signals			√						Such as ECG, plethysmography, respiratory rate	Bed-side monitor of wearable
Physical examination and traits		√	√						Such as length, weight, aspect of skin	Electronic patient file, general practitioner, ambulance care/MMT, observations and measurements
Radiological examination			√						Outcome point-of-care ultrasound (POCUS), chest X-ray, abdomen, CT cerebrum, chest CT, CT abdomen if performed	Electronic patient file
Blood and urine tests	√[3]	√	√	√[3]	√[3]	√[3]	√[3]		Cytometric, biochemical and microbiological results	Electronic patient file
Transfer/discharge			√						Admission department(s) and date of discharge	Electronic patient file
Health status and functionality										
Nutrition and weight			√	√	√				- Patient-Generated Subjective Global Assessment (PS-SGA Short Form/Short Nutritional	Electronic patient file, (hetero)anamnesis , questionnaires

									Assessment Questionnaire, SNAQ) - Malnutrition Universal Screening Tool (MUST)	
Frailty of the elderly			√[2]						- Acute presenting elderly patient in the emergency room (APOP) - Estimate older/younger than calendar age	(Hetero)anamnesis, observations
Global functioning, complaints, mood and experienced health			√	√	√				- Karnofsky - 5-level EQ-5D version 5L (EQ-5D-5L+VAS) - Patient Health Questionnaire 2 (PHQ-2) - Patient Health Questionnaire-15 (PHQ-15) - Wearing glasses, hearing aid	(Hetero)anamnesis, questionnaires
Fatigue				√	√				Piper Fatigue Scale-12 (PFS-12)	
IADL			√[2,4]	√[2,4]	√[2,4]				Katz ADL-15	Questionnaires
Mood			√[5]	√[5]	√[5]				**≤ 65 years old:** Patient Health Questionnaire 9 (PHQ-9) **> 65 years old:** Geriatric Depression Scale-15 (GDS-15)	Questionnaires
Cognitive functioning (delirium and dementia, hospitalization)			√[2]						- 4AT - 6-Item Cognitive Impairment Test (6-CIT) - Delier observatie score (DOS)	(Hetero)anamnesis, Electronic patient file and observations
Physical activities			√[6]	√[6]	√[6]				- Utrechtse activities list (UAL) (19) - Short Questionnaire to Assess Health-Enhancing Activity (SQUASH) (20,21)	Questionnaires
Biomaterial										
Plasma			√[7]						Citrate, 1x 6 ml; EDTA, 1x 10 ml; Li-heparin, 1x 9ml[9]	

Buffy coat			√[7]						From EDTA tube[9]	
Serum			√[7]						Coagulation tube, 1x 10 ml[9]	
Whole blood/RNA			√[7]						PAXgene whole blood, 1x 10 ml[9]	
Urine			√[7]						1x 11 ml (<24 hr after start ER visit)[9]	
Feces			√[7]						1 container (<24 hr after start ER visit)[9]	
Hair			√[8]						0.5 cm of hair	

Footnotes Supplementary Table 1.

1. Only when triage colour is red or orange, or when patient presents with shock or sepsis, confined to ED stay.
2. Only when aged >70.
3. Confined to electrolytes, renal function, liver function, lipids, albimin, NTproBNP, HsTropT, CRP, CBC, sedimentation rate and PaO2.
4. Only when EQ-5D-5L demonstrates problems with ADL or Karnofsky ≤ 70.
5. Only when PHQ-2 positive.
6. Only when Karnofsky >70.
7. Only when triage color is red or orange, or when patient presents with shock or sepsis; for blood limited to ED stay, urine/feces to be collected within 24 hours.
8. Only when presenting with COPD exacerbation.

References Supplementary Table 1

1. Thayaparan AJ, Mahdi E. The patient satisfaction questionnaire short form (psq-18) as an adaptable, reliable, and validated tool for use in various settings. Med Educ Online. 2013;18:21747.

2. Stegmann ME, Festen S, Brandenbarg D, et al. Using the outcome prioritization tool (opt) to assess the preferences of older patients in clinical decision-making: A review. Maturitas. 2019;128:49-52.

3. Walter FM, Prevost AT, Birt L, et al. Development and evaluation of a brief self-completed family history screening tool for common chronic disease prevention in primary care. Br J Gen Pract. 2013;63:e393-400.

4. Brusselaers N, Lagergren J. The charlson comorbidity index in registry-based research. Methods Inf Med. 2017;56:401-406.

5. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update of the utstein resuscitation registry templates for out-of-hospital cardiac arrest: A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (american heart association, european resuscitation council, australian and new zealand council on resuscitation, heart and stroke foundation of canada, interamerican heart foundation, resuscitation council of southern africa, resuscitation council of asia); and the american heart association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, perioperative and resuscitation. Circulation. 2015;132:1286-1300.

6. Quinten VM, van Meurs M, Wolffensperger AE, et al. Sepsis patients in the emergency department: Stratification using the clinical impression score, predisposition, infection, response and

organ dysfunction score or quick sequential organ failure assessment score? Eur J Emerg Med. 2018;25:328-334.

7. Veldhoven CMM, Nutma N, De Graaf W, et al. Screening with the double surprise question to predict deterioration and death: An explorative study. BMC Palliat Care. 2019;18:118.

8. Balstad TR, Bye A, Jenssen CR, et al. Patient interpretation of the patient-generated subjective global assessment (pg-sga) short form. Patient Prefer Adherence. 2019;13:1391-1400.

9. Rabito EI, Marcadenti A, da Silva Fink J, et al. Nutritional risk screening 2002, short nutritional assessment questionnaire, malnutrition screening tool, and malnutrition universal screening tool are good predictors of nutrition risk in an emergency service. Nutr Clin Pract. 2017;32:526-532.

10. de Gelder J, Lucke JA, Blomaard LC, et al. Optimization of the apop screener to predict functional decline or mortality in older emergency department patients: Cross-validation in four prospective cohorts. Exp Gerontol. 2018;110:253-259.

11. Perez Valdivieso JR, Bes-Rastrollo M, Monedero P, et al. Karnofsky performance score in acute renal failure as a predictor of short-term survival. Nephrology (Carlton). 2007;12:533-538.

12. Janssen MF, Bonsel GJ, Luo N. Is eq-5d-5l better than eq-5d-3l? A head-to-head comparison of descriptive systems and value sets from seven countries. Pharmacoeconomics. 2018;36:675-697.

13. Mitchell AJ, Yadegarfar M, Gill J, et al. Case finding and screening clinical utility of the patient health questionnaire (phq-9 and phq-2) for depression in primary care: A diagnostic meta-analysis of 40 studies. BJPsych Open. 2016;2:127-138.

14. Gierk B, Kohlmann S, Toussaint A, et al. Assessing somatic symptom burden: A psychometric comparison of the patient health questionnaire-15 (phq-15) and the somatic symptom scale-8 (sss-8). J Psychosom Res. 2015;78:352-355.

15. Reeve BB, Stover AM, Alfano CM, et al. The piper fatigue scale-12 (pfs-12): Psychometric findings and item reduction in a cohort of breast cancer survivors. Breast Cancer Res Treat. 2012;136:9-20.

16. Laan W, Zuithoff NP, Drubbel I, et al. Validity and reliability of the katz-15 scale to measure unfavorable health outcomes in community-dwelling older people. J Nutr Health Aging. 2014;18:848-854.

17. Lakkis NA, Mahmassani DM. Screening instruments for depression in primary care: A concise review for clinicians. Postgrad Med. 2015;127:99-106.

18. O'Sullivan D, Brady N, Manning E, et al. Validation of the 6-item cognitive impairment test and the 4at test for combined delirium and dementia screening in older emergency department attendees. Age Ageing. 2018;47:61-68.

19. Post MWM. Utrechtse activiteitenlijst. In: van Asbeck FWA, editor. Handboek dwarslaesierevalidatie. Houten: Bohn Stafleu van Loghum; 1998. p. 356-357.

20. Wendel-Vos GC, Schuit AJ, Saris WH, et al. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56:1163-1169.

21. Campbell N, Gaston A, Gray C, et al. The short questionnaire to assess health-enhancing (squash) physical activity in adolescents: A validation using doubly labeled water. J Phys Act Health. 2016;13:154-158.

BMJ Open

Cohort profile of Acutelines: a Large Data-/Biobank of Acute and Emergency Medicine.

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Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Infectious diseases, Research methods, Emergency medicine
Keywords:	ACCIDENT & EMERGENCY MEDICINE, GENERAL MEDICINE (see Internal Medicine), INTERNAL MEDICINE

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Cohort profile of Acutelines: a Large Data-/Biobank of Acute and Emergency Medicine.

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Abstract

Purpose: research in acute care faces many challenges, including enrollment challenges, legal limitations in data sharing, limited funding, and lack of singular ownership of the domain of acute care. To overcome these challenges, the Center of Acute Care of the University Medical Center Groningen in the Netherlands, has established a de novo data-, image- and biobank named "Acutelines".

Participants: clinical data, imaging data and biomaterials (*i.e.* blood, urine, feces, hair) are collected from patients presenting to the Emergency Department (ED) with a broad range of acute disease presentations. A deferred consent procedure (by proxy), is in place to allow collecting data and biomaterials prior to obtaining written consent. The digital infrastructure used ensures automated capturing of all bed-side monitoring data (*i.e.* vital parameters, electrophysiological waveforms), and securely importing data from other sources, such as the electronic health records of the hospital, ambulance and general practitioner, municipal registration and pharmacy. Data are collected from all included participants during the first 72-hours of their hospitalization, while follow-up data is collected at 3-months, 1-year, 2-years and 5 years after their ED visit.

Findings to date: enrollment of the first participant occurred on September 1st 2020. During the first month, 653 participants were screened for eligibility, of which 180 were approached as potential participants. In total 151 (84%) provided consent for participation of which 89 participants fulfilled criteria for collection of biomaterials.

Future plans: the main aim of Acutelines is to facilitate research in acute medicine by providing the framework for novel studies and issuing data, images and biomaterials for future research. The protocol will be extended by connecting with central registries to obtain long-term follow-up data, for which we already request permission from the participant.

Registration: the Acutelines biobank is registered under trial registration number NCT04615065 at ClinicalTrials.gov (table1).

Strengths and limitations

- Presence of a dedicated research team to screen and include patients in the emergency department and perform data entry, quality control and quality assurance.
- Deferred consent procedure, when applicable by proxy, to allow the collection of data and biomaterials prior to obtaining consent.
- Digital infrastructure to automatically capture all bed-side monitor data (*i.e.* electrophysiological waveforms, vital parameters) from every patient in the emergency department.
- Software to securely connect with other sources, such as the electronic health records of the hospital-, ambulance- and general practitioner, municipal registration, health insurance companies and pharmacy.
- A potential limitation is the relative inefficiency as patients are included based on broad inclusion criteria (*i.e.* transport, urgency, complaints), while data and biomaterials will mostly be used for subsequent studies based on specific discharge diagnosis.

Introduction

Research in Acute Care is important to prevent diseases, and to establish best practices for treatments of many acute conditions. Over the past 50 years, medical knowledge has grown exponentially, and specialties as Emergency Medicine and Acute Internal medicine have developed rapidly.[1] Despite this, knowledge gaps still exist. Amongst these are logistics of care (optimal patient disposition, triage, and prevention of crowding), the development of tools for early recognition of acutely sick patients (including risk prediction models, biomarkers and/or artificial intelligence), and the development of more patient centered and personalized care for specific subgroups presenting in the emergency department (ED), such as the frail elderly population, patients with psychiatric illnesses and patients with (early) sepsis. [2-4]

However, conducting research in acute care may prove difficult for various reasons. First, enrollment challenges often limit the number of participants eligible to participate in clinical studies [5,6]. As many acute conditions are time sensitive and expedited diagnostic evaluation and/or initiation of treatment is warranted, this is normally prioritized over study enrollment. Further, obtaining consent from acutely ill patients to participate in clinical studies can be challenging or even impossible, especially when a proxy or legal representative is not available to emergency medical services (EMS) or emergency department (ED) personnel to discuss study aims- and risks within the enrollment window [7,8]. Finally, availability of staff for enrollment of participants can be an issue with increasing pressure on healthcare systems and the resultant crowding of Emergency departments (ED's) in many countries. [9]

Second, in order to gain more insight into the natural course of acute diseases, and to be able to investigate which patients will deteriorate rapidly during the course of their disease, it is important

to collect data from the start of their disease onwards until they are fully recovered or died. However, this is often difficult to achieve due to legal limitations in data sharing. Data transfer for clinical research between various organization involved in the care for a particular patient and the secondary research use of data- and or biomaterials can only occur with explicit permission of the patient. [10]. As with consent, timely permission is often not possible to obtain. Further, no single specialism is the "owner" of acute care. Although the organization of healthcare systems may vary from one country to the other, acute care is multidisciplinary by nature. Research interests and priorities may vary between specialties involved, which may complicate conduct of clinical studies. Finally, it can be a challenge to obtain funding for acute care research. Although researchers may apply for government sponsored grants of organizations as the National Institute of Health (NIH) or the Dutch research Council (NWO), the number of grants funded by these institutions related to acute care are low [11], and additional funding is often required.

In an attempt to overcome some of these aforementioned challenges, the Center of Acute Care of the University hospital Groningen in the Netherlands, has established a de novo data, image- and biobank named "Acutelines". AcuteLines is unique, as it is not aimed at one specific disease or condition as other critical care biobanks [12,13], but instead collects data, imaging and biomaterials from as many patients presenting with acute conditions as possible, aiming to explore the association between pre-existing health, acute illness and (long term) outcome. (Figure 1) The objective of this manuscript is to describe the process by which we established Acutelines, and how we integrated operations into ED clinical workflow allowing Acutelines to operate 24 hours a day, seven days a week (24/7).

Cohort description

Study design

Acutelines is a prospective data-, image- and biobank including patients with a broad spectrum of acute conditions. Its aim is to facilitate interdisciplinary research on the etiology and development of acute diseases with the aid of systematically collected biomaterials and medical data over various time points, both during the course of the patient's disease and after recovery. Acutelines is initiated by the departments of Emergency Medicine and Internal Medicine of the University Medical Center Groningen, the Netherlands, and registered in ClinicalTrials.gov (see table 1 for WHO trial registration dataset) and in the Groningen data catalogue. The latest biobank protocol and regulations are accessible via http://acutelines.umcg.nl. The biobank is governed by a three-person scientific committee (HB, JtM and EtA) with oversight of a trustee (BvM), and supported by two data managers (RvW and ST) and a team of research assistants, led by team captains (StH, TTH, LvH FvB, FvdV).

Setting

All patients admitted to the ED of the UMCG, a large tertiary care center with approximately 26,000 ED visits per year, for specialties participating in Acutelines are screened for eligibility. Participating specialties during the (current) initiation phase of the biobank are: emergency medicine, internal medicine (including sub-specializations as allergology, acute medicine, oncology, hematology, infectiology, nephrology, vascular medicine, geriatric medicine), pulmonology, gastro-enterology and rheumatology. The scientific board of Acutelines aims to allow participation of other specialties as well in the near future after the initiation phase. The ultimate goal of Acutelines is to generate a biobank for acute diseases with a high scientific merit, that is logistically efficient and financially sustainable, and can become a resource to both academic and industry partners. The sample size of

the biobank is directly related to available funding, which allows us to include approximately 3,500 participants/year in the initiation phase. This number is likely to expand once more specialties will participate, and/or when external parties will apply for the use of data and samples from the bank. The first participant was enrolled on September 1st, 2020. Acutelines does not have a fixed end date or sample size.

Eligibility criteria

To be eligible for inclusion, according to the latest version of the Acutelines protocol participants have to meet at least one of the following criteria (Figure 2):

- Patients with the highest- and second highest urgency triage categories (red or orange) of the Emergency Severity Index (ESI) [14].
- Patients with the third highest category urgency triage category (yellow) of the ESI when arriving by (Helicopter) Emergency Medical Service
- Patients with several specific conditions regardless their triage category are included: sepsis, shock, syncope, anaphylaxis, acute renal failure, electrolyte disturbances intoxications, COPD and asthma exacerbations, (suspicion of) deep venous thrombosis or pulmonary embolism, gastrointestinal bleeding and patients who are bleeding (any source) whilst using vitamin-K antagonists or DOAC.

While data- and imaging will be collected from all included participants, biomaterials will only be collected from participants fulfilling the first criterion and from participants with shock or a suspicion of sepsis (irrespective of their triage category, figure 1). Criteria to define sepsis and shock are intentionally left broad in order to recruit participants who might present with aspecific complaints and in addition include cases to serve as controls in future studies as well. Sepsis is defined based on either the physician's gestalt [15] , or when sepsis-2 or sepsis-3 criteria are met [16]. Shock is defined

as hypotension (systolic blood pressure < 90 mmHg or a decrease of > 40 mmHg compared to pre-existent) in combination with tachycardia (heart rate > 100 beats/minute). Inclusion criteria will be adapted and broadened with each new specialty participating in the biobank.

Participant recruitment

In order to allow biomaterial collection when applicable upon first contact, primary screening of patients for eligibility upon arrival in the ED is performed 24/7 by the ED-(triage)nurse together with a trained dedicated research team (*i.e.* research assistants), and it is the ambition to recruit patients 24/7 staffing allowed. After identification of potentially eligible participants, the ED nurse will briefly inform participants about Acutelines. If the potential participant or his/her proxy does not refuse potential participation at that stage, blood specimens for Acutelines are collected during venipuncture for regular care. Subsequently, the research assistant informs participants and their relatives, obtains consent (by proxy), and collects and processes data and biomaterials in the ED.

Data collection

In total four team captains perform quality control by verifying all entered data according to a data verification protocol, while data managers periodically perform quality assurance of entered and imported data. Most data are captured automatically either from the hospital electronic health record (EHR; EPIC) or directly from bed-side monitors (electrophysiological waveforms and vital parameters). Surveys are used to obtain information regarding health status, frailty (if age ≥ 70), mood and depression, cognitive function (if age ≥ 70 years) and physical activities [17-23]. Surveys are filled in by participants (whenever possible) or their relatives using a tablet device at the time of presentation in the ED, their smartphone (after scanning a QR-code) or using pen/paper. Digital responses are entered directly into the research database, whilst paper responses will be entered by

the research assistant and verified by the team captain. In order to obtain information about co-morbidity and medication use at the moment of presentation, data are imported from other health care providers and from central registries when corresponding consent is given.

Study data are collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at UMCG, either by direct entry by research assistant, participant or next of kin; or by importing data from EPIC [24,25]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages and procedures for data integration and interoperability with external sources. Traffic between REDCap and the web browser is encrypted, and data are directly stored on a database server located in the UMCG and protected by a firewall. These systems are compliant with Good Clinical practice (GCP) and are ISO 27001 certified. All participants are registered under a study number, which is used during both data collection and data processing. Table 2 and supplementary figures 1 and 2 provide an overview of data collection at various time points. Acutelines' complete protocol and the actual, full data dictionary is available via https://acutelines.umcg.nl, while a summarized version of the data dictionary is shown in supplementary document 1.

Vital parameters and cardiorespiratory waveforms

Vital parameters (Respiration rate (RR), Oxygen saturation (SaO_2) Blood pressure (BP), Heart rate (HR), Glasgow Coma Scale (GCS) and temperature are collected from prehospital data provided at handover, and the first set of observations at triage in the ED is registered. In addition, high frequency (100-500 Hertz) cardiorespiratory waveforms (electrocardiogram, arterial blood pressure,

photoplethysmogram, transthoracic impedance and airway flow and pressure) are recorded continuously for all participants from the moment of arrival-until discharge from the ED. Availability of waveforms is dependent on necessity for standard care. Waveform data are transferred from the monitoring equipment (Philip IntelliVue MX550, Koninklijke Philips N.V., Eindhoven, the Netherlands) and ventilators (Dräger Primus, Dräger, Lubeck, Germany), to a waveform platform using a hub (Capsule Neuron, CapsuleTech) with dedicated drivers (Enovation) and automatically uploaded in the bank database. Waveform data are highly valuable for development of outcome prediction models and to monitor effects of ED interventions in future studies.

Biomaterials

During the initiation phase, we will collect four types of biomaterials from participants: blood, urine, feces and hair. Once inclusion criteria are met, the following blood samples for Acutelines are drawn combined with regular blood sampling as part of standard clinical care (to streamline research efforts with clinical workflow and to avoid extra vena punctures): Plasma (citrate, EDTA, Li-heparin), Buffy coat (collected from EDTA), Serum (clot tube) and Whole blood (PAXgene RNA). In addition, the participant is asked to donate urine and feces (at the time of or within 24 hours of ED visit) and hair. The collected materials are processed in the ED and stored by trained research assistants, in accordance with Acutelines standard operating procedures (SOPs) and applicable hospital regulations: samples are logged into the REDCap database where the link between participant identity and sample barcodes is stored. Pseudonymised samples are then aliquoted into 2.0 mL QR-coded screwcap microtubes (Sarstedt, Nümbrecht, Germany) and subsequently stored in the UMCG Central Freezer Facility at -80°C. The location of samples will be registered in the biobank information management system (BIMS), which is only accessible to researchers associated with the project.

Imaging data

Indication, type of imaging performed and conclusion arising from imaging studies performed during the ED visit (including Point of care Ultrasound [POCUS] carried out for clinical- and research purposes, X-rays and CT-scans) are read from the reports by research assistants and entered in the databank. Related images are stored on the hospital Picture Archiving and Communication System (PACS) system, and linked to the Acutelines database via a unique accession number. Additionally, to be able to unravel the factors that contribute to the phycisians' clinical impression and develop a computer-driven clinical impression using artificial intelligence (AI), we will ask participants for their permission to capture a photograph and short movie (10 seconds) of the face of the participant. These photographs data will be stored on a secured server within the UMCG network, coded by an image ID and separate from other research data. The image ID can be used to look up the subject ID and in turn, using the EHR, identify the patient. This method precludes the ability to directly related image information to other personal data of the participant.

Follow-up data

At 3-months and 1-year after their ED visit patients are asked to fill in follow-up surveys about their health status and functioning, which will be send by email or regular mail. In addition, at 3-months, 1 year , 2-years and 5 years after the initial visit to the ER, laboratory results are retrieved from the hospital information system (when performed for routine patient care), and demographic data (including mortality), co-morbidities, hospitalizations and medication use can be linked with data from the general practitioner, pharmacy, municipal registry, Dutch Statistics' Office and other registries.

External data sources

To facilitate (large scale) data importation from sources outside the hospital, we aim to make use of existing connections between health care databases, such as the national support center for pharmacy (in Dutch: Landelijk Schakelpunt, LSP) the drug interaction database (IADB/Lareb) and health insurance companies (Vektis), the integral cancer center of the Netherlands (IKNL), the Pathological-Anatomical National Automated Archive (PALGA), and the Dutch institute for health care research (NIVEL) as much as possible. To obtain information about the potential date and cause-of-death, consent is sought to obtain data from the Municipal registry (in Dutch: basisregistratie personen, BRP) and the Dutch Statistics' office (in Dutch: Centraal Bureau Statistiek, CBS) containing up-to-date mortality data of all Dutch citizens. Linking these registries to the Acutelines database will be performed using pseudonymization and encryption, preferably via a Trusted Third Party (TTP).

Findings to date

Enrollment of the first patient occurred on September 1st 2020. During the first month, 653 patients were screened for eligibility, of which 180 were approached as potential participants. In total 151 (84%) provided consent for participation of which 89 patients fulfilled criteria for collection of biomaterials.

Collaboration

Patient and public involvement

Acutelines was initiated based on input provided by patients who expressed a specific interest in optimization of early recognition- and treatment of acute diseases, and into long-term patient centered outcomes (such as quality of life) of acute diseases. The Acutelines protocol and regulations were written in accordance with this interest and in line with templates provided by the institutional review board, wherein the public is represented.

Data sharing

Data and biomaterials of Acutelines can be used for future studies nested within the scope of the scientific aim of Acutelines, to facilitate interdisciplinary research on the etiology and development of acute diseases. The data management plan is in line with current best practices, including the FAIR principles for optimal reusability of data (i.e. Findable, Accessible, Interoperable and Reusable), and the GDPR regulations. The data management plan covers aspects of data standardization, harmonization, security and privacy protection, ICT infrastructure, measures to ensure data preservation and reuse. To make the data findable for others, a description of the data is included in the Groningen Data Catalog (https://groningendatacatalogus.nl/) and data is findable via Google Dataset Search (https://datasetsearch.research.google.com/). A detailed data dictionary is available upon request via acutelines@umcg.nl.

Data and/or biomaterials can be made available after filing a data access request form (supplementary document 2 : data access request form) explaining the purpose of use, for researchers inside and outside the institute. To obtain data and/or biomaterials, researchers can submit a study proposal to the scientific board, wherein the research question is described together with type and number of biomaterials requested from the bank and a data management plan (see http://acutelines.umcg.nl/ for instructions). The board can seek epidemiological, statistical, legal or

ethical advice when they evaluate the proposal based on scientific merit and solidity. If a study proposal is approved by the scientific board, subsequent medical ethical approval will have to be sought from the central review board (in Dutch: centrale toetsingscommissie: CTc) in case of non-WMO-compliant research or the medical ethical committee (in Dutch: METc) in case of WMO-compliant research. Data access will be unrestricted and non-exclusive for the purpose of the proposed study, in return for co-authorship and a financial compensation dependent on both the number of data points/ biomaterial required and the funding source (academic request vs. industry). When data and/or biomaterials will be sent to external parties for processing or analysis, contracts and a Material and Data Transfer Agreement [MDTA) will have to be drawn up and signed in coordination with the UMCG Contract Research Office. Thereafter, data and/or biomaterials can be transferred anonymized or coded to another institute. Biometry data in the form of a photograph and small movie (10 seconds) cannot be shared with third parties. Upon data extraction subjects are labeled with a project specific identifier to prevent the possibility of cross linking large amounts of data using multiple data requests.

Dissemination plan

Results of studies performed with Acutelines data will be presented on (inter)national conferences, published in (inter)national peer-reviewed journals, and will also be made available to a broader (lay) public and Acutelines participants through the dedicated website (http://acutelines.umcg/) and via social media (twitter: @Acutelines; LinkedIn: https://www.linkedin.com/company/acutelines). To facilitate outreach to general public and health care professionals, we request every researcher using data and/or biomaterials to submit a lay person summary for social media and the website, when publishing a scientific paper.

Further details

Ethical considerations

The Medical Ethics Board (in Dutch: Medisch-Ethische Toetsingscommissie, METc) and the Central Review Board (in Dutch: Centrale Toetsingscommissie, CTc) of the University Medical Center Groningen have evaluated and approved the protocol of Acutelines (2019/589), which has also been ISO certified (9001:2008 Healthcare). In general, biobanks in the Netherlands do not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (in Dutch: Wet medisch-wetenschappelijk onderzoek met mensen, WMO). Any future amendments to the bank protocol that may potentially impact patient safety, data collection or data analysis will need to be approved by the Central Review Board of the University Medical Center Groningen.

The biobank is compliant with the UMCG guidance for data-biobanking (available upon request, in Dutch only), the Dutch Medical Treatment Agreement Act (in Dutch: Wet op de geneeskundige behandelingsovereenkomst, WGBO) and with general data protection regulations (GDPR): a minimal amount of data from the specified population will be acquired and stored coded with a pseudonym (data minimization principle), and data will only be made available on an individual level if required to answer the research question; in other cases aggregated data will be made available. The keylist that can be used to identify subjects and obtain personal data (*e.g.* name, address and other contact information, date of birth) can only be used by researchers employed by Acutelines who specifically need this information to fulfill their function. By exception and as allowed by the Data Protection Officer of the UMCG email address, country of origin and biometry data are stored in the research database. E-mail address is stored in a specific field labeled “identifier” to prevent it from being exported with data, while allowing us to send digital follow-up surveys. Country of the patient and his/her parents will be collected, since genetic background can be a risk factor and of influence on

the presentation and course of certain diseases, which we explain to the patient when collecting these optional data.

Consent procedure: deferred consent (by proxy) and opt-out

All potentially eligible patients arriving in the ED are requested to provide verbal consent first to collect data, images and biomaterials that cannot be collected at a later moment. If the patient has no capacity to consent at that moment, oral consent by a proxy will be sought. Written consent of the candidate-participant is subsequently obtained according to the principle of deferred consent: the patient is given a maximum of 30 days to read the information provided about the biobank, to ask questions (to the scientific board or to an independent expert), and to reflect on the decision to participate. If the candidate-participant is not able to give permission to participate, we will aim to obtain written permission from their legal representative according to the principle of deferred consent by proxy. In the exceptional situation that potential candidate-participants and their legal representatives cannot be reached, data/biomaterials may be stored for future research according to an opt-out procedure whereby the UMCG research objection registry will be checked.

Consent is asked explicitly for collection and storage of data and biomaterials for research purposes, for obtaining data from other health care providers involved in patient care (general practitioner, EMS, pharmacist), for contacting the patient for follow-up purposes, and finally for making the (pseudo-anonymized) data available to researchers allowing them to collaborate with commercial parties. Patients are informed explicitly that their genetic code may be read from the biomaterials they provided. Additional (optional) consent is sought for automated acquisition of data from health care registries, including the request to access communication data and identifying data. We request permission to contact the participant again in the future (e.g., for additional informed consent or data collection). Once patients decide to withdraw a previously given consent (possible at any

moment), they will no longer be approached for follow-up, and they can in addition request to delete and destroy all collected data and biomaterials. Finally, patients are asked whether they would like to be informed about incidental findings that might arise.

Strength's and limitations

Our data-and biobank stands out compared to other banks in several aspects. First, as mentioned, we have a dedicated research team to screen and include patients and to perform data entry, quality control and quality assurance. Further, inclusion of acutely (very) sick patients who do not have capacity to consent to participate is facilitated by a deferred consent procedure (when applicable by proxy) as well as an opt-out procedure. This allows the collection of data and biomaterials at the earliest moment in time upon presentation to the ED. Our digital infrastructure enables automatically capturing of all bed-side monitor data (*i.e.* electrophysiological waveforms, vital parameters) from every patient in the ED, as well as a secure connection with other sources if needed for specific research questions, such as the electronic health records of the hospital-, ambulance- and general practitioner, municipal registration, health insurance companies and pharmacy. This not only facilitates data collection, but also improves data reliability. A limitation of our data-and biobank is the potential inefficiency of our screening and inclusion process: all patients are screened and a lot of patients are included based on broad criteria that are present upon ED presentation (e.g. transport mode to hospital and urgency), while post-hoc information (e.g. diagnosis upon hospital discharge) will be used to identify specific subjects for subsequent studies.

This leaves a significant amount of data and biomaterials unused. Furthermore, clinical research in acute medicine warrants the presence of researchers in the ED waiting for patients to arrive at some moments, whilst at other moments, there is a risk of missing inclusions due to ED overcrowding.

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Authors' contributions

HRB conceived the idea of the biobank, and drafted the first version of the biobank protocol, which was critically reviewed and edited by EtA, BCvM and JCtM. Data management and design- and development of technical infrastructure is performed by RJvW and ST. Data acquisition- and verification on a day to day basis is performed by STH,TTH, LEvH, FEvB and FSvdV. HRB, EtA and JtM are steering committee members of the biobank ,and responsible for design, performance surveillance, and evaluation of external requests for data use. BvM is the biobank director. EtA drafted the manuscript of this paper describing the Acutelines Data- and Biobank, which was critically reviewed by all authors before submission.

Competing interests

The authors have not competing interests to disclose.

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References

[1] Densen P. Challenges and opportunities Facing medical education. *Trans Am Clin Climatl Assoc* 2011;122: 48-58.

[2] Smith J, Keating L, Flowerdew L et al. PSP Steering Group. An Emergency Medicine Research Priority Setting Partnership to establish the top 10 research priorities in emergency medicine. *Emerg Med J* 2017;34:454-456.

[3] van de Glind I, Berben S, Zeegers F et al. A national research agenda for pre-hospital emergency medical services in the Netherlands: a Delphi-study. *Scandinavian J Trauma, Resusc Emerg Med* 2016:24:2.

[4] NIV kennisagenda. Nederlandse internisten vereniging. Accessed on October 22th 2020 https://www.demedischspecialist.nl/sites/default/files/Kennisagenda-NIV.pdf

[5] Sole ML, Middleton A, Deaton L et al. Enrollment Challenges in Critical Care Nursing Research. *Am J Crit Care* 2017;26:395-400.

[6] Dahlber J, Eeriksen C, Robertsen A et al. Barriers and challenges in the process of including critically ill patients in clinical studies. *Scandinavian J Trauma, Resusc Emerg Med* 2020:28:6:51.

[7] Garde A, O'Hearn K, Nicholls S et al. reporting of consent rates in critoical care studies: room for improvement. *J Clin Epidemiol.* 2016;74:51-56.

[8] Appelbaum PS. Clinical practice. Assessment of patients'competence to consent to treatment. *N Engl J Med* 2007;357:1834-40.

[9] Morley C, Unwin M, Peterson GM et al. Emergency department crowding: A systematic review of causes, consequences and solutions. *PLoS One* 2018;13:e0203316

[10] Peloquin D, DiMaio M, Bierer B et al. Disruptive and avoidable: GDPR challenges to secondary research uses of data. *European Journal of Human Genetics* 2020;28:697-705.

[11] Coopersmith CM, Wunsch H, Fink MP et al. A comparison of critical care research funding and the financial burden of critical illness in the United states. *Crit care Med* 2012:40;1072-79.

[12] H Jalalzadeh, R Indrakusuma, JD Blankensteijn et al. Design and protocol of a comprehensive multicentre biobank for abdominal aortic aneurysms. *BMJ Open* 2019;9:e028858.

[13] CM Clements, JR Anderson, J Uhl et al. Biobanking in the emergency department: implementation of the Mayo Clinic Emergency Department Sepsis Biorepository. *Crit Care*. 2014; 18: P41.

[14] DR Eitel, DA Travers, AM Rosenau, N Gilboy, RC Wuerz. The emergency severity index triage algorithm version 2 is reliable and valid. *Acad Emerg Med* 2003;10:1070-80.

[15] Quinten VM, van Meurs M, Wolffensperger AE et al. Sepsis patients in the emergency department: Stratification using the clinical impression score, predisposition, infection, response and organ dysfunction score or quick sequential organ failure assessment score? *Eur J Emerg Med.* 2018;25:328-334.

[16] Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315:801-810.

[17] Perez Valdivieso JR, Bes-Rastrollo M et al. Karnofsky performance score in acute renal failure as a predictor of short-term survival. *Nephrology* 2007;12:533-538.

[18] Rabito EI, Marcadenti A, da Silva Fink J et al. Nutritional risk screening 2002, short nutritional assessment questionnaire, malnutrition screening tool, and malnutrition universal screening tool are good predictors of nutrition risk in an emergency service. *Nutr Clin Pract.* 2017;32:526-532.

[19] Laan W, Zuithoff NP, Drubbel I et al. Validity and reliability of the katz-15 scale to measure unfavorable health outcomes in community-dwelling older people. *J Nutr Health Aging*. 2014;18:848-854.

[20] Lakkis NA, Mahmassani DM. Screening instruments for depression in primary care: A concise review for clinicians. *Postgrad Med*. 2015;127:99-106.

[21] Reeve BB, Stover AM, Alfano CM et al. The piper fatigue scale-12 (pfs-12): Psychometric findings and item reduction in a cohort of breast cancer survivors. *Breast Cancer Res Treat*. 2012;136:9-20.

[22] Gierk B, Kohlmann S, Toussaint A et al. Assessing somatic symptom burden: A psychometric comparison of the patient health questionnaire-15 (phq-15) and the somatic symptom scale-8 (sss-8). *J Psychosom Res.* 2015;78:352-355.

[23] de Gelder J, Lucke JA, Blomaard LC et al. Optimization of the apop screener to predict functional decline or mortality in older emergency department patients: Cross-validation in four prospective cohorts. *Exp Gerontol.* 2018;110:253-259.

[24] PA Harris, R Taylor, R Thielk et al. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, *J Biomed Inform.* 2009;42:377-81.

[25] PA Harris, R Taylor, BL Minor et al. The REDCap consortium: Building an international community of software partners, *J Biomed Inform.* 2019;95:103208

Figure legends

Figure 1. Schematic overview of the Acutelines biobank. By collecting data from pre-hospital up to long after hospital discharge, Acutelines follows the complete acute patient journey. Specially trained research assistants screen potential participants in the ED (24/7). Waveform data and vital parameters from bed-side monitors are captured automatically, and biomaterials (i.e. blood, urine, feces) will be collected whilst awaiting deferred consent (by proxy). ED facilities allow rapid processing and storage of biomaterials (-80oC). Wearable devices are used to continue capturing waveforms and vital parameters during the first 72 hours of hospital admission. Connections with the electronic health record (EHR) and external databases (e.g. GP, pharmacy, health insurance companies) allow to collect relevant clinical data when applicable for specific research questions, such as medication use and co-morbidity up to 5 years after presentation. Digital survey-based patient-reported outcomes will be collected on fixed intervals and survival will be monitored indefinitely using the municipal registration.

Figure 2. Inclusion criteria of patients for Acutelines in the initiation phase. Data (demographic- and medical data, waveforms) will be collected from all patients, but surveys and biomaterials will only be collected from patients with the highest- and second highest urgency triage categories (red or orange) of the Emergency Severity Index (ESI) or patients with a suspicion of sepsis or shock. Blood tube: biomaterials, pen/paper: survey, database: health data (i.e. from EHR and central registries), ECG: waveform data with vital parameters.

Supplementary figure 1. Overview of data collection in Acutelines. EHR: electronic health record; CCI: Charlson comorbidity index; LSP: national pharmacy database (in Dutch: Landelijk Schakelpunt Pharmacy); ECG: electrocardiogram; APOP: acute presenting elderly patient in the emergency room; VMS: safety management system (in Dutch: veiligheidsmanagementsysteem), Vektis: national health care insurance database; NIVEL: national database of general practitioners (GPs, in Dutch: nederlands instituut voor onderzoek van de gezondheidszorg), 4AT, 4 'A's delirium Test; 6-CIT, 6 item Cognitive Impairment Test; DOS, Delirium Observation Screening.

Supplementary figure 2. Overview of data collection using surveys in Acutelines. FHQ-6, Family History Screening Questionnaire; PSQ-18, patient satisfaction questionnaire-18; PHQ-2/9/15, Patient Health Questionnaire-2/9/15 ; GDS-15, Geriatric Depression Score-15; SNAQ, Patient-Generated Subjective Global Assessment (PS-SGA Short Form/Short Nutritional Assessment Questionnaire, SNAQ); MUST, Malnutrition Universal Screening Tool; EQ-5D-5L, 5-level EQ-5D test; Katz ADL-6, Katz activities of daily living-6; SQUASH, Short Questionnaire to Assess Health-enhancing physical activity; OPT, outcome priorization tool.

TABLE 1.WHO trial registration dataset.

Primary registry and trial identifying number	ClinicalTrials.gov: NCT04615065
Date of registration in primary registry	October 18, 2020
Secondary identifying numbers	University Medical Center Groningen Research Registry Number 201900635
Sources of monetary of material support	University Medical Center Groningen, University of Groningen, The Netherlands
Primary sponsor	University Medical Center Groningen, University of Groningen, The Netherlands
Secondary sponsor	None
Contact for public queries	Acutelines steering group (acutelines@umcg.nl)
Contact for research queries	Acutelines steering group (acutelines@umcg.nl)
Public title	Acutelines
Scientific title	Acutelines de novo data-/biobank
Country of recruitment	Netherlands
Health conditions	Acute conditions
Interventions	None
Key inclusion-exclusion criteria (biobank protocol version 5, 09-2020)	Included are ED patients with the highest- and second highest urgency triage categories of the Manchester triage system, and patients with the third highest category when arriving by (Helicopter) Emergency Medical Service. In addition, patients with several specific conditions regardless their triage category are included: Sepsis, shock, syncope, anaphylaxis, acute renal failure, intoxications, COPD exacerbations, deep venous thrombosis or pulmonary embolism, gastrointestinal bleeding and patients who are bleeding (any source) whilst using warfarin-or DOAC.
Study Type	Observational, biobank
Date of first enrollment	September 1, 2020
Sample size	Anticipated at 3,500 per year
Recruitment status	Recruiting
Ethics approval	Status: approved Date of approval: April 8, 2020 Name and contact details of ethics committees: Institutional Review Board and Central Review Board University Medical Center Groningen Phone: +31503613564 Email: nwmoloket@umcg.nl Address: PO Box 30001 9700 RB Groningen The Netherlands
Completion Date	Not applicable (no end date defined)
Summary statement	No results yet
IPD sharing statement	Individual participant data (IPD) may be available to other researchers if needed for their specific research purposes, which amongst others must be in line with the study protocol, the informed consent form and the general data protection regulations (GDPR). Each request for re-use of data will be reviewed by Acutelines' steering group, manager and local review board (LRb), prior to establishing a material and data transfer agreement (MDTA). No IPD will be shared if not required to answer research question.

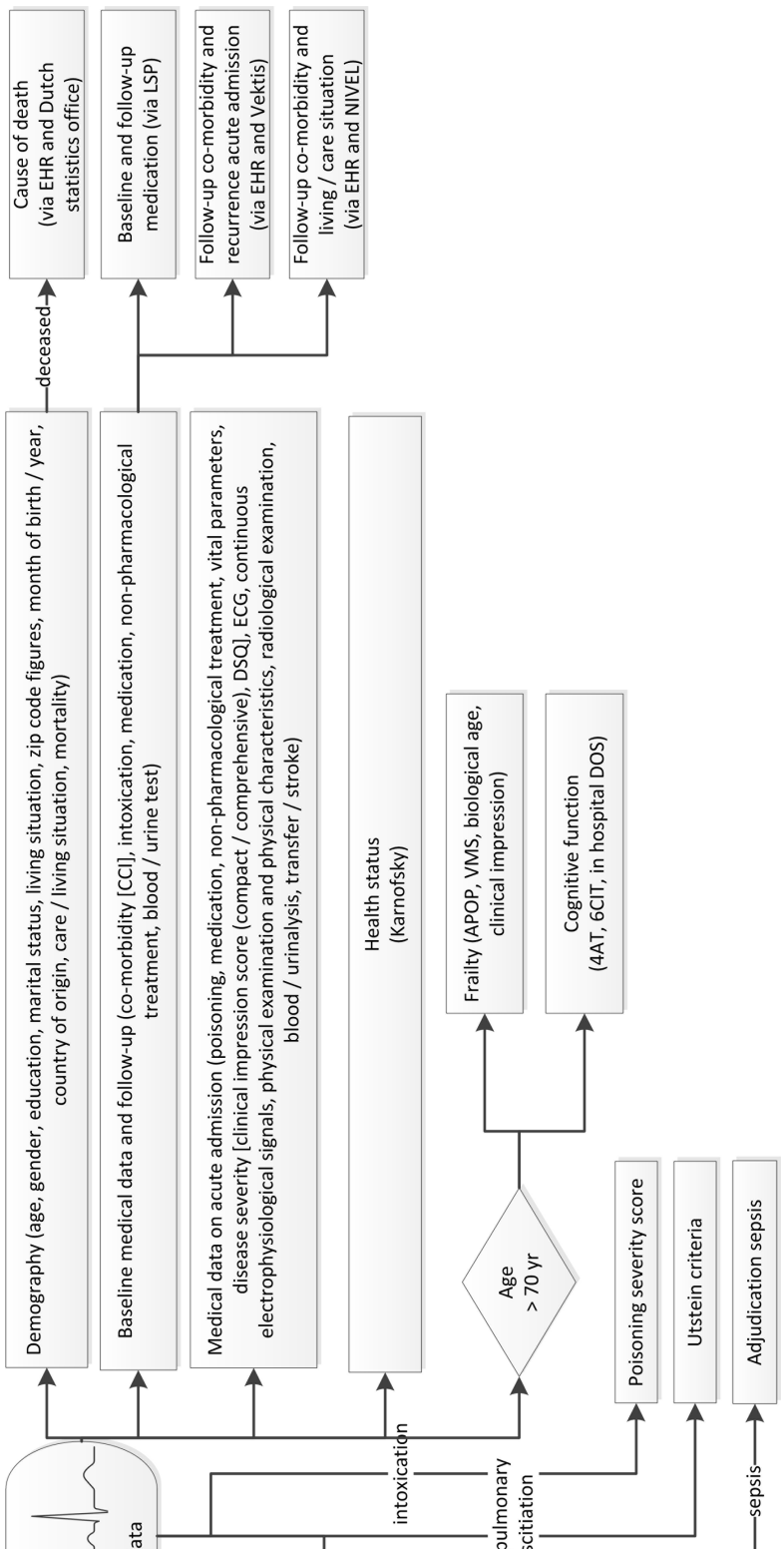
TABLE 2. Overview of data collection Acute Lines biobank

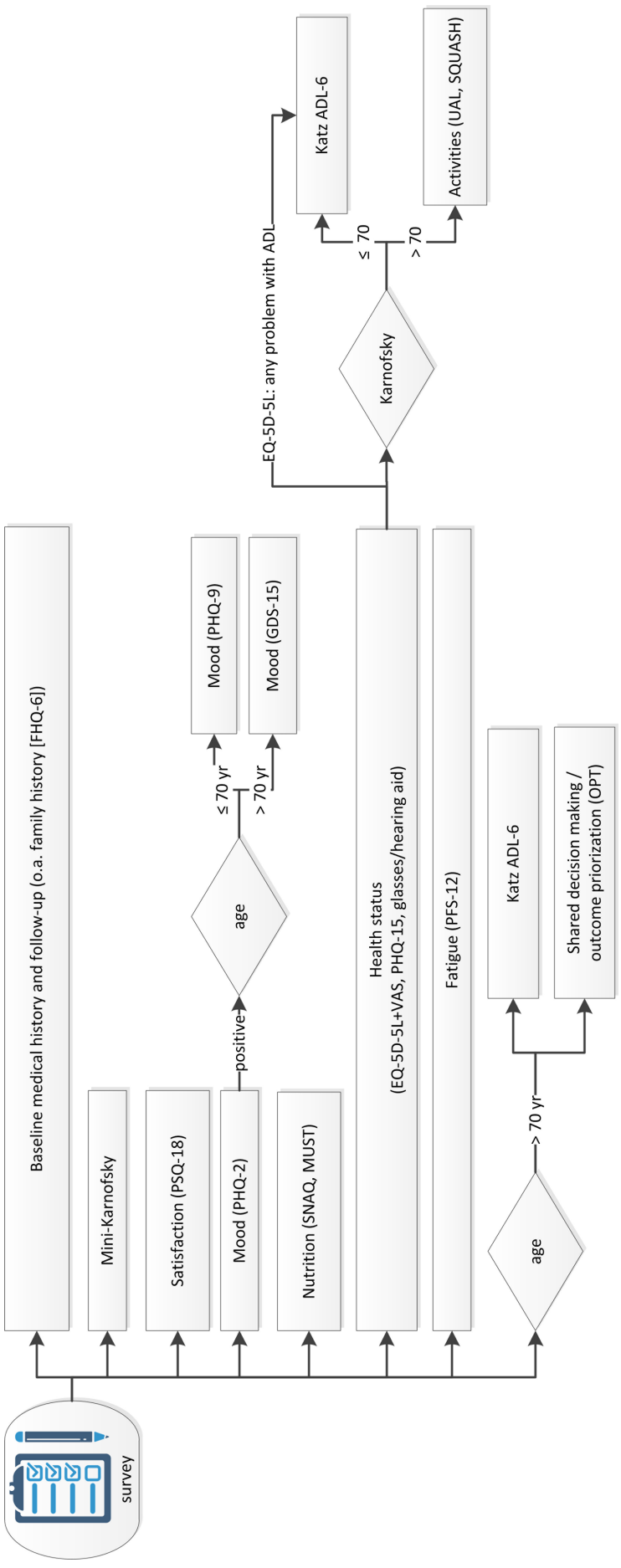
Data and biomaterials	<1yr – ED visit	Pre-hospital	**ED – 72h**	3 months	1 year	2 years	5 years	∞	
Contact info and deferred consent			**√**						Consent within 30 days and opt-out (if unreachable)
Meta data ED visit (i.e. referral, mode of transport, triage category, length of stay, decision making, final disposition)			**√**						
Presenting complaints		√	**√**						
Demographic data (i.e. gender, age, living situation, mortality, country of origin)		√	**√**	√	√	√	√	√	
Medical (family) history			**√**						
Medication use and intoxications		√	**√**	√	√	√	√		ATC level 1, 3 and 5 as defined daily dose (DDD)
Non-pharmacological treatment		√	**√**						
Vital parameters, physical examination and disease severity		√	**√**						
ECG		√	**√**						
Radiologic results			**√**						Including point-of-care ultrasound (POCUS)
Biometry			**√**						Photograph or movie (< 10 sec) of face to capture clinical impression
Laboratory results (full)		√	**√**						
Laboratory results (core set)	√	√	**√**	√	√	√	√		Kidney and liver function, lipid profile, albumin, cardiac markers, ESR and CRP
Health status			**√**	√	√				Nutrition, Karnofsky, EQ-5D-5L, PHQ-2, PHQ-15, Katz ADL-15 [if Karnofsky < 70]
Frailty screening *[if age > 65 years]*			**√**						APOP
Fatigue				√	√				Piper fatigue scale
Mood and depression *[if PHQ-2 positive]*			**√**	√	√				PHQ-9 [if age ≥ 70 years: GDS-15]
Cognitive function *[if age ≥70 years]*			**√**	√	√				4AT [in hospital], 6-CIT [in hospital], DOS [in hospital]
Physical activities *[if karnofsky > 70]*			**√**	√	√				SQUASH
Biomaterials (plasma, serum, buffy coat, RNA, feces, urine, hair)			**√**						If triage color red or orange (hair only if COPD/asthma exacerbation)

Legend Table 2: ED, Emergency Department; ECG, Electrocardiogram; RNA, ribonucleic acid. ATC; Anatomical Therapeutic Chemical Classification system; EQ-5D-5L, 5-level EQ-5D test; PHQ-2/9/15, Patient Health Questionnaire-2/15; GDS-15, Geriatric Depression Score; 4AT, 4 'A's delirium Test; 6-CIT, 6 item Cognitive Impairment Test; DOS, Delirium Observation Screening; SQUASH, Short Questionnaire to Assess Health-enhancing physical activity. A visual overview of data to be collected is presented in supplementary figures 1 and 2.

Rapid biomaterial processing
Biometry capturing
Automated data capturing
24/7 screening and inclusion
Pre-hospital data connection
Data transfer from the EHR
Wireless monitoring
Patient-reported outcomes
Connect with external sources to obtain long-term health data
in-patient
out-patient
Acutelines

Adult patients visiting emergency room for: internal medicine (and subspecialities), gastro-enterology, pulmonology, rheumatology, emergency medicine (non-trauma)
Triage urgency
any
any
+
Complaints
Sepsis
Shock
Anaphylaxis
Intoxication
Syncope
Trombosis/embolism
GI-bleeding
Bleeding + anticoagulants
Electrolyte disturbance
Acute kidney injury
COPD exacerbation
Data / biomaterials


Cause of death (via EHR and Dutch statistics office)
Baseline and follow-up medication (via LSP)
Follow-up co-morbidity and recurrence acute admission (via EHR and Vektis)
Follow-up co-morbidity and living / care situation (via EHR and NIVEL)
deceased
Demography (age, gender, education, marital status, living situation, zip code figures, month of birth / year, country of origin, care / living situation, mortality)
Baseline medical data and follow-up (co-morbidity [CCI], intoxication, medication, non-pharmacological treatment, blood / urine test)
Medical data on acute admission (poisoning, medication, non-pharmacological treatment, vital parameters, disease severity [clinical impression score (compact / comprehensive), DSQ], ECG, continuous electrophysiological signals, physical examination and physical characteristics, radiological examination, blood / urinalysis, transfer / stroke)
Health status (Karnofsky)
Frailty (APOP, VMS, biological age, clinical impression)
Cognitive function (4AT, 6CIT, in hospital DOS)
Age > 70 yr
Poisoning severity score
Utstein criteria
Adjudication sepsis
data
intoxication
cardiopulmonary resuscitation
sepsis


survey
Baseline medical history and follow-up (o.a. family history [FHQ-6])
Mini-Karnofsky
Satisfaction (PSQ-18)
Mood (PHQ-2)
positive
Nutrition (SNAQ, MUST)
age
≤ 70 yr
> 70 yr
Mood (PHQ-9)
Mood (GDS-15)
Health status
(EQ-5D-5L+VAS, PHQ-15, glasses/hearing aid)
Fatigue (PFS-12)
EQ-5D-5L: any problem with ADL
Karnofsky
≤ 70
> 70
Katz ADL-6
Activities (UAL, SQUASH)
age
> 70 yr
Katz ADL-6
Shared decision making /
outcome priorization (OPT)

Supplementary table 1.

	<1jr-ER	Prehospital	ER-72h	3Mos	1Yr	2Yr	5Yr	∞	Explanation	Source
Communication data and consent										
Name, phone number, address, zip code, place of residence, e-mail address and the UMCG-number of participants			√						This data will not be stored in the research database, but will be kept in the electronic patient file	Participant and/or representative
Relationship with participant, name, phone number and e-mail address form first contact			√						This data will not be stored in the research database, but will be kept in the electronic patient file (except e-mail address, which will be stored in a hidden field in the research database to be able to send digital surveys)	Participant and/or representative
Consent			√						Consent from participant and/or representative, date	Participant and/or representative
Biometry: photograph/short movie of face			√[1]						Photograph and short movie (10 seconds) of face	Participant
Data regarding ER visit										
Logistics		√	√						Such as type of transport, time of notification, time of patient arrival, zip code (numbers), urgency (A1, A2, B), date and time of entering ER, time leaving ER, number of patients in ER (in treatment and waiting room), number of consultations	Electronic patient file, general practitioner, Ambulance Care/MMT Electronic File , observations and measurements
Triage			√						Such as triage time, triage urgency code	Electronic patient file
Practitioner			√						Such as department to which the patient is assigned, time of	Electronic patient file, interview with

									arrival of practitioner (first patient contact), practitioner type (resident, attending), years of work experience after completion of study/training, algorithm primary care	practitioner
Complaints			√						Main complaint (s) and findings at anamnesis, graded by severity and categorized by tract	Electronic patient file, general practitioner, Ambulance Care/MMT Electronic File , observations and measurements
Shared decision making			√[1]						- Patient satisfaction questionnaire (PSQ-18)(1) - Outcome Priorization Tool (OPT) (2)	Questionnaires
Demographic data										
Age when visiting ER			√							Electronic patient file
Gender			√							Electronic patient file
Highest completed education			√							Electronic patient file, (proxy) history, questionnaire
Marital status			√	√	√					Electronic patient file, (proxy) history, questionnaire
Living situation			√	√	√					Electronic patient file, (proxy)history, questionnaire
Zip code (only numbers)			√	√	√					Electronic patient file
Birth month and year			√							Electronic patient file
Country of origin (self and parents)			√							Electronic patient file, (proxy) history, questionnaire
Care/living situation			√	√	√	√	√		Such as use of home care, living independently, care/nursing home, recurrence acute	Electronic patient file, general practitioner, health insurance,

									admissions	questionnaire
Mortality			√	√	√	√	√	√	Date and cause of death	Electronic patient file, general practitioner, municipal registration, Dutch statistics' office
Medical and physical data										
Family history			√						Family History Screening Questionnaire (FHQ-6)	
Intoxication			√	√	√				Such as alcohol, tobacco, drugs (in case of intoxication as reason of visiting, supplemented with ingested agent, dose, route of exposure, intention)	(hetero)anamnesis , questionnaire
Comorbidity			√	√	√	√	√		Charlson Comorbidity Index , supplemented with pregnancy, transplant (year, type) and malignancy (type, curative/palliative treatment)	Electronic patient file, general practitioner, integral cancer center of the Netherlands (IKNL), Pathological-Anatomical National Automated Archive (PALGA), Dutch institute for health care research (NIVEL), (hetero)anamnesis
Medication		√	√	√	√	√	√		Anatomical Therapeutic Chemical Classification System (ATC) level 1, 3 and 5, defined daily dose (DDD)	Electronic patient file, general practitioner, pharmacy, Ambulance Care/MMT Electronic File , (hetero)anamnesis
Non-pharmacological treatment		√	√						Including treatment instructions, oxygen administration, intravenous line, resuscitation (Utstein criteria , use of AED), advanced treatment (such as intubation, transfusion, thoracostomy), decontamination (in	Electronic patient file, general practitioner, ambulance care/MMT, observations, (hetero)anamnesis

									case of CBRN)	
Vital parameters		√	√						Such as blood pressure, heart rate, respiratory rate, oxygen saturation, consciousness, temperature, diuresis, pain score	Electronic patient file, general practitioner, Ambulance Care/MMT Electronic File, observations and measurements
Disease severity			√						Such as clinical eye score , double surprise question (DSQ)	Interview practitioner at ER (estimation practitioner), (proxy) history (own estimation)
ECG		√	√						Such as rhythm, beats per minute, P-top, conduction times (PR, QRS, QT), type of AV block, ST depression/elevation	Electronic patient file
Continuous electrophysiological signals			√						Such as ECG, plethysmography, respiratory rate	Bed-side monitor of wearable
Physical examination and traits		√	√						Such as length, weight, aspect of skin	Electronic patient file, general practitioner, ambulance care/MMT, observations and measurements
Radiological examination			√						Outcome point-of-care ultrasound (POCUS), chest X-ray, abdomen, CT cerebrum, chest CT, CT abdomen if performed	Electronic patient file
Blood and urine tests	√[3]	√	√	√[3]	√[3]	√[3]	√[3]		Cytometric, biochemical and microbiological results	Electronic patient file
Transfer/discharge			√						Admission department(s) and date of discharge	Electronic patient file
Health status and functionality										
Nutrition and weight			√	√	√				- Patient-Generated Subjective Global Assessment (PS-SGA Short Form/Short Nutritional	Electronic patient file, (hetero)anamnesis , questionnaires

									Assessment Questionnaire, SNAQ) - Malnutrition Universal Screening Tool (MUST)	
Frailty of the elderly			√[2]						- Acute presenting elderly patient in the emergency room (APOP) - Estimate older/younger than calendar age	(Hetero)anamnesis, observations
Global functioning, complaints, mood and experienced health			√	√	√				- Karnofsky - 5-level EQ-5D version 5L (EQ-5D-5L+VAS) - Patient Health Questionnaire 2 (PHQ-2) - Patient Health Questionnaire-15 (PHQ-15) - Wearing glasses, hearing aid	(Hetero)anamnesis, questionnaires
Fatigue				√	√				Piper Fatigue Scale-12 (PFS-12)	
IADL			√[2,4]	√[2,4]	√[2,4]				Katz ADL-15	Questionnaires
Mood			√[5]	√[5]	√[5]				**≤ 65 years old:** Patient Health Questionnaire 9 (PHQ-9) **> 65 years old:** Geriatric Depression Scale-15 (GDS-15)	Questionnaires
Cognitive functioning (delirium and dementia, hospitalization)			√[2]						- 4AT - 6-Item Cognitive Impairment Test (6-CIT) - Delier observatie score (DOS)	(Hetero)anamnesis, Electronic patient file and observations
Physical activities			√[6]	√[6]	√[6]				- Utrechtse activities list (UAL) (19) - Short Questionnaire to Assess Health-Enhancing Activity (SQUASH) (20,21)	Questionnaires
Biomaterial										
Plasma			√[7]						Citrate, 1x 6 ml; EDTA, 1x 10 ml; Li-heparin, 1x 9ml[9]	

Buffy coat			√[7]					From EDTA tube[9]	
Serum			√[7]					Coagulation tube, 1x 10 ml[9]	
Whole blood/RNA			√[7]					PAXgene whole blood, 1x 10 ml[9]	
Urine			√[7]					1x 11 ml (<24 hr after start ER visit)[9]	
Feces			√[7]					1 container (<24 hr after start ER visit)[9]	
Hair			√[8]					0.5 cm of hair	

Footnotes Supplementary Table 1.

1. Only when triage colour is red or orange, or when patient presents with shock or sepsis, confined to ED stay.
2. Only when aged >70.
3. Confined to electrolytes, renal function, liver function, lipids, albimin, NTproBNP, HsTropT, CRP, CBC, sedimentation rate and PaO2.
4. Only when EQ-5D-5L demonstrates problems with ADL or Karnofsky ≤ 70.
5. Only when PHQ-2 positive.
6. Only when Karnofsky >70.
7. Only when triage color is red or orange, or when patient presents with shock or sepsis; for blood limited to ED stay, urine/feces to be collected within 24 hours.
8. Only when presenting with COPD exacerbation.

References Supplementary Table 1

1. Thayaparan AJ, Mahdi E. The patient satisfaction questionnaire short form (psq-18) as an adaptable, reliable, and validated tool for use in various settings. Med Educ Online. 2013;18:21747.

2. Stegmann ME, Festen S, Brandenbarg D, et al. Using the outcome prioritization tool (opt) to assess the preferences of older patients in clinical decision-making: A review. Maturitas. 2019;128:49-52.

3. Walter FM, Prevost AT, Birt L, et al. Development and evaluation of a brief self-completed family history screening tool for common chronic disease prevention in primary care. Br J Gen Pract. 2013;63:e393-400.

4. Brusselaers N, Lagergren J. The charlson comorbidity index in registry-based research. Methods Inf Med. 2017;56:401-406.

5. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: Update of the utstein resuscitation registry templates for out-of-hospital cardiac arrest: A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (american heart association, european resuscitation council, australian and new zealand council on resuscitation, heart and stroke foundation of canada, interamerican heart foundation, resuscitation council of southern africa, resuscitation council of asia); and the american heart association emergency cardiovascular care committee and the council on cardiopulmonary, critical care, perioperative and resuscitation. Circulation. 2015;132:1286-1300.

6. Quinten VM, van Meurs M, Wolffensperger AE, et al. Sepsis patients in the emergency department: Stratification using the clinical impression score, predisposition, infection, response and

organ dysfunction score or quick sequential organ failure assessment score? Eur J Emerg Med. 2018;25:328-334.

7. Veldhoven CMM, Nutma N, De Graaf W, et al. Screening with the double surprise question to predict deterioration and death: An explorative study. BMC Palliat Care. 2019;18:118.

8. Balstad TR, Bye A, Jenssen CR, et al. Patient interpretation of the patient-generated subjective global assessment (pg-sga) short form. Patient Prefer Adherence. 2019;13:1391-1400.

9. Rabito EI, Marcadenti A, da Silva Fink J, et al. Nutritional risk screening 2002, short nutritional assessment questionnaire, malnutrition screening tool, and malnutrition universal screening tool are good predictors of nutrition risk in an emergency service. Nutr Clin Pract. 2017;32:526-532.

10. de Gelder J, Lucke JA, Blomaard LC, et al. Optimization of the apop screener to predict functional decline or mortality in older emergency department patients: Cross-validation in four prospective cohorts. Exp Gerontol. 2018;110:253-259.

11. Perez Valdivieso JR, Bes-Rastrollo M, Monedero P, et al. Karnofsky performance score in acute renal failure as a predictor of short-term survival. Nephrology (Carlton). 2007;12:533-538.

12. Janssen MF, Bonsel GJ, Luo N. Is eq-5d-5l better than eq-5d-3l? A head-to-head comparison of descriptive systems and value sets from seven countries. Pharmacoeconomics. 2018;36:675-697.

13. Mitchell AJ, Yadegarfar M, Gill J, et al. Case finding and screening clinical utility of the patient health questionnaire (phq-9 and phq-2) for depression in primary care: A diagnostic meta-analysis of 40 studies. BJPsych Open. 2016;2:127-138.

14. Gierk B, Kohlmann S, Toussaint A, et al. Assessing somatic symptom burden: A psychometric comparison of the patient health questionnaire-15 (phq-15) and the somatic symptom scale-8 (sss-8). J Psychosom Res. 2015;78:352-355.

15. Reeve BB, Stover AM, Alfano CM, et al. The piper fatigue scale-12 (pfs-12): Psychometric findings and item reduction in a cohort of breast cancer survivors. Breast Cancer Res Treat. 2012;136:9-20.

16. Laan W, Zuithoff NP, Drubbel I, et al. Validity and reliability of the katz-15 scale to measure unfavorable health outcomes in community-dwelling older people. J Nutr Health Aging. 2014;18:848-854.

17. Lakkis NA, Mahmassani DM. Screening instruments for depression in primary care: A concise review for clinicians. Postgrad Med. 2015;127:99-106.

18. O'Sullivan D, Brady N, Manning E, et al. Validation of the 6-item cognitive impairment test and the 4at test for combined delirium and dementia screening in older emergency department attendees. Age Ageing. 2018;47:61-68.

19. Post MWM. Utrechtse activiteitenlijst. In: van Asbeck FWA, editor. Handboek dwarslaesierevalidatie. Houten: Bohn Stafleu van Loghum; 1998. p. 356-357.

20. Wendel-Vos GC, Schuit AJ, Saris WH, et al. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56:1163-1169.

21. Campbell N, Gaston A, Gray C, et al. The short questionnaire to assess health-enhancing (squash) physical activity in adolescents: A validation using doubly labeled water. J Phys Act Health. 2016;13:154-158.

<study title>

<STUDY ACRONYM (if available); Research Register number>

(non-WMO study protocol to obtain data/biomaterials from the Acutelines biobank)

Readers's guide:

This template supports researchers to describe their retro-/prospective non-WMO study (or research program with a broad research question), irrespective of whether informed consent will be asked from one or more participants - or not. Items or sections that are not applicable for the present study should not be deleted but responded to by using the words/letters: 'Not Applicable' or 'NA'. After submission to Acutelines steering group and the CTc or an LTc, the METc will assess whether the study is indeed outside the scope of the WMO and return - if applicable - a non-WMO statement to the applicant. Subsequently the non-WMO study will be reviewed by the CTc/LTc.

IMPORTANT NOTES:

- *Researchers from departments that do not have a LTc (Local ethics Review Committee) can submit the completed protocol to the CTc (Central ethics Review Committee).*
- *This document contains pop-ups: put the cursor on top words in blue*
- *Check the nWMO Kaderreglement UMCG (especially chapters 5 and 6) with relevant information on the UMCG research policy for non-WMO studies.*
- *The applicant is responsible that information in this protocol (study title, name of the project leader, etc.), **corresponds exactly** with the information in the UMCG Research Register and the Application form (to be completed during submission to the CTc/LTc), also after future improvements/amendments.*
- *This template should **not** be used to start a bio- or databank for future research. Check the Research Toolbox for the right templates.*

Finally:

- *Remove this Reader's guide and all comments on the right side before submission. Make sure to have complete all yellow marked text and remove the yellow markings prior to submission.*

Date of protocol:<dd-mm-yyyy>
Version number: <X.X>

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1. STUDY ORGANIZATION

Study title	Acutelines: <study title>
Planned start date	<dd-mm-yyyy>
Estimated completion date	<dd-mm-yyyy>
Project leader (UMCG)	Dr. H.R. Bouma, project leader Acutelines, Internist acute medicine/pharmacologist, Depts. of Internal Medicine, Center for Acute Care and Clinical Pharmacy & Pharmacology, UMCG Email: h.r.bouma@umcg.nl Phone: 69649 (H.R. Bouma)
(Principal) investigator UMCG	<name, function, department, email, telephone>
Researcher(s) UMCG	• <name, function, department, email, telephone> • etc.
Corresponding researcher UMCG	<name, function, department, email, telephone
Sponsor (in Dutch: verrichter/opdrachtgever)	UMCG (Acutelines)
Financial support/subsidising party	**Geldstroom**: 1e/2 e /3 e /4 e • UMCG and/or <organization> • etc.
Collaboration with non-profit Laboratory / research sites (in- and outside UMCG)	NA or • <name contact person, location, email, telephone, summary of contribution to the study> • etc.
Collaboration with commercial parties / companies (in- and outside UMCG)	NA or • <name contact person, location, email, telephone, summary of contribution to the study> • etc.
Name bio- or databank and bankmanager	**Acutelines** (research register number 201900635) Center for Acute Care UMCG Email: acutelines@umcg.nl Phone: 68943 Manager: prof.dr. B.C. van Munster, internal medicine Project leader: dr. H.R. Bouma, internal medicine ☒ approved by the Board of Directors UMCG ☐ not approved by the Board of Directors UMCG
Name previous study ('FAIR data')	Acutelines

2. PROTOCOL SIGNATURE SHEET

The undersigned (Principal) investigator and head of department UMCG confirm that the study and its procedures will comply with the present study protocol and the nWMO Kaderreglement UMCG, and in addition agree with the Acutelines regulations for further use of data and biomaterials as stated in the current document. Without ethical approval the data/biomaterials will not be used for other (research) purposes (e.g. 'FAIR data').

Name	Signature	Date
(Principal) investigator UMCG:	<name and function>	<dd-mm-yyyy>
Head of the department UMCG:	<name and function>	<dd-mm-yyyy>
Bank manager Acutelines	Prof.dr. B.C. van Munster	<dd-mm-yyyy>
Steering group Acutelines	Dr. H.R. Bouma	<dd-mm-yyyy>

3. ABSTRACT (max. 250 words)

- **Background**
  <text>
- **Main research question**
  <text>
- **Design (including population, confounders/outcomes)**
  <text>
- **Expected results**
  <text>

4. BACKGROUND

- **Introduction and rationale**
  <text>
- **Research question**
  <text>

5. METHOD

5.1 Description study design

<give short description of the study design>

5.2 Design

5.2.1 Mono- or multicenter study	Mono-center study, use of data/biomaterials from Acutelines (de novo biobank)	
5.2.2 Retrospective study (available data/ biomaterials only) or prospective study (data/ biomaterials from [some] participants will be collected in the future).	Retrospective study: yes~~/no~~	Prospective study: YES (Acutelines)
Note: while Acutelines is a prospective data/biomaterial collection, additional data may be collected retrospectively. <text>		
5.2.3 Cross-sectional or follow-up study	Cross-sectional study: yes/no	Follow-up study yes/no
<text>		
5.2.4 Quantitative or qualitative study (click both if mixed-method)	Quantitative study yes/no	Qualitative study yes/no
<text>		
5.2.4 Pilot study	yes/no	
<text>		

5.3 Population

5.3.1 Inclusion and exclusion criteria	
• Inclusion criteria: <text> • Exclusion criteria: <text>	
5.3.2 Number of participants	
• Target total number of participants: <number> • Target number of UMCG participants: <number>	
5.3.3 Study subjects (tick all that apply)	
• Healthy volunteers • Patients	**NO** **YES**
5.3.4 Subject classification (tick all that apply)	
• Participants ≥ 16 years • Children between 12 and 16 years *(if applicable, written informed consent will be obtained from child and both parents - if both have authority, or guardian [or parents/guardian only if incapacitated child])* • Children < 12 years *(if applicable, written informed consent will be obtained from both parents - if both have authority, or guardian)*	**YES** **NO** **NO**
5.3.5 Incapacitated adults	
Participants are incapacitated/ decisionally incompetent adults *(if applicable, written informed consent will be obtained from legal representative)*	**YES**

5.4 Recruitment and informed consent/objection

5.4.1	Retrospective study (tick all that apply)

	☐ Not applicable (see section 5.2.2) ☐ Data will be copied from (electronic) patient records (e.g. 'EPD UMCG') ☒ Data/biomaterials will be obtained from an already existing internal or external (UMCG/non-UMCG) bio- or databank (see Section 1. Study organization). **Data/biomaterials will be obtained from the 'de novo' biobank Acutelines.** ☐ Data/biomaterials will be obtained from a previous study ('FAIR data' - internal/external; see Section 1. Study organization).
5.4.3 Objection (Registry)	
in case one or more participants will not be asked informed consent, the objection registry will be checked for these participants and the data from those who objected will be excluded from the analyses.	**YES**
All participants will be asked informed consent (Acutelines).	
5.4.4 Informed consent (IC): access to identifiable participant data	
in case one or more study team members will have access to direct/indirect identifiable participant data, informed consent will be/has been obtained for this access.	**YES**
5.4.5 IC: Collaboration with commercial parties	
In case of collaboration with commercial/profit organizations, informed consent will be/has been obtained for this type of collaboration	**YES**
5.4.6 IC: Linking with other registries	
In case the data will be linked with other registries, informed consent will be/has been obtained for this linkage(s)	**YES**
5.4.7 IC: Incidental findings	
In case there is a risk of incidental findings, informed consent will be/has been obtained to return findings to the participant	**YES**
Participants are asked (written, consent form) whether they would like to be informed about incidental findings.	
5.4.8 IC: FAIR Data	
In case data collected for the present study will be shared for future studies, informed consent will be obtained for this	**YES**
5.4.9 IC: other aspects	
NA or <other relevant aspects of the study for which informed consent will be/has been obtained>	
5.4.10 Withdrawal	
• Can participants withdraw informed consent before publication and will all data/ biomaterials of that participant be destroyed	**NO**
• Does the participant information letter contain information on how to withdraw	**YES**
If data or biomaterials have already been used, it cannot be destroyed anymore as stated in the consent form.	

5.5 Research Data Management Plan (RDMP)

In this study the data will be collected, processed, and archived in accordance with the General Data Protection Regulation (GDPR) and the FAIR (Findable, Accessible, Interoperable, Reusable) principles under the responsibility of the Principal Investigator. A research data management plan (RDMP) has been drawn up to describe the further operational details and procedures.	
☒ the RDMP section below is completed ☐ a separate RDMP document will be attached to this protocol (appendix)	
5.5.1 Data collection	
• Only essential baseline characteristics and data required to answer the research question(s) will be collected (retrieved from Acutelines)	**YES/NO**
Primary outcome: <describe which type of data will be collected> Secondary and other outcomes:	

<describe which type of data will be collected>	
• Tooling (eg. software and procedures) used for collecting, processing, analysing, and storing data will be compliant with the UMCG policy and Standard Operating Procedures in the UMCG Research Toolbox.	**YES/NO**
<if no, explain>	
5.5.2 Anonymization and pseudonymization	
• Data will be anonymised during data collection (i.e. data cannot be linked back to the participant)	**NO** (only partially)
To allow follow-up of participants through surveys and importing data from the electronic health records or external sources, data cannot be anonymised upon collection in Acutelines, but have to be stored pseudonymized.	
• Data will be pseudonymized by use of a code list stored in the electronic patient file (EPD) during data collection.	**YES**
• Indirect and direct identifiable information collected will be minimized and only collected for the purpose of this study	**YES**
• Direct identifiable information (e.g. contact details, code list/encryption key/subject identification log) will be stored separately from pseudonymized data in the electronic patient files (EPD), while the email address is stored in RedCap (field marked and protected as "identifier").	**YES**
5.5.3 Data access (during the study)	
• Direct identifiable information can only be accessed by the Principal Investigator and study delegates after authorization by the Principal Investigator.	**YES**
• Pseudonymized/anonymized data can only be accessed by the Principal Investigator and study delegates after authorization by the Principal Investigator.	**YES**
• Data roles, responsibilities, access and authorization - during the study and after study completion - will be managed and documented (e.g. in the RDMP, on study delegation log).	**YES**
5.5.4 Data sharing (during and after study completion)	
In case data (and biomaterials) will leave the UMCG, will you contact the loket Contract Research to arrange the proper contracts? (Loket_Contract_Research@umcg.nl)	**NA/YES/NO**
<if no, explain>	
In case data (and biomaterials) will leave the UMCG, will you contact the Acutelines steering group and manager to arrange the proper contracts? (acutelines@umcg.nl)	**NA/YES/NO**
<if no, explain>	
5.5.5 Data storage (during and after study completion)	
• Digital data will be archived on the UMCG network complying with strict UMCG security and back-up policy.	**YES**
• Paper source data and study files will be archived within the UMCG facilities.	**YES**
• Source data, study files and digital data will be stored 15 years after the study is completed.	**YES**
5.5.6 Data re-use and access after completion of the present study ('FAIR data')	
• Data will become available and shared for re-use and participants will be asked informed consent for this ('FAIR data')	**YES**
Acutelines stimulates re-use and access of data ("FAIR data"), which is the primary aim of Acutelines and for which participants are asked informed consent.	
• Data will be made findable by including the description of the study (and type of data (i.e. metadata) in the UMCG FAIR data catalogue and other discipline specific catalogue(s).	**YES**
Data and biomaterials are findable through the website (acutelines.umcg.nl), where a data dictionary can be found and a link to the Groningen data catalogue.	
• Review procedure, conditions and agreements for re-use of data and access to data by	**YES/NO**

other researchers will be drawn up.	
<if no, explain>	
• For this study a discipline specific metadata standard will be chosen (i.e. to increase interoperability and re-use).	**YES/NO**
<if no, explain>	
• All new data derived in this study will be returned to Acutelines to enrich the dataset (i.e. to increase interoperability and re-use).	**YES/NO**
<if no, explain>	

5.6 Management of biomaterials

Will biomaterials be collected, processed, analyzed and/or stored for the purpose of this study	**YES**
Data and biomaterials are collected as part of Acutelines (de novo biobank)	
5.6.1 Retrospective study (see sections 1, 5.2.2, and 5.4.1) If biomaterials will be used from a secondary/further use biobank that has not been approved by the Board of Directors of the UMCG, how will be prohibited that biomaterials necessary for future diagnostic/treatment purposes will be used in the present study.	**NA**
5.6.2 Biomaterials collection	
• Only biomaterials required to answer the research question(s) will be collected	**NO**
• What biomaterials will be collected Plasma (EDTA, Li-Heparin, citrate), buffy coat (EDTA), wholeblood RNA (PAXGene), serum, urine, feces	
• How will the biomaterials be collected and processed Biomaterials are collected and processed according to the procedures as described by Acutelines.	
5.6.3 Pseudonymization and access to biomaterials	
• Does the storage unit of the biomaterials comprise information that the participant (in)directly identifies, other than the participant's number and / or the sample number.	**NO**
• Biomaterials can only be accessed by the Principal Investigator and study delegates after authorization by the Principal Investigator	**YES**
5.6.4 Sharing of biomaterials (during and after study completion)	
In case biomaterials (and data) will leave the UMCG, will you contact the loket Contract Research to arrange the proper contracts? (Loket_Contract_Research@umcg.nl)	NA/yes/no
<if no, explain>	
5.6.5 Biomaterials storage (during and after study completion)	
• Where and how will the biomaterials be stored Biomaterials are collected and stored by Acutelines in the Central Freezer facility UMCG.	
• Biomaterials will be stored 15 years after the study is completed	NA
Biomaterials are collected and stored by Acutelines, for at least 15 years.	
• What will be done with the remaining biomaterials after study completion (eg. destroyed, returned to biobank/previous study, stored) <text>	
5.6.6 Biomaterials re-use and access after completion of the present study **Note**: Acutelines stimulates re-use and access of data ("FAIR data"), which is the primary aim of Acutelines and for which participants are asked informed consent. Data and biomaterials are findable through the website (acutelines.umcg.nl), where a data dictionary can be found and a link to the Groningen data catalogue.	NA ☒

5.7 Burden, Risks & Benefits

• If participants are patients: Can be deviated from the standard care / diagnostic	NA/~~yes/no~~

procedures (e.g. can medical treatment be postponed or limited)			
Note: burden is minor, data and biomaterials are collected as part of Acutelines.			
• Will the participants risk any injuries and/or other discomfort when they participate in the proposed study	Yes, minimal risk/burden ☐	Yes, more than minimal risk/burden ☐	No ☒
Note: data and biomaterials are collected as part of Acutelines			
• Participant benefits/reward/incentives: not applicable.			

5.8 Incidental findings

• Is there a risk of incidental findings?	yes, minimal risk ☐	yes, ≥ substantial risk ☐	No ☐
<text>			
If yes, ○ Procedure to assess if a finding should be returned to the participant, or not <text> ○ Procedure to inform the participant <text>			

5.9 Data analysis

- Justification of sample size (e.g. power analysis)
  <text>
- Statistical analysis
  <text>

5.10 Participant information after the study

Will participants be informed about the study results	**YES**
Acutelines aims to inform (former) participants, general public and health care professionals through their media channels (i.e. website, social media; LinkedIn and Twitter). Participants are informed about these media channels in the patient information brochure and via a "thank-you-for-participating-email".	

5.11 Research revenue

In case the study will result in revenues (e.g. as a result of the use of data/biomaterials or successful licensing of intellectual property or manufactured products), will you contact the loket Contract Research to arrange the proper contracts?	**YES**
Reveneus resulting from use of data/biomaterials or successful licensing of IP or manufactured products will be re-invested in the Acutelines biobank, in case no other agreements are made.	

6. Acutelines agreements

Return of investments	
• Return of investment in kind, as follows: xxx	**YES/NO**
• Return of investment in cash according to the specified budget (6.1)	**YES/NO**
<if both of the above are no, explain>	
Output	
• Sharing scientific output in the form of (a) co-authorship(s) for xxx (name person[s])	**YES/NO**
• Sharing intellectual property with xxx (name person[s]) for which further contracts will be signed prior to the initiation of the project	**YES/NO**
• The required text for manuscripts (8.1) will be included in all publications arising from data or biomaterials derived from Acutelines	**YES**
• Any publication (a.o. [non]scientific manuscript, conference proceeding, presentation at conference, laid press, social media) arising from data or biomaterials derived from Acutelines will be send to acutelines@umcg.nl to obtain permission prior to publication	**YES**
Promoting outreach of results	
• Lay-person summary for website (text [100-150 words], infographic [A5, color] or animation [< 2 min.] in Dutch and English	**YES**
• Lay-person summary for Twitter in Dutch and English	**YES**

6.1 Acutelines budget for acquisition, storage and transfer

Note: this is a required section prior to submitting the protocol. Obtain this information by sending the protocol to acutelines@umcg.nl to ask the steering committee to complete the budget below.

Description	Number	Cost	Total
Data acquisition/storage	xxx	€ xxx	€ xxx
Biomaterial acquisition/storage	xxx	€ xxx	€ xxx
Preparation and transfer of data	xxx	€ xxx	€ xxx
Preparation and transfer of biomaterials	xxx	€ xxx	€ xxx
Total			**€ xxx**

7. REFERENCES

8. APPENDICES

8.1 Required text for manuscript

"Data/ samples were obtained from Acutelines: a data-, image and biobank at the Emergency Department (ED) of the University Medical Center Groningen (UMCG) [1]. In order to allow collection of data and biomaterials when applicable upon first contact, primary screening of patients for eligibility upon arrival in the ED is performed 24/7 by the ED-nurse together with a trained research team. Biomaterials were collected upon triage, before starting treatment, and processed immediately at the ED followed by storage at -80°C. Bedside monitoring data (i.e. electrophysiological waveforms, vital parameters) are automatically captured and stored, and information from other data sources (such as the electronic health records of the hospital-, emergency medical services- and the general practitioner, the municipal registration, health insurance companies and the pharmacy) is securely imported. Follow-up data were collected for all included patients during the first 72-hours of their hospitalization and 3-months, 1-year, 2-years and 5 years after their ED visit. Study data were collected and managed using REDCap electronic data capture tools hosted at the UMCG [2,3]. Acutelines' complete protocol and overview of the actual, full data dictionary is available via https://acutelines.umcg.nl. A deferred consent procedure (by proxy) is in place to allow the collection of data and biomaterials prior to obtaining written consent. Acutelines is approved by the medical ethics board of the UMCG and registered under trial registration number NCT04615065 at ClinicalTrials.gov."

References

1. E ter Avest, BC van Munster, RJ van Wijk, S Tent, S ter Horst, TT Hu, LE van Heijst, FS van der Veer, FE van Beuningen, JC ter Maaten, HR Bouma. Cohort profile of Acutelines : a large de novo data/ biobank of acute and emergency medicine. BMJ Open.

2. PA Harris, R Taylor, R Thielke, J Payne, N Gonzalez, JG. Conde, Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr;42(2):377-81.

3. PA Harris, R Taylor, BL Minor, V Elliott, M Fernandez, L O'Neal, L McLeod, G Delacqua, F Delacqua, J Kirby, SN Duda, REDCap Consortium, The REDCap consortium: Building an international community of software partners, J Biomed Inform. 2019 May 9 [doi: 10.1016/j.jbi.2019.103208].