Research project title

Automated detection of adverse drug events from older inpatients' electronic medical records using structured data mining and natural language processing

Study Type:	Further use of biological material and health-related personal data for research in absence of informed consent in accordance with Article 34 HRA
Study Categorization:	Category A
Study Registration:	The clinical trial will be registered through clinical trial.org once the appropriate ethics committee has approved it.
Study Identifier:	**SwissMADE**
Principal Investigator:	Prof. Chantal Csajka
Sponsor:	Service of Clinical Pharmacology, CHUV Rue du Bugnon 46, 1011 Lausanne - SUISSE
Investigational Product:	Antithrombotic drugs
Protocol Version and Date	Version 1.0 dated 06.02.2018

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With my signature I have approved the research protocol version 1 (dated 06.02.2018), and I confirm hereby to conduct the project according to the protocol and the local legally applicable requirements, and in particular the data protection therefore.

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Co-Investigators have approved the protocol version 1.1 .2014 and confirm hereby to conduct the study according to the protocol, current version of the Declaration of Helsinki (1964), ICH-GCP guidelines and the local legally applicable requirements.

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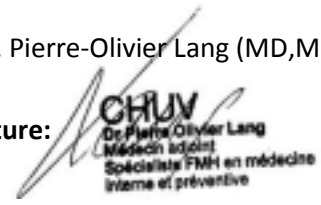
Date: 25.01.2018 **Signature:** 

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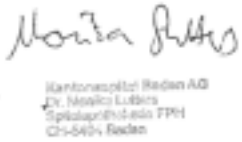
Date: 02.01.2018 **Signature:** 

Abbreviations

ADEs - Adverse drug events

ATC - Anatomical therapeutic chemical classification system

CDS - Clinical decision support

CFR - Code of federal regulations

CIRS - Critical Incident Reporting System

CHOP Codes - Swiss classification of surgical interventions

CTCAE - Common terminology criteria for adverse events

EC - Ethics committee

EMRs - Electronic medical records

HRA - Human Research Act

HRO – Human Research Ordinance

ICD-10-GM Codes - The International Statistical Classification Of Diseases And Related Health Problems 10th revision, German Modification

LOINC - Logical observation identifiers names and codes

MedDRA - Medical dictionary for regulatory activities

NLP - Natural language processing

PRN orders - « Pro re nata » orders

SDM - Structured data mining

SNOMED-CT - Systematic nomenclature of medical clinical terms

SwissMADE DB - SwissMADE database

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1. Background and rationale

Patient injury resulting from medication use [1, 2], also known as adverse drug events (ADEs), is the second most frequent complication experienced by hospitalized patients, accounting for one-third (10% to 40%) of all hospital care-related adverse events [3-5]. Between 0.2% and 65% of hospitalized patients experience at least one ADE during their stay [6-9]. Apart from increasing patient morbidity and mortality, ADEs seriously impact on hospital utilization (i.e. increased lengths of stay and readmissions) and costs [2, 4, 9-12].

Older inpatients (aged ≥ 65 years) are especially at risk of ADEs. Over 30% of older inpatients experience at least one ADE during their hospital stay and up to 70% of these events are deemed preventable [8, 13-15]. ADEs also have more severe consequences in older inpatients, inducing or worsening frailty, functional and cognitive disability, and leading to loss of autonomy, frequent and longer hospital stays, as well as an increased risk of institutionalization and death [13, 14, 16].

Cardiovascular drugs are frequently associated with ADEs in older patients, in particular the classes of antithrombotic and antihypertensive drugs. Although recommended and widely used in elderly patients at increased risk of cardiovascular events, antiplatelet and anticoagulant treatments are highly associated with bleeding complications in the older population [17-19], and are a major cause of emergency department admissions and death in elderly patients [20-22]. Antithrombotic therapy is thus like the sword of Damocles, conferring protection against thrombosis while exposing to bleeding, with severe consequences in both cases [18, 23]. A recent study indicated that bleeding events were the most common ADE (36%) in patients over 65 [24]. The drugs most frequently involved in serious ADEs were antithrombotic agents (31%). Disregarding drug interactions, contra-indications and precautions caused 20% of ADEs, and drug overdoses were present in 17% [25]. In addition, combinations of these factors and inefficacy raise particular concerns from an individual and public health point of view.

Many interventions have been conducted to improve the quality and safety of medication prescribing in older inpatients [4, 26-30]. The most recent and significant ones include the provision of evidence- based prevention tools (e.g. specific guidelines [31], lists of criteria for inappropriate medication use [30, 32]), pharmacist-based interventions (e.g. patient counselling, medication reconciliation, clinical pharmacist rounding) [29], team-based interventions (e.g. multidisciplinary geriatric teams [27]), and information and communication technologies such as computerized clinical decision support (CDS) tools within computers. Some CDS tools, called clinical event monitors, detect and monitor drug-related problems and provide feedback through alerts and reminders when certain signals regarding pharmacy orders (i.e. sudden stop orders, antidote ordering, and dose correction orders), laboratory test results or patient characteristics have been triggered [33-38].

In Switzerland, CDS systems have been developed and implemented in hospital information systems [36,38]. However, current systems generate many false-positive alerts, target inappropriate prescriptions instead of clinically relevant ADEs, and do not consider the type of hospital or unit (e.g. medical, surgical), nor the patients' medical characteristics [33, 35, 39, 40]. Owing to their limitations (poor specificity, overalerting) [35, 39] and to the amount of information contained in electronic medical records (EMRs), new ADE detection and monitoring systems are currently being developed based on multiple sources of data (structured data and free texts from EMRs) and methods involving structured data mining (SDM) and natural language processing (NLP) [40-44]. These new systems' performance depends on their ability to process meaning and content from either structured or unstructured data. EMR entries that comprise drug names, doses, treatment durations and administration routes, laboratory results, diagnoses or procedure codes based on the International Classification of Diseases, Tenth Revision, German

Modification (ICD-10-GM) and the Swiss classification for surgical procedures (CHOP) can be considered as structured. Other information such as reasons for admission, patient history and conditions, nursing and medical progress notes, inpatient reports and discharge summaries are essentially available in unstructured free text or narratives.

Apart from CDS system targeting drug interactions, dosing errors, or prescription orders [25, 38, 45, 46], no ADE detection and monitoring system based on EMRs' structured data mining and natural language processing is currently available in Switzerland. Nor can "ready-made" systems from other countries be adapted as they were developed for EMRs written essentially in English [41, 42, 44].

2. Objectives

Our research hypothesis is that the automated detection of ADEs from EMRs using structured data mining and natural language processing (SDM and NLP) could significantly improve risk management and patient safety in hospitalized older inpatients with multimorbidity, frailty and polypharmacy. It could additionally provide reliable data on incidence of ADEs for health care professionals, patient safety organisations and policy-makers.

The main objective of the project is to develop and validate an electronic application for the automated detection of ADEs related to antithrombotics based on structured data and free text mining.

Secondary objectives are :

- To quantify the incidence of ADEs associated with and caused by antithrombotic drugs,
- To assess the causality, severity and preventability of detected ADEs induced by antithrombotic drugs,
- To develop strategies for the implementation of the project results to improve risk management of antithrombotic drugs in hospital settings.

3. Patients' eligibility criteria

3.1. Inclusion criteria

The project is a multicenter observational cohort study using routinely collected health-related personal data.

The inclusion criteria are as follows:

- Patients aged ≥65
- A hospital admission between 01.01.2015-31.12.2016
- At least one antithrombotic drug prescription during each stay
- Hospital stays >24 h

3.2. Exclusion criteria

We will exclude from our study any patient for whom an explicit refusal to be involved in research projects or to give access to their personal health data is documented.

4. Study procedures

4.1. Data

4.1.1. Participating centers

Four hospitals will participate in the project:

- 2 hospitals in the French speaking part of Switzerland : Hôpitaux Universitaires de Genève (HUG) and Centre Hospitalier Universitaire Vaudois (CHUV)
- 2 in the German speaking part : Universitätsspital Zürich (USZ) and Kantonspital Baden (KSB)

4.1.2. Source data

This project will make use of health-related information routinely collected during daily practice. Relevant health-related data as defined below will be extracted by each participating hospital for all patient stays fulfilling the inclusion criteria.

For this project, we will focus on five different classes of antithrombotic drugs, i.e. heparins (unfractionated heparin and low molecular weight heparins), vitamin K antagonists (coumarin derivatives), DOACs (direct oral anticoagulants), fondaparinux (direct thrombin and factor Xa inhibitors), and antiplatelet drugs. The list of selected classes of drugs is presented in Table 1 and the list of drugs presented in Annexe 1.

Table 1: B01A Antithrombotic agents

ATC Code *	Classes of antithrombotic drugs
B01AA	Vitamin K antagonists
B01AB	Heparin group
B01AC	Platelet aggregation inhibitors excl. heparin
B01AE	Direct thrombin inhibitors
B01AF	Direct factor Xa inhibitors
B01AX05	Other antithrombotic agents : Fondaparinux

* ATC Code: Anatomical Therapeutic Chemical Classification System

Health-related data comprise: General administrative data, patient location and transfer within the hospital, pertinent clinical and laboratories biological measurements, drug-related prescriptions, diagnoses (ICD-10 codes) and surgical procedures (CHOP). All diagnostic or procedure codes will be considered a priori, and their pertinence with regard to haemorrhages or thromboses will be evaluated upon the elaboration of the algorithm. Dates will be provided with all extracted items.

A case identification number (CaseID) will be attributed to each patient's stay (from 1 to n). CaseID will be grouped by patient using a patient identification number (PID). The extracted items are presented in **Table 2** for structured data. Documents that will be extracted as free texts are presented in **Table 3**. Details of the extracted items are presented in Annexe 2.

Data will be split in a learning set and different validation sets for NLP and predictive analyses of ADEs (see 4.2)

Table 2 : Structured data extracted for the project

Data type	Extracted data	Comments (Unit)
General Administrative Data	Patient identification number	(value)
	Case identification number (admission ID, hospitalization ID, or stay ID)	(value)
	Insurance type	(category)
	Region of residence (MedStat region)	(category)
	Admission mode: admission via emergency department, planned admission, transfer, etc.	(category)
	Nationality	(category)
	Date of birth	(date)
	Gender	(category)
	Date of death (if any; enables calculation of in-hospital mortality)	(date)
Clinical measurements*	Blood pressure	(value)
	Weight	(value)
	Height	(value)
	Sum of alcohol withdrawal syndrome score	(value)
Patient location(s) and transfers*	Unit of hospitalization	(category)
	Transfers (medicine, surgery, intermediate care, intensive care)	(category)
	Date and time of admission	(date, time)
	Date and time of discharge	(date, time)
Diagnoses and procedures*	DRGs codes	(category)
	CHOP codes (with ancillary information)	(category)
	ICD-10 codes (with ranking information)	(category)
	Readmissions and reasons for readmissions (1st, 2d, 3rd, 4th, subsequent readmissions)	(category)
	Drugs coded for reimbursement	(category)

	Intensive Care Unit length of stay (in hours)	(category)
	Duration of mechanical ventilation (in hours)	(category)
	Disease severity and scores	(category)
	Nine Equivalents of Nursing Manpower use Score » (NEMS) score	(category)
Laboratory values* Laboratory results that were ordered or received within the time frame of any of the recorded/extracted stays (if available)		(value in specific unit)
	electrolytes and ions	
	Blood Ionogram (Sodium and Potassium)	(mmol/L)
	Serum lactate and bicarbonate	(mmol/L, mmol/L)
	Uric acid	(mmol/L)
	Urea	(mmol/L)
	Serum iron, Transferrin saturation and Serum Ferritin	(mmol/L , µg/L)
	enzymes	
	Serum aminotransferases	AST/ALT (UI/L)
	Serum 5'Nucleotidase activity	(UI/L)
	Creatine kinase (CK)	(UI/L)
	Gamma-glutamyltransferase (GGT)	(UI/L)
	Alkaline phosphatase (ALP)	(UI/L)
	Complete Blood count (CBC)	
	Red blood cell count	(Absolute value / mm3)
	Hemoglobin	(mmol/L)
	Hematocrit	(percentage of total blood volume)
	Mean Corpuscular Volume	(μ^3)
	White blood cell count	(Absolute value / mm3)
	Platelet count	(Absolute value / mm3)
	Reticulocyte count	(Absolute value / mm3)
	Hemostasis	
	Prothrombin time (PT)	(time)
	Activated partial thromboplastin time (APTT)	(time)
	Thrombin time (TT)	(time)

	International normalized ratio (INR)	-
	Plasma Fibrinogen	(g/L)
	Procoagulant balance	Antithrombin (g/L), Protein C and S (nmol/L), Anti-cardiolipin antibody (GPL Unit), Anti-bêta-2-glycoprotéine 1 antibody (GPL Unit)
	Individual coagulation factors	(% relative to a reference pool)
	Fibrinolysis	D-dimer (µg/L)
	Anticoagulation monitoring	Anti-Xa (% relative to a reference value), Anti-IIa (% relative to a reference value)
	Markers of coagulation	Thrombin-Antitrombin III Complex TAT (ng/ml), Fragment 1 + 2 of prothrombin (% relative to a reference value)
	Other	
	Albumin	(g/dL)
	Serum total protein	(g/dL)
	Oxygen saturation	(% relative to a reference value)
	C-reactive protein (CRP)	(mg/L)
	Myoglobin (Mb)	(µg/L)
	Troponin	(µg/L)
	Creatinine and Creatinine Clearance	(mg/L, ml/min)
	Total bilirubin, direct and indirect bilirubin	(mg/L, mg/L, mg/L)
	Glycated hemoglobin	(% relative to a reference value)
	Tumor markers available	-
Prescription/medication*	ATC code (and product ID)	(category)

All medication orders that have: (i) a planned start date ≤ discharge date AND *(ii)* a planned discontinuation date ≥ admission date	Information on dose and planned administration frequency, incl. unit (e.g. MG=milligrams)	(value, category)
	Information on administration route (e.g. intravenous administration vs. oral)	(category)
	PRN orders ("as needed": drugs available on patient's request, e.g. analgesics)	(category)
	Administrations performed (signed by nurses)	(category)

* (incl. time stamps), linked to patient ID and to case ID/admission ID

Table 3 : Free-texts and narratives extracted for the project

Extracted data	Comments (Unit)
Patient identification number (metadata)	(free-text)
Case identification number (admission ID, or hospitalization ID, or stay ID) (metadata)	(free-text)
Notes taken at admission	(free-text)
Discharge summaries and letters	(free-text)
Nurses' progress notes	(free-text)
Imaging/radiology reports	(free-text)
Specialists' (e.g. hematologist, cardiologist, angiologist, and particularly endoscopy reports) consultation notes	(free-text)
Clinical pharmacology or pharmacy service consultation notes	(free-text)
ADE / Pharmacovigilance Reports	(free-text)
CIRS Reports	(free-text)

4.2. Data analysis

All extracted data will be used to develop algorithms, which will identify ADEs. Thus, based on developed algorithms, we will be able to indicate for each hospital stay of the extracted database whether an ADE has potentially occurred. To test for the algorithms' accuracy, we will then randomly select a validation dataset from the extracted database and verify in the corresponding EMRs (gold standard) whether an ADE has truly occurred or not. As a result, algorithms will be improved according to the results of the

validation (maximization of sensitivity and specificity, as well as of positive and negative predictive values). In the end, validated algorithms will serve to identify ADEs accurately (validated outcomes). For a more detailed description of the development and validation process of algorithms, see section 4.2.4.
To identify best predictors of ADEs, we will also use predictive modelling, such as various machine learning algorithms or logistic regression models. Outcomes of interest will be the validated outcomes described above. Predictors (i.e. ADE risk factors) will be selected from structured and textual information available in extracted data. Predictive models will also undergo internal and external validation: k-fold cross-validation and accuracy assessment of predicted outcomes, respectively [47].

At last, we will study the causal relationship between ADE risk factors and validated outcomes using causal analysis [48, 49].

4.2.1. Identification of antithrombotic ADEs

In order to identify ADEs induced by antithrombotics, computational algorithms based on logical rules will be developed based on direct and indirect indicators of ADEs (Table 4). This study will focus on two types of events: hemorrhage and thromboembolic events, which will be defined according to international references [50-52]. Potential confounding factors in the causal relationship between antithrombotic drugs and related ADEs will be identified from the scientific literature (including concomitant drugs, patient characteristics and concomitant health conditions).

Table 4 : Direct and indirect ADE indicators

ADE markers	clinical signs or symptoms indicating that an antithrombotic-related ADE occurred
ADE triggers	clinical signs, symptoms, procedures, prescription and imaging orders, biological results that indicate that an antithrombotic-related ADE may have occurred
ADE confounding conditions / risk factors	conditions or factors that increase the potential for an antithrombotic-related ADE or for a spontaneous bleed or thombotic event to occur. Risk factors include patient characteristics, specific concomitant health conditions that may interact with antithrombotics, concurrent use of more than one antithrombotic
ADE causes	causal factors are risk factors that are responsible for antithrombotic-related ADEs, including inappropriate prescribing (under-, over-, mis-prescribing), interactions (drug-disease, drug- food and drug-drug interactions), inappropriate administration, and insufficient monitoring.

4.2.2. Elaboration of algorithms based on structured data (SDM)

Computational algorithms based on logical rules applied to structured data will be developed to identify ADE markers, triggers, confounding conditions /risk factors and causes.

Detection algorithms for clinical markers of ADE (i.e. hemorrhagic events or thromboembolism) and confounding clinical conditions (e.g. chronic liver or kidney disease, hypertension, diabetes, cancer,

multimorbidity) will target ICD-10-GM diagnostic codes in hospital discharge data. Regarding ADE triggers, clinical conditions (e.g. hypotension, shock, and acute kidney failure) and procedures (e.g. postoperative *control of haemorrhage*, drainage of hematoma, or surgical treatment of venous or arterial thromboembolism) will be identified from hospital discharge data by algorithms based on ICD-10-GM diagnostic codes and CHOP codes, respectively. Biological triggers of ADEs (i.e. abnormal laboratory values) will be detected by algorithms applied to laboratory results. Similarly, some algorithms based on prescription orders will search for pharmacological triggers of ADEs including sudden medication stop orders, antidote ordering, dose correction orders, under- and overdosing, misprescribing, insufficient monitoring, and drug-drug or drug-disease associations. Finally, some algorithms based on imaging orders will flag imaging triggers of ADEs (e.g. emergency head or abdominal CT-scan orders, upper endoscopy orders for haemostasis).

4.2.3. Elaboration of algorithm based on free texts and narratives (NLP):

Based on ADE markers and triggers, and confounding conditions, a set of relevant concepts will be identified in existing knowledge representation frameworks. This set of concepts will be organized in a coherent and pertinent taxonomy validated by pharmacologists, pharmacists, and geriatricians from the research team. This taxonomy will serve as a placeholder for a text-based approach of the variables of interest (e.g. clinical ADEs, laboratory or imaging results, comorbidity). For example, a structured rule for hyperkalemia could be "[LabVal: K+] $\geq$ 3.5 [unit: mmol/l]", whereas this would be expressed in a text (i.e. discharge letter, medical or nursing notes) in numerous ways, including "kaliémie élevée", "hyperkaliémie", etc. for EMRs written in French. This taxonomy will be encoded using standardized codes from existing classifications such as the Medical Dictionary for Regulatory Activities (MedDRA), the Systematic Nomenclature of Medical Clinical Terms (SNOMED-CT) and the Logical Observation Identifiers Names and Codes (LOINC) [53, 54].

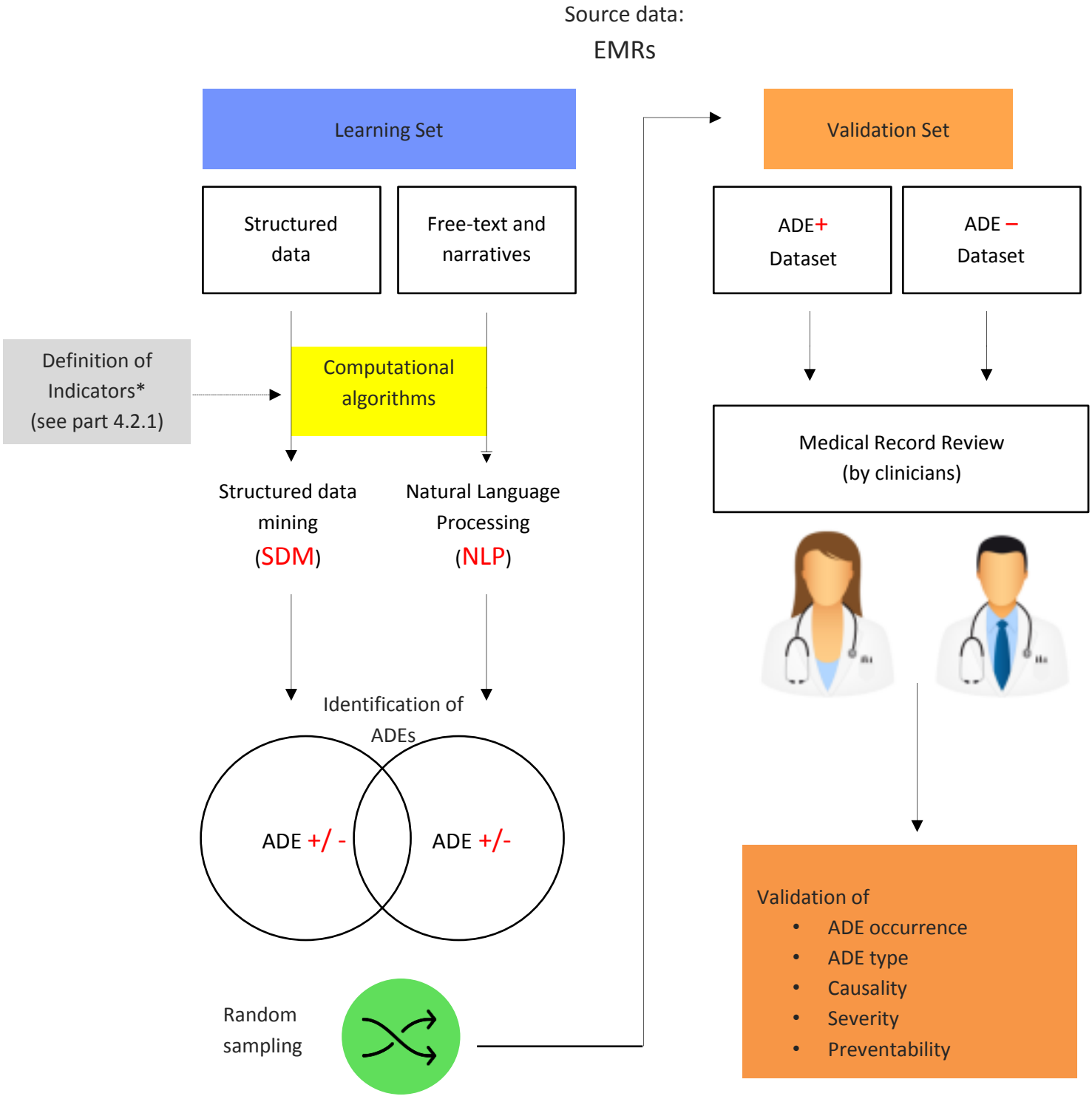
Already developed devices such as known mapping lists of free text medication orders and NLP algorithms to map drug orders to the ATC codes will help to make fast progress in terms of the inclusion of uncoded free text order entries (Table 5). The mapped ATC codes and the hierarchy of the ATC classification system will enable us to compare drugs and drug groups otherwise designated by brand names in free text orders.

Table 5: Examples of raw data medication orders that require a time-consuming mapping process in order to enable their consideration in the analysis.

Drug orders and free text entries (extracted raw data)	ATC code added by manual and automated mapping
Novalgin(Novaminsulfon sintetica 50% 1g/2ml	N02BB02
Novalgin1gr	N02BB02
Novalgin50%InjLsg1g/2ml	N02BB02
Novalgin i/v	N02BB02
Novaminsulfon (Inj Lös 1 g/2ml) Amp / Metamizol 500mg/ml	N02BB02
Novaminsulfon SIN injektionlösung	N02BB02
Minalgin 50% (Inj Lös 1 g/2ml) i.m./i.v. Amp / Metamizol 500mg/ml	N02BB02
Minalgin 500	N02BB02
Novaminsulfon 1g in 100ml NaCl 0,9%	N02BB02
Novalgin 1gr.	N02BB02

In the end, we will obtain for each 2015 and 2016 hospital stays of patients aged ≥65 years treated with antithrombotics a CaseID of positive ADE detected from the developped algorithms based on structured data (SDM), unstructured data (NLP), and on both types of data (SDM+NLP)(Figure 1).

Figure 1 : diagrams presenting the study procedure



ADE +/- = Hemorrhagic and thromboembolic events detected/ not detected

* defined according to scientific literature (standard pharmacological references) and clinical guidelines

4.2.4. ADE detection tool assessment

To assess the performance (sensitivity, specificity, positive and negative predictive values) of the ADE detection tool, a validation will be performed on a random sample of 600 hospital stays. ADE occurrence, type, causality, severity and preventability will be assessed by means of a patient medical record review, analysed by a team of pharmacologist, pharmacists and geriatrician from the research team (Figure 1).

To ensure that the ADE assessment and data abstraction are structured and reliable, pharmacologists and pharmacists from the research team will develop a common "ADE assessment form" both in French and German based on existing good pharmacovigilance practice rules, which will be disseminated in their original languages and English after study completion. Pairs of trained clinicians (pharmacists, pharmacologists, geriatricians) will then assess all selected medical records using this form. The causality between having taken a drug and the advent of an ADE will be assessed using existing causality assessment scales [55, 56]. The severity of the ADEs will be scored according to the Common Terminology Criteria for Adverse Events (CTCAE). Finally, an ADE will be deemed preventable if caused by a medication error that occurred during prescribing, transcribing, dispensing, administering, and monitoring or if it was due to a lack of medication adherence.

To test for the reliability of ADE assessment by pharmacists and pharmacologists, we will calculate intra- and inter-rater agreements for overall ADE occurrence, causality, severity, and preventability. For each pair of trained pharmacists and pharmacologists, the inter-rater agreement will be tested by comparing the results of the ADE assessment between members of the pair. To test for intra-rater agreement in each participating hospital, a random sample including 100 ADEs detected by SDM and NLP will be re-assessed by the assigned pair, 3 months after their first assessment. For both intra- and inter-rater agreements, the measure of agreement will be the Cohen's or uniform kappa statistic [57].

After excluding "false positive" ADEs, we will measure the cumulative incidence of "true positive" preventable ADE and non preventable ADEs for each hospital, medical units and overall.

5. Data management

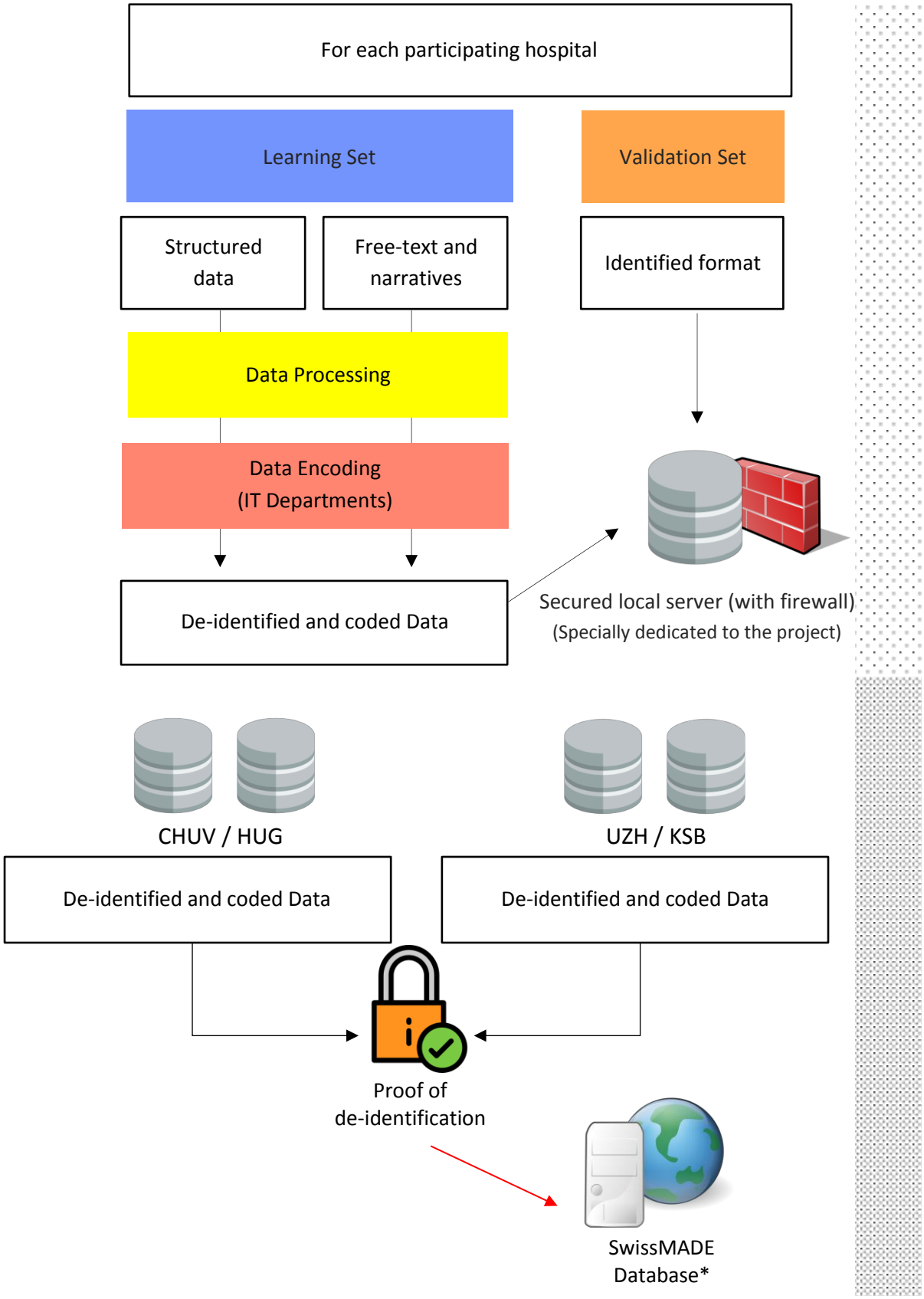
5.1. Data extraction procedures

Data will be extracted from inpatients' electronic medical records (EMRs) by the Information Technology (IT) departments of each hospital. Before being processed, structured data will be standardized in a unique common format (common data model) and unstructured data will be transformed in a machine-readable format, when necessary.
Regarding data extraction for the validation of the algorithms, individual data will be manually collected in EMRs at each hospital site and entered on a secured web-based electronic case report form that ensures traceability.

5.2. Data governance

As a consequence of the multi-site and bi-lingual (French and German) nature of the project, we will use a centralized and de-centralized data governance strategy, as presented in Figure 2.

Figure 2 : diagrams presenting the **de-centralized data governance strategy** (Step 1)



* Unless otherwise authorized, study investigators will only have access to this shared database

A two step approach will be undertaken for data processing.

Step 1. Centralized data processsing

Raw data from the EMRs will be managed and processed by the IT team of each hospital according to established protocols. For structured data, the nominative identifiers will be coded (there are 18 identifiers to delete as described in HIPAA Privacy Rule, Code of federal regulations (CFR) - Title 45: Public Welfare, Subtitle A §164.514). Free text and narratives of the learning set will be de-identified and coded locally before being transferred to secured servers specially dedicated to the project within each hospital. Each hospital's IT team will be responsible for processing their own data.
First data processing and analyses will be performed within each hospital.
EMRs used for the validation of the algorithms will be available in an identified format. Data will remain on a secured server in each hospital and made available to authorized investigators within each hospital.

Step 2. De-centralized data processsing

Locally extracted coded data of the learning set from the German-speaking part of Swizlerland (UZH and Baden) and from the French-speaking part (CHUV and HUG) will be transferred to a centralized common SwissMADE database (SwissMADE DB). Processed coded structured items from free texts and narratives will be transferred to the SwissMADE DB.

One authorized person per site will be allowed access to personal data and will decide who can access to which data linked to which analysis (see 5.2.3). Remote access to the local working databases within each hospital and the SwissMADE database to authorized investigators will be made possible through a virtual Private Network (VPN).

5.2.1. Persons responsible of data protection

According to the governance plan described above, a main representative of the project within each hospital will take full responsibility of data use and protection. The responsible person per hospital is as follows:

CHUV	Pr. Chantal Csajka, PI of the project
HUG	Pr. Christian Lovis, co-investigator
UZH	Dr. Patrick E. Beeler, co-investigator
Baden	Dr. Monika Lutters, project partner

The main local representative will keep the correspondence file « coded/de-idenfified identifier »/« nominative identifier » in a secured place separately from the dataset.

5.2.2. Persons entitled to receive the personal data

The main representative for data protection per site will provide the authorisations to access data to other co-investigators. According to article 5 ORH, the use of personal health data is limited to those who need it to perform their tasks.

Personal data from the validation test will not be accessible by any investigators before completion of the algorithms. For validation purposes, such data will be accessible to authorized clinicians (clinical pharmacists, clinical pharmacologists and geriatricians) of the research team.

The SwissMADE database will be accessible for analyses to authorized investigators. The responsible investigator per site will make sure that all relevant information produced by each research lab will be transmitted to other groups. Extracted data might be reused for further related research projects.

5.2.3. Data storage

Each hospital's IT team will be responsible for processing their own data until transfer to the SDM and NLP working databases and the final transfer to the SwissMADE DB. The SwissMADE DB will be hosted in a secured environment backed up and linked to the academic network http://tribu.intranet.chuv/content_details.htm?cid=21945.

Any correction or deletion will be traced by the investigators in accordance with Article 5 of the law on data protection (LPD). The data will be stored until the publication of the results of the study. The correspondance file « coded identifier »/« nominative identifier » will be destroyed once the study is completed.

These measures comply with the requirements of Article 5 ORH on operational and technical measures to prevent unauthorized or inadvertent publication, modification, deletion and copying of personal health data.

5.2.4. Scientific steering committee

A scientific steering committee will be set up to allow regular discussions of the PNR74 study progress. All sub-projects ancillary to or related to the present project will be submitted to the scientific committee for approval. The scientific committee is composed of Prof. Chantal Csajka, Dr. Marie-Annick LePogam, Dr Pierre-Olivier Lang from the CHUV, Prof Christian Lovis, Dr Nicole Vogt-Ferrier from the HUG, Dr Fabio Rinaldi, Dr P. Beeler from Zürich and Dr. Monika Lütters from Baden.

6. Scientific methodology

6.1. Sample size calculation for the retrospective medical record review

The sample size was estimated to assess the performance of the SDM+NLP tool in detecting haemorrhagic adverse events. Indeed, the SDM+NLP tool is considered the critical outcome determining the feasibility of the project, and haemorrhage the most important adverse event related to antithrombotic drugs. We used a test-result based sampling method to minimize the number of medical records to be abstracted [58]. Given that CI is the cumulative incidence of ADEs detected from both structured and unstructured data ; N is the number of 2016 hospital stays of patients at risks (i.e. patients aged ≥65 years treated with antithrombotic drugs) ; P(ADE+) is the proportion of hospitals stays with an ADE detected by the SDM+NLP tool among all at-risk hospital stays (it is calculated as the number of true positive and false positive ADEs detected divided by N) ; Se is the expected sensitivity of the SDM+NLP tool (and Se 95%CI its 95% confidence interval) ; Sp is the expected specificity of the SDM+NLP tool ; PPV, its expected positive predictive value ; NPV, its negative predictive value ; we calculated sample sizes for CI ranging from 3% to 24%, a desired Se of 80%, a 20% width for Se 95%CI, volumes of at-risk hospital stays ranging from N=2000 to 20'000 and a balanced sample of ADE+ and ADE- hospital stays (i.e. hospital stays with and without ADE, respectively) (Table 6). CI values were elicited from the literature (i.e. range for ADE cumulative incidence: 30-40% and range for proportion of haemorrhagic ADEs among ADEs: 10-40%)[13]. The values for N were estimated from annual numbers of at-risk stays in the 4 participating hospitals. We considered, in particular, selecting hospital units with a high prevalence of antithrombotic prescription (i.e. acute geriatric unit, internal medicine, cardiology, angiology, orthopaedic surgery, thoracic surgery, and cardio-vascular- surgery), which would increase the number of at-risk stays. The frequencies of 2015 at-risk stays in these selected units are 4711, 5130, 5564, 5016 for CHUV, HUG, USZ, and KSB, respectively (N=20421). The sample size calculation was performed using STATA IC, V 14.

Table 6. Minimum sample size (all medical records, ADE + medical records and ADE – medical records) according to the ADE cumulative incidence (CI), the number of at-risk hospital stays (N), a desired Se of 80%, a 20% width for Se 95%CI, and relevant values of the proportion of positive tests [P(ADE+)]

		Sample Size: total			Sample size: ADE+			Sample size: ADE-		
		N			N			N		
CI	P(ADE+)	2000	20000	Undefined	2000	20000	Undefined	2000	20000	Undefined
3%	5%	all	1840	1957	all	141	150	all	1699	1807
	10%	all	1941	2016	all	247	257	all	1694	1759
	20%	all	2000	2055	all	381	392	all	1619	1663
	30%	all	1979	2018	all	475	484	all	1504	1534
5%	7%	1169	1088	1208	97	90	100	1072	998	1108
	10%	1186	1128	1217	136	130	140	1050	998	1077
	20%	1207	1173	1231	222	216	226	985	957	1005
	30%	1192	1167	1207	280	274	284	912	893	923
10%	12%	547	524	613	53	51	60	494	473	553
	20%	569	552	610	93	91	100	476	461	510
	30%	567	555	596	126	123	132	441	432	464
	40%	552	541	573	149	146	155	403	395	418
20%	22%	245	240	289	31	30	36	214	210	253
	30%	254	248	287	47	47	53	207	201	234
	40%	249	245	276	62	60	68	187	185	208
	50%	237	233	261	72	70	79	165	163	182
24%	26%	195	192	235	27	26	32	168	166	203
	30%	201	196	234	34	33	39	167	163	195
	40%	199	196	226	47	46	53	152	150	173
	50%	190	186	214	56	55	63	134	131	151

Thus, assuming CI equal 10%, p(ADE+) equal 12%, 20'000 at-risk hospital stays, and an expected Se equal 80% with a 20% width for Se 95%CI, a random sample of at least 524 medical records (51 ADE+ medical records and 473 ADE- medical records) will be necessary to assess the SDM+NLP tool. Considering that some medical records might not be available (let's say 1%), the validation will finally require 530 medical records. We will thus abstract 15 medical records flagged as ADE+ and 120 medical records flagged as ADE- by the SDM+NLP tool in each of the 4 participating hospitals (135 medical records per hospital). Under these assumptions, the expected values and confidence intervals for Se, Sp, PPV and NPV should be respectively:

- Se = 80%; 95% CI Se= [68%; 88%]
- Sp= 96%; 95%CI Sp = [94%; 97%]
- PPV= 67%; 95%CI PPV = [52%; 79%]
- NPV= 98%; 95%CI NPV= [96%; 99%]

Regarding external validation of predictive models, we will compare predicted outcomes with true outcomes based on medical record screening for a small sample of 20 to 30 hospital stays for which predicted and validated outcomes diverge.

7. Ethical and regulatory aspects

The research project will be carried out in accordance with the research protocol, the Human Research Act (HRA) and the Human Research Ordinance (HRO). The protocol has been submitted to the local competent Ethics Committee (EC) and the study will be initiated after approval from CEC.

7.1. Motive for a proxy consent obtained from the ethics committee

Because of the high number of patients included in the study and the retrospective design of the study, an individual informed consent will not be sought. In this project, abiding by the procedure of a proxy consent obtained from the ethics committee is in keeping witharticle 34 of the “Loi relative à la recherche sur l’être humain ». Furthermore, obtaining individual informed consent would indeed imply all study investigators have access to nominal personal data, which is to be avoided in this retrospective research project.

Any medical records in which it is documented that the patients have expressed their refusal on the use of their personnal data for research purposes or have refused to sign the general consent (BIL) will not be included in the study.

7.2. Notification requirements

Significant changes to the protocol must be approved by the ethics committee in advance. The regular end of the research project is reported to the EC within 90 days upon completion of the project.

8. Funding, publication and declaration of interest

The results of the study will be submitted to local, national and/or international congresses and to peer reviewed journals for publication.

The authors of this protocol have no conflict of interest to declare. This study has been funded by the PNR74 project of the SNF.

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Annexe 1: ATC Codes of the drugs concerned by the study

Class	ATC	Antithrombotic
Vitamin K antagonists	B01AA04	Phenprocoumon
	B01AA07	Acenocoumarol
Heparins	B01AB01	Heparin
	B01AB02	Antithrombin III
	B01AB04	Dalteparin
	B01AB05	Enoxaparin
	B01AB06	Nadroparin
	B01AB09	Danaparoid
Platelet aggregation inhibitors	B01AC04	Clopidogrel
	B01AC06	Acetylsalicylic acid
	B01AC09	Epoprostenol
	B01AC11	Iloprost
	B01AC13	Abciximab
	B01AC16	Eptifibatide
	B01AC17	Tirofiban
	B01AC21	Treprostinil
	B01AC22	Prasugrel
	B01AC24	Ticagrelor
	B01AC25	Cangrelor
	B01AC27	Selexipag
Direct thrombin inhibitors	B01AE03	Argatroban
	B01AE06	Bivalirudin
	B01AE07	Dabigatran etexilate
Direct factor Xa inhibitors	B01AF01	Rivaroxaban
	B01AF02	Apixaban
	B01AF03	Edoxaban
Other antithrombotic agents	B01AX05	Fondaparinux

Annexe 2: Justification of the extracted items for structured data

Data type	(Descriptive) Justification	References
General Administrative Data	Descriptive value	
Clinical measure		
Blood pressure	(To identify blood pressure disorders) Risk factor that influence hemorrhagic, thromboembolic events	(Zhu, He et al. 2015)
Weight/Height	Descriptive value and risk factor that influence hemorrhagic, thromboembolic events	(Lip, Frison et al. 2011, Bene, Dubart et al. 2014)
Sum of alcohol withdrawal syndrome score	Risk factor that influence hemorrhagic, thromboembolic events	(White, Beyth et al. 1999, Olesen, Lip et al. 2011)
Patient location(s) and transfers	Identify triggers that indicate that an antithrombotic-related ADE may have occurred	
Diagnoses and procedures	(Select hospital stays eligible for the denominator of indicators) Identify an hemorrhagic, thromboembolic event (markers)	[59-61]
Laboratory values		
Measured electrolytes and ions		
Blood Ionogram: Sodium and Potassium	(Abnormal values can be a sign of a vital organ failure) Risk factor that influence hemorrhagic, thromboembolic events	[62]

Lactic acid	(Abnormal values may indicate different states of shock, severe anemia or ventricular failure) Risk factor that influence hemorrhagic, thromboembolic events	[63]
Uric acid	(To diagnose kidney disorder or to reveal hematopathies, chronic renal failure, severe hepatic insufficiency (with decreased uric acid synthesis) or signs of tumors) Risk factor that influence hemorrhagic, thromboembolic events	[64]
Urea	(To assess kidney function and in particular to detect renal failure. High values can also be indicative of heart damage or gastrointestinal hemorrhage) Risk factor that influence hemorrhagic, thromboembolic events	[65, 66]
Iron and Ferritin Level	(The determination of iron and ferritin makes the identification of anemia possible) Identify an hemorrhagic, thromboembolic event (markers) and risk factor	[63]
Measured enzymes		
Liver transaminases	(To screen for, detect, evaluate and monitor acute and chronic liver inflammation, liver infection, liver disease and/or damage) Risk factor that influence hemorrhagic, thromboembolic events	[62, 66, 67]
Creatine kinase	(In particular CK-MB and CK-BB- Sign of myocardial or neurological lesion) Risk factor that influence hemorrhagic, thromboembolic events	[64, 66]
Gamma-glutamyltransferase	(To evaluate for a possible liver disease or bile duct disease, sometimes to screen for or monitor alcohol abuse) Risk factor that influence hemorrhagic, thromboembolic events	[64]
Alkaline phosphatase	(To screen for or monitor treatment for a liver disorder) Risk factor that influence hemorrhagic, thromboembolic events	[62, 68]
Complete Blood count (CBC)	(The blood count can reveal a large number of pathologies: anemia, coagulation problem, viral infections or consumption of platelets) Identify an hemorrhagic, thromboembolic event and risk factors	[50-52, 63, 65]

Hemostasis assessment	Identify an hemorrhagic, thromboembolic event and risk factors	[50-52]
Other measured biological values available		
Albumine	(To screen for and help diagnose a liver disorder or kidney disease) Risk factor that influence hemorrhagic, thromboembolic events	[65, 69]
C-reactive protein	(To identify the presence of inflammation) Risk factor that influence hemorrhagic, thromboembolic events	[65, 70]
Myoglobin	(To determine various cardiovascular disorders) Risk factor that influence hemorrhagic, thromboembolic events	[65, 68]
Troponin	(May be a sign of myocardial infarction, pulmonary embolism or myocarditis) Risk factor that influence hemorrhagic, thromboembolic events	[63, 68]
Creatinine and Creatinine Clearance	(To help diagnose kidney disease) Risk factor that influence hemorrhagic, thromboembolic events	[63, 71]
Bilirubin	(To screen for or monitor liver disorders or hemolytic anemia) Risk factor that influence hemorrhagic, thromboembolic events	[63, 72]
Glycated hemoglobin	(To monitor a person's diabetes) Risk factor that influence hemorrhagic, thromboembolic events	[73, 74]
Tumor markers avalaible	Risk factor that influence hemorrhagic, thromboembolic events	[68, 75, 76]
Prescription/medication	Identify an hemorrhagic, thromboembolic event (markers), risk factors, triggers and causal factors	[66]

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