Detection and Prediction of Adverse Drug Events in Routine Healthcare Data from German University Hospitals

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"Man muss die Wissenschaft lieben, dann kann man es schaffen."

Lise Meitner

List of publications

This cumulative doctoral thesis is based on the following publications:

1. Haerdtlein A[†], Boehmer AM[†], Karsten Dafonte K, Rottenkolber M, Jaehde U[‡], Dreischulte T[‡]. Prioritisation of Adverse Drug Events Leading to Hospital Admission and Occurring during Hospitalisation: A RAND Survey. J Clin Med. 2022; 11 (15): 4254. doi: 10.3390/jcm11154254.

2. Wermund AM, Haerdtlein A, Fehrmann W, Weglage C, Dreischulte T, Jaehde U. Drug-Event Pairs as Indicators for the Detection of Adverse Drug Reactions during Hospitalization in Routinely Collected Electronic Data Sources. Clin Pharmacol Ther. 2025; 117 (6): 1811-1819. doi: 10.1002/cpt.3635

3. Wermund AM, Thalheim T, Medek A, Schmidt F, Peschel T, Strübing A, Neumann D, Scherag A, Loeffler M, Kesselmeier M[‡], Jaehde U[‡]; POLAR_MI Consortium. Challenges in detecting and predicting adverse drug events via distributed analysis of electronic health record data from German university hospitals. PLOS Digit Health. 2025; 4 (6): e0000892. doi: 10.1371/journal.pdig.0000892

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List of abbreviations

AE	Adverse event
ADE	Adverse drug event
ADR	Adverse drug reaction
CDS	Core dataset
CDSS	Clinical decision support system
DIC	Data integration centre
DIR	Directive
eCRF	Electronic case report form
EC	European Commission
EHR	Electronic health record
EMA	European Medicines Agency
ETL	Extract, transform and load
FHIR® R4	Fast Healthcare Interoperability Resources Release 4
GI	Gastrointestinal
GVP	Good pharmacovigilance practices
HL7®	Health Level Seven
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10th Rev.)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INTERPOLAR	INTERventional POLypharmacy - drug interActions - Risks
IT	Information technology
LOINC®	Logical Observation Identifiers Names and Codes
MII	Medizininformatik-Initiative (Medical Informatics Initiative)
NSAID	Non-steroidal anti-inflammatory drug
POLAR_MI	Use case "POLypharmacy, drug interActions and Risks" of the MII
RAM	RAND®/UCLA Appropriateness Method
ROC AUC	Median area under the receiver operating characteristic curve
SSRI	Selective serotonin reuptake inhibitor
WHO	World Health Organization
WHO-UMC	WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre

1. Introduction

1.1 Digitalisation of the German healthcare system: Generation and utilisation of routine healthcare data

Germany has made substantial progress in the digitalisation of its healthcare system through regulatory frameworks such as the Digital Healthcare Act (*Digitale-Versorgung-Gesetz*) and the Hospital Future Act (*Krankenhauszukunftsgesetz*) [1,2]. While the Digital Healthcare Act focuses on the digital transformation of healthcare systems in primary care and outpatient services, the Hospital Future Act focuses more on the modernisation of hospitals' information technology (IT) infrastructures, including the implementation and modernisation of hospital information systems and integrated electronic health records (EHRs) [1,2]. EHRs are the cornerstone for a digital and centralised archival storage of clinical information, as they comprise longitudinal data relevant to a person's care and billing processes that are collected during routine delivery of healthcare. Thereby, advancements in medical informatics have enabled the integration of a diverse range of clinical data in EHRs, such as demographics, vital signs, diagnoses, medications, medical history and laboratory values [3–6]. With the widespread realisation of the Digital Healthcare Act and the Hospital Future Act objectives in German university hospitals, what has been possible in other countries for several years is now becoming a reality in Germany: The ability to analyse large volumes of structured routine healthcare data and to embed continuous performance measures in clinical practice [3,5,6]. When EHRs are integrated and managed properly in clinical practice, this enhances not only patient care but also improves clinical research and data science through the quantity and dynamic nature of clinical patient information captured in these structured EHRs [3,6]. For example, these routine healthcare data can be used to study and monitor population health, develop classification and prediction models for decision support, identify optimal treatment strategies, or even simulate randomised clinical trials [7]. Thereby, the cross-institutional exchange and statistical analyses of EHR data would further boost the potential to gain insights into health risks and subsequently improve decision-making in healthcare at local, national, and global levels [8–11]. Improvements in local data processing, data quality, and analysis are necessary for the realisation, as is the quick and uniform transfer of EHR data between institutions. However, the use of routine healthcare data as well as the data exchange between different university hospitals is hampered by a lack of semantic, syntactic, and organisational interoperability [3,12–14]. At the local level, the integration of various health IT systems (e.g. hospital software, laboratory systems, imaging systems) to work seamlessly with the hospital IT infrastructure remains challenging. At the cross-institutional level, data protection regulations and disparate clinical systems with different documentation standards complicate data exchange, as each of the 36 German university hospitals operates independently, running its own hospital information system [3,12,15].

The situation in Germany is further aggravated by the different federal states and their individual laws and regulations, further hindering the exchange of routine healthcare data between German university hospitals [14].

1.1.1 Medical Informatics Initiative Germany

In 2015, the German Federal Ministry of Education and Research launched the Medical Informatics Initiative (MII), a nationwide project to promote the digitalisation of healthcare and to overcome the obstacles described above [16,17]. The MII specifically aims to establish a nationwide infrastructure for the secure, interoperable and privacy-preserving cross-institutional exchange of routine healthcare data to enable multicentric analyses. In this way, the MII fulfils its overall goal of enhancing research opportunities and patient care. Additionally, it is a strategic initiative that brings together the development of IT infrastructure and scientific research projects as well as the support of young researchers and education in medical informatics [17].

Harmonised data extraction is a key prerequisite for the aforementioned interoperable cross-institutional exchange of routine healthcare data. This means that data must be provided in uniform formats with clear definitions used by all centres so that the extracted data can be merged and analysed in multicentre analyses. In the context of the MII, this is realised through the establishment of a new facility at each university hospital, called "data integration centre (DIC)". At each DIC, data from healthcare and research activities are collected from diverse IT systems, merged and standardised [18–20]. Thereby, all participating centres have agreed upon the MII core dataset (CDS), which defines what data records must, at a minimum, be stored by each DIC for all inpatients [16,19]. The MII CDS comprises multiple modules. Each module defines a data structure for the storing of a specific and clearly defined section of routine healthcare data. Each DIC has to provide the basic modules of the MII CDS in the same interoperable format, which include the following: Person, Case, Consent, Diagnosis, Procedure, Laboratory test results and Medication. Additional discipline-specific and project-specific data is mapped in extension modules of the MII CDS, which are initially only implemented in some DICs [19]. The MII CDS modules are based on international IT and terminology standards. As an interoperable standard for the technical specification of all CDS modules, FHIR®[1] R4 (Fast Healthcare Interoperability Resources Release 4) of Health Level Seven (HL7®; http://hl7.org/fhir/ [21]) is used [19,21]. To achieve semantic interoperability, the data stored in the modules are encoded and described using established international medical terminologies and consented metadata [19]. For example, diagnoses can be classified by the International Statistical

[1] "FHIR® is the registered trademark of HL7® and is used with the permission of HL7®. Use of the FHIR® trademark does not constitute endorsement of this product by HL7®".

Classification of Diseases and Related Health Problems (10th Revision, ICD-10), laboratory values by Logical Observation Identifiers Names and Codes (LOINC®), and medications by the Anatomical Therapeutic Chemical Classification System [22–24].

Through the described standardisation and harmonisation of routine healthcare data by the DICs, the analysis of data from multiple centres with acceptable effort becomes possible [18,19]. Thereby, the DICs also ensure compliance with data protection regulations [16–18]. In general, there are two possible approaches to fulfil the data protection regulations when analysing the aforementioned datasets of the DICs. On the one hand, the DICs can provide pseudonymised datasets, including only data from patients who provided informed consent (broad consent). This strategy gives the analysts direct access to the provided data. On the other hand, analysis scripts can be shared with the centres and executed locally by the DICs on their stored data. Using this approach, analysts have no direct access to the patient data [19,25]. This second approach is referred to as "distributed analysis" and enables research to be carried out without patient consent while ensuring data security and privacy [3].

1.1.2 The use case POLAR_MI

Various use cases have been promoted to facilitate collaboration and data sharing between the MII centres and to demonstrate the feasibility of retrieving and using routine healthcare data on a large scale through the overall MII infrastructure [16,17]. One of these was the collaborative use case "POLypharmacy, drug interActions and Risks" (POLAR_MI), which brought together researchers from 21 partner institutions, including 13 university hospitals across Germany [26]. Applying the MII processes and methods to data from routine hospital healthcare, POLAR_MI was designed to retrospectively detect medication-related risks in hospitalised adults through five different research projects: (1) identification of potentially inadequate medication; (2) identification of contraindicated drug prescriptions; (3) identification of potentially inadequate prescribing in renal insufficiency; (4) identification of emergency hospital admissions and readmissions due to suspected adverse drug events (ADEs); and (5) development of risk models predicting ADEs [26]. To address these objectives, a distributed analysis approach (hereafter abbreviated as "POLAR_MI ETL Pipeline", where ETL stands for extract, transform and load data) was developed. The POLAR_MI ETL Pipeline ensured that only aggregated data, i.e. the results of statistical analyses conducted at each DIC, left the centres for inclusion in a meta-analysis. This allowed multicentre data sharing and analysis to be carried out in compliance with data protection regulations without informed patient consent. In addition, the POLAR_MI ETL Pipeline enabled multicentre evaluations independently of the different local IT

requirements, as it was based on the infrastructure of the DICs and the data interoperability standards of the MII, above all the MII CDS (see chapter 1.1.1) [26].

1.2 Medication-related risks

Undesirable medication-related effects have been highlighted as a major patient safety and public health challenge in the last two decades by the World Health Organization (WHO) [27–30], the Council of Europe [31], and national health authorities, including those in Germany [32,33]. In this context, ADEs must be differentiated from adverse drug reactions (ADRs). According to the definitions presented in Table 1, a causal relationship between the medicinal product and the occurrence of an undesirable event is suspected for an ADR but not required for an ADE [34,35]. Thus, the term ADE includes the term ADR [36]. In literature, the terms "adverse event" (AE), "ADE", and "ADR" are often used interchangeably. For this reason, the term "ADE" is used throughout the following description of the current literature in this work.

Table 1. Definitions according to the guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 5); (EMA/876333/2011)

Undesirable effect	Definition
Adverse drug event (ADE) *Synonym:* *Adverse event (AE)*	"Any untoward medical occurrence in a patient to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment (based on ICH-E2D Guideline, see GVP Annex IV). An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product (see GVP Annex IV, ICH-E2D Guideline)." [34]
Adverse drug reaction (ADR)	"A response to a medicinal product which is noxious and unintended [DIR 2001/83/EC Art 1(11)]. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see GVP Annex IV, ICH-E2A Guideline). An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected." "Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure [DIR 2001/83/EC Art 101(1)]. Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors." [34]

Abbreviations: ADE, adverse drug event; ADR, adverse drug reaction; AE, adverse event; Art, article; DIR, directive; EC, European Commission; EMA, European Medicines Agency; GVP, good pharmacovigilance practices; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Rev, revision.

1.2.1 Prevalence of adverse drug events

Even in the 21st century, ADEs are a common and unintended outcome of both outpatient and inpatient care [37–42]. Moreover, they are one of the rising causes of morbidity and mortality and will continue to be a major public health concern given the increased complexity of medication treatment for various diseases in an ageing society [42]. Numerous studies have sought to examine the prevalence of ADEs [42–48]. The reported ADE rates vary considerably between these studies, depending on event definitions, detection methods, clinical contexts and study populations, which complicates the assessment of their true prevalence [44,49]. Systematic reviews with meta-analyses report ADE prevalences of around 8% among patients in primary care settings, as well as among patients being admitted to emergency departments or inpatient wards [45,46]. Another systematic review indicates that the percentage of patients admitted to the hospital due to an ADE ranges from 0.5% to 12.8% of all patients admitted [47]. In a retrospective cohort study from 2018, the prevalence of ADEs at hospital admission was even higher, with ADEs being identified in nearly one in four admissions [48]. The percentage of patients who experience at least one ADE during their hospital stay also varies widely across different studies. According to two systematic reviews, the percentage of patients experiencing at least one ADE during hospital stay ranges from around 2% to between 50% and 58% [43,47]. This extensive variability in estimated ADE prevalences underscores the complexity of accurately detecting and quantifying them (see chapter 1.3).

1.2.2 Characteristics of adverse drug events during hospitalisation

Hospitals house a diverse and critically ill patient population, frequently receiving complex drug regimens due to the severity of their conditions, making them a high-risk setting for the occurrence of ADEs. Consequently, it is unsurprising that ADEs frequently occur during hospitalisations, with approximately one third of these ADEs deemed preventable [43,44,47,50]. The occurrence of inpatient ADEs constitutes a considerable healthcare burden, as they can lead to serious health consequences, including emergency department visits, drug-related hospital readmissions, prolonged hospital stays and even death [43,45–48,51–60]. A systematic review and meta-analysis of the characteristics of ADEs in hospitalised older adults indicates that 31% of ADEs are severe, resulting in the described serious health consequences and mortality [61]. The occurrence rate of drug-related deaths among deceased inpatients in Europe is approximately 7% [62]. This is also highlighted by the European Commission, which reports that ADEs result in 197,000 deaths annually and represent the fifth leading cause of death among hospitalised patients [63,64].

The average duration of a hospital stay is extended from 8 days for patients without ADEs to 20 days for those with ADEs [50,65]. As a consequence of these extended hospital stays and the necessity for

supplementary clinical assessments and interventions, inpatient ADEs are associated with increased healthcare costs, leading to substantial financial burdens for healthcare systems [65–68]. However, the magnitude of these additional costs varies between studies [69]. Rottenkolber et al. estimated that inpatient ADEs in German hospitals elevate the average treatment costs per patient experiencing an ADE by EUR 970 [66]. According to a systematic review of observational studies, the costs associated with ADEs can be even higher, as it shows that the cost per patient with an ADE during hospitalisation increases between EUR 943.40 and EUR 5,972.74 compared to a patient without an ADE [67]. The wide range of estimated costs due to ADEs can be explained by the methodological heterogeneity across studies. For instance, certain studies only considered serious ADEs (e.g. acute skin toxicity) or were conducted in costly settings (e.g. intensive care units or with paediatric populations), resulting in higher estimated costs per ADE [67].

Despite notable efforts to raise awareness and reduce ADEs in recent years, a considerable proportion of ADEs is still recognised too late or remains undetected in routine clinical practice, causing more suffering for patients and higher healthcare costs [70–72]. The inability of hospitals to systematically detect and prevent ADEs has been identified as one fundamental reason for this stagnation [73]. Therefore, it is still essential to improve ADE prevention strategies in hospital settings.

1.3 Detection and prevention of adverse drug events

1.3.1 Detection of adverse drug events

The occurrence of ADEs is an inherent risk of each drug therapy, making their continued occurrence inevitable even in the most sophisticated settings [74]. Therefore, detecting and quantifying ADEs and their underlying causes is essential to ameliorate adverse effects, prevent further harm, identify safety priorities and improve the quality of care through the development of remedial action plans [75–77]. In cases where ADEs are not recognised in time and the causative agents are continued, there is a risk of symptom exacerbation and subsequent treatment of these as a new medical condition with additional drugs, leading to unintended prescribing cascades. The newly administered drugs can result in additional ADEs without resolving the underlying problem. Furthermore, the longer ADEs remain undetected, the more likely they are to result in additional consultations, hospitalisations and deaths. Therefore, it is important that all ADEs are recognised as such in a timely manner, thus enabling their appropriate management, which often simply involves discontinuing or replacing the offending drug [78].

In recent decades, the ability to efficiently and accurately identify ADEs has improved considerably. Conventional methods of ADE detection, such as voluntary incident reporting, direct observation in prospective ADE surveillance, and retrospective or concurrent chart review, have been complemented

by the use of electronic trigger tools: computer-based algorithms that automatically screen routinely collected, readily available electronic patient-level data and flag simple patterns suggestive of a past, present, or future ADE [77,79–81]. As the types of detected ADEs vary between the detection methods, and each method has its own shortcomings, there is no single detection method that is considered the gold standard for detecting ADEs [77,79,81,82]. To approximate the true ADE rate, it is necessary to combine several methods [75,83].

Voluntary reporting of ADEs

Voluntary reporting of ADEs can be carried out by healthcare professionals, patients, or their relatives, whereby paper forms, emails, faxes, phone calls, or interactive computer-based mechanisms are utilised for this purpose [77,79]. These reports are centrally collected through reporting systems implemented in most countries, such as the U.S. Food and Drug Administration's Adverse Event Reporting System or the European Union Drug Regulating Authorities Pharmacovigilance database of suspected ADR reports [84,85]. While voluntary reporting is a common method used to identify ADEs, recommended by many organisations, and one of the best ways to generate signals regarding unexpected and rare ADEs, it is associated with substantial under-detection bias [64,86,87]. Evidence suggests that only between 2% and 10% of all ADEs are reported through this method [86–89]. A systematic review by Hazell and Shakir examined 37 studies from various nations and discovered that the underreporting rate of ADEs exceeded 90% in many cases, impacting all categories of ADEs, including life-threatening events [87]. The under-reporting results from the voluntary nature and the reliance on unstructured spontaneous recognition of ADEs. Individual awareness and knowledge, the safety culture of the institution, the ease of reporting, the lack of time and the fear of penalties all influence whether an event is reported [90–95]. Therefore, higher percentages of incident reports were obtained in studies when providers were specifically encouraged to report occurrences [77].

Direct observation in prospective ADE surveillance

Direct observation in prospective studies is considered the most precise and accurate method of detecting ADEs [77,79,96]. It is a proactive, structured process in which trained observers are present in clinical environments to systematically monitor, identify, and record events in real-time. When an event is identified, the collected information describing the event is passed to designated experts who determine whether the event represents an ADE, a preventable ADE, or an ADR [73,97]. This method has been shown to be more efficient and accurate compared to voluntary reporting of ADEs and chart reviews [73,98]. In comparative studies, the number of ADE reports was up to 400 times higher than the number reported by incident report reviews, chart reviews or trigger tool-based chart reviews [77]. While direct observation in prospective ADE surveillance may capture the most ADEs, it

is very resource intensive, making it the most expensive approach [98–100]. Given its costs and workload, the conduction of direct observation is only feasible over a relatively short amount of time, making it inappropriate for long-term ADE monitoring [77].

Chart review

The term "chart review" includes concurrent or retrospective review of health records, including, for example, doctor's letters, discharge summaries, medication dispensing sheets, and laboratory data [77,79]. Thereby, a comprehensive and detailed scan of the medical record data is performed by experienced healthcare professionals. Compared to the voluntary reporting of ADEs, chart review is a more systematic method for identifying ADEs, consistently yielding more ADE reports [101–104]. However, inconsistencies in the definition of ADEs, inadequate, incomplete, or unclear recordings in medical records, and resource intensity are some of the issues associated with this detection technique. In addition, the lack of awareness of certain ADEs among healthcare professionals performing the chart review further limits this method [105].

Using an ADE trigger tool, such as the Global Trigger Tool for Measuring ADEs developed by the Institute for Healthcare Improvement, can facilitate chart reviews and increase the ADE detection rate [106–108]. Trigger tools consist of a list of clinical "clues", i.e. data elements within health records that alert reviewers to the potential presence of ADEs, prompting a more detailed chart review [107,108]. Examples of such triggers include specific medications (e.g. anti-diarrhoeal drugs), antidotes (e.g. naloxone for opioid-related ADEs) and abnormal laboratory test results (e.g. elevated transaminase), which may indicate medication-related toxicity [107]. One advantage of trigger tool-based chart reviews is that the triggers guide the identification of various types of ADEs within the medical records. In addition, implementing ADR triggers does not require high levels of technological or financial resources. Consequently, researchers have found that using trigger tools during chart reviews is more time-efficient, less expensive, and produces more reproducible results than chart reviews that do not include trigger tools [77].

Electronic trigger tools for the detection of ADEs (computerised surveillance)

Although the trigger tool methodology was developed as a manual approach, i.e. for use by healthcare professionals reviewing paper-based patient records, with the widespread implementation of EHRs, the application of trigger tools for semi- or fully-automated ADE detection becomes possible [49,109]. Implemented in EHRs, the trigger tools can be used efficiently at the point of care to automatically screen for potential ADEs, assess the overall harm caused by medical care, and measure changes in the occurrence of potential ADEs on a large scale for clinical surveillance and research (e.g. outcome measures) [40,80,110]. Several sets of triggers have been developed for this purpose, ranging from

global lists of triggers for a large number of ADEs [106,108] to very specific lists that differ according to the specific type of ADE (e.g. ADR) [111], clinical setting (e.g. nursing homes, oncology, emergency departments), or patient population they target (e.g. paediatrics, elderly patients) [112–116]. Studies indicate that electronic trigger tools detect many ADEs not captured by voluntary reporting, especially those underreported by health professionals [117–121]. Compared to manual chart review, some studies report a higher rate of ADEs when using electronic trigger tools, while others report the opposite [77]. Thereby, the usefulness of an electronic trigger tool depends on its sensitivity and specificity. When validated properly, it is as sensitive as a chart review and more sensitive than an incident report review in detecting ADEs [77]. The number of detected ADEs is directly related to the specificity of the applied triggers, which varies from 19.6% to 76% across different studies [77,122]. Low specificity leads to over-alerting, which particularly impacts the performance of trigger tools in patients with multiple diseases taking several drugs [77,121]. An improvement of the specificity of triggers can be achieved by implementing more stringent and therefore often more complex rules. However, this complicates their applicability and handling [77]. Despite their moderate effectiveness, electronic trigger tools are inexpensive and time-efficient to use. They have also been shown to be practical and less burdensome than conventional methods of ADE detection [123–126]. This makes them a suitable tool for the detection of ADEs in EHR data within the POLAR_MI project (see chapter 1.1.2).

1.3.2 Prediction of adverse drug events

The detection of an ADE becomes unnecessary if its occurrence is prevented in advance. Studies indicate that up to 83% of ADEs are preventable, underlining that there is considerable scope for improvement in this area [43,50,127,128]. The prevention of ADEs requires the identification of risks before the occurrence of an ADE. Thereby, the initial step is to identify the subgroup of individuals most predisposed to experiencing or developing an ADE [129]. For this purpose, ADE prediction models can be used to estimate the likelihood of a patient developing an ADE based on known patient characteristics. These are referred to as prognostic prediction models. ADE prediction models can also be utilised to estimate how likely it is that a patient currently has an ADE. This type of ADE prediction model is then called a diagnostic prediction model [130,131]. Both types of ADE prediction models can be applied in clinical practice to inform healthcare professionals and support decision-making [130]. In addition, information gathered by such prediction models about the causes and timing of ADEs could guide the development and implementation of targeted medication safety interventions, such as medication reconciliation or structured medication reviews [96,132]. Additionally, ADE prediction models can also be applied to prioritise these medication safety interventions for patients at high risk

of ADEs. This could facilitate the efficient use of available resources and maximise the impact of these interventions on medication safety [133].

Many models predicting ADEs in the hospital setting have already been developed, often based on prospectively collected data (e.g. data from cohort studies, nested case-control, or case-cohort studies) [132–134]. Prospective data collection allows for optimal measurement of both predictors and outcomes, with data collection tailored to the study objectives, giving researchers control over the required data and documentation quality [135]. However, prospective data collection is often resource-intensive and costly, limiting the sample size and number of predictors. Furthermore, due to the controlled conditions of these studies, they often only partly reflect real inpatient care [132,135]. This results in many of these prediction models having limited generalisability [133,134,136]. The generalisability is further reduced as they frequently lack external validation. This type of validation involves testing the developed model using a completely independent dataset of patients who differ from those in the development dataset [130,133,134,136,137]. The use of EHR data, as is done in the context of the MII, can overcome some of the limitations described above while introducing new drawbacks [138,139]. As EHR data are derived from the documentation of treatment and care, they capture structured, dynamic and longitudinal clinical patient information, more appropriately reflecting the reality of healthcare provision [3,132,138,139]. Therefore, they can provide more realistic rates of ADEs and information on real-world drug utilisation, including knowledge of rare ADEs, which are often not captured in randomised controlled trials [3]. Furthermore, EHR data can be routinely collected on a large scale and made readily available for analysis [4,132,138,140,141]. This includes the observation of more predictors and outcomes, on more individuals, at more time points, and at a fraction of the cost of prospective cohort studies [138]. As a result, the data size is often large, which increases statistical power and facilitates rapid model development and validation, leading to more generalisable and applicable models across diverse populations [4,7,138,139]. In addition, prediction models based on EHR data can often be readily implemented, as a translation to the clinical environment is not necessary [138]. Finally, through the real-time availability of EHR data, prediction models built on this kind of data can be used to automatically screen for potential ADEs at the point of care [132].

However, the de-facto collection of data at many time points by many clinicians, based on the need for treatment or driven by billing incentives, lacks standardisation and can lead to an incomplete data capture, as patient and clinician decisions directly dictate whether information is documented [3]. As a result, clinical workflows and the design of the hospital information system directly affect the collected EHR data [7]. Compared to prospective observational study data, there are more missing data, coding errors, inconsistencies and losses to follow-up when dealing with EHR data [138,142].

Consequently, the analysis of EHR data is challenging and must involve investigators with specialised knowledge in the domain of interest, ranging from care practices to data processing [7].

Especially the potential to observe changes over time in patients and to build dynamic prediction models based on the repeated, longitudinal observations captured in EHR data is not yet fully utilised. Reasons are that the integration of such repeated observations is challenging from a statistical perspective and is further hampered by missing, not interpretable or overlapping timestamps [3,138]. Not only are timestamps often missing or incorrect, but the presence of missing data and inconsistencies across all data categories is one of the largest challenges in EHR-based analyses [3,138,142]. These inaccuracies in data can impact the precision of research outcomes and lead to misinterpretation of specific risk factors [4]. To face the inaccuracies, techniques improving the process of data collection can be used to gather more complete data. For example, fit-for-purpose user interfaces, standard operating procedures, automated documentation of some data or performing quality control are techniques used in previous works [8]. Statistical methods often used in EHR-based studies to address missingness are multiple imputation techniques [4,138,142]. These techniques involve creating multiple complete datasets, analysing them separately, and combining the results, whereby it is assumed that data are missing at random [4,143]. This is a condition often not applicable to EHR data, in which the presence or absence of data can be informative about the health status of patients [8,138,144]. This is referred to as "informative presence", when considering any given time point, and "informative observation", when considering the timing, frequency, or rate of a patient's longitudinal pattern of observation [144]. The very act of visiting a healthcare facility leads to EHR data that will, on average, contain sicker people, leading to biased associations [138,144,145]. Furthermore, it has been found that there is a relationship between EHR completeness and patient health status, with more data being recorded for sicker patients [8,144,146]. Informative presence and observation are therefore challenging from a statistical perspective, as they imply a missing-not-at-random process [144].

Over the past two decades, EHR data resulting from routine healthcare, with the described advantages and disadvantages, have been increasingly used to complement data from prospective studies for the development of predictive models [3,5,132,138,140]. Many EHR-based models are only internally validated, for example, by using cross-validation. This is a model evaluation technique that uses the same dataset for model development and validation by splitting it into training and validation sets [131]. Nevertheless, as with studies relying on prospective data collection, external validation remains challenging [137,138]. A key area for future improvement would therefore be the conduction of multicentre studies, in which external model validation on data from different systems and different patient populations becomes possible [131,138].

1.3.3 Establishing causality for detection and prediction of adverse drug reactions

Proving the causal relationship between an ADE and a drug is a crucial element in detecting and predicting ADRs as a subgroup of ADEs. The gold standard for assessing this causality is a judgement made by independent medical experts, using validated algorithms or assessment criteria such as the "Adverse Drug Reaction Probability Scale" by Naranjo and colleagues or the "WHO-UMC System for Standardised Case Causality Assessment" developed by the WHO's Uppsala Monitoring Centre (UMC) [76,147–149]. Depending on how many criteria are satisfied, the causal relationship is deemed nearly certain, probable, possible or unlikely by the involved expert [64,132]. Despite the aforementioned examples, there are many other algorithms available for assessing causality, none of which is universally accepted [64,147]. Even though many of these algorithms have similar key criteria, like timing, biological reasonableness, and documented cases, it has been reported that using different algorithms for the same ADR can produce substantially different results [64,147,150]. Therefore, causality assessments depend on the algorithm used. Another limitation of experts' causality judgements is that the results can be influenced by the evaluator's subjectivity, leading to inter-rater and intra-rater inconsistencies. Furthermore, the causality assessment based on experts' judgements is very time-consuming, making it impractical in clinical practice [64,76,151,152]. Concerning the development of prediction models, the challenges due to the time requirement are even more critical, as hundreds or even thousands of ADR cases might be required to attain appropriate model performance [132,153]. Due to the described subjectivity and the time constraints of experts' judgements, the causality assessment is a fundamental challenge in ADR detection and prediction. Without establishing the causal relationship, it is only possible to detect ADEs with certainty. ADE triggers from the above-described trigger tools (see chapter 1.3.1) can be used as a proxy for the formal ADR causality assessment. However, as this approach only identifies ADE signals and does not assess causality, the triggers must be embedded in a "causal prediction modelling framework" to allow for causal interpretations and ADR prediction. In this framework, both the bias of the applied trigger (e.g. confounding factors) and the functional relationship between the drug and the ADE are considered in order to establish a reliable link between the drug and the event [132]. For instance, the occurrence of the trigger "increased potassium value" could be examined in conjunction with a drug that has been demonstrated to cause this event with a high degree of probability (e.g. angiotensin receptor blockers). Concurrently, confounding factors such as decreased kidney function should be taken into account. Together with the potentially causative drug, a causal prediction modelling framework is established, which makes the presence of an ADR not certain but at least more likely.

2. Aim and objectives

The overall aim of this work was to develop and evaluate various methods for the detection and prediction of adverse drug events (ADEs) using routine healthcare data collected from several university hospitals participating in the POLAR_MI project between 2018/01/01 and 2021/12/31. Based on the results, the potential for detecting and predicting ADEs was to be explored. As a large amount of routine healthcare data was available for a distributed analysis across multiple university hospitals, preparations for the detection (chapters 3 and 4) and prediction (chapter 5) of ADEs had to be made. Another objective was to assess the general feasibility of developing models for ADE detection and prediction within a distributed analysis approach (chapter 5). The specific objectives of each project are described below.

Prioritisation of adverse drug events leading to hospital admission and occurring during hospitalisation: A RAND survey [154]

The aim of the first project was to identify and prioritise ADEs that lead to hospital admissions, as well as those occurring during hospitalisation, as a basis for defining medication safety measures that facilitate the detection of the most important ADEs in clinical practice, surveillance and research. It was further intended to investigate differences in the prioritisation of ADEs between the two different settings and to assess how the overall importance of an ADE is influenced by the ADE's severity and likelihood of being drug-related.

Drug-event pairs as indicators for the detection of adverse drug reactions during hospitalisation in routinely collected electronic data sources [82]

The second project was designed to assess the likelihood of specific drugs contributing to clinically important inpatient ADEs to compile a consensus-based list of drug-event pairs indicating adverse drug reactions (ADRs) in routine healthcare data. The determined indicators of ADRs were categorised according to the likelihood of an ADR being present.

Challenges in detecting and predicting adverse drug events via distributed analysis of electronic health record data from German university hospitals [155]

In the third project, we investigated whether two ADEs (gastrointestinal bleeding and drug-related hypoglycaemia) could be detected and their associations with potential risk factors assessed, using a distributed analysis approach without direct data access for the analyst. Using these two ADEs as examples, we analysed the feasibility and challenges of building predictive models within the framework established by the Medical Informatics Initiative. This included an assessment of the impact of integrating laboratory values and accounting for the temporal sequence of events.

3. Prioritisation of adverse drug events leading to hospital admission and occurring during hospitalisation: A RAND survey

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Contribution: For the inpatient setting, I designed and conducted the consensus process. This included (1) selecting experts, (2) conducting the pretest, (3) performing the systematic literature search, (4) developing and preparing the assessment form, (5) writing the evidence report, (6) managing the rating process, (7) analysing and visualising the rating results, and (8) writing the manuscript.

Introduction: The detection of adverse drug events (ADEs) and their underlying causes is crucial to ameliorate harm and prevent recurrence [75–77]. As ADEs differ considerably in their clinical relevance, depending on factors such as their frequency, severity, and preventability, developing and implementing medication safety screening tools that focus on the most relevant ADEs can lead to a more targeted and efficient use of limited healthcare resources in both clinical practice and research [37,41,156]. Furthermore, ADE patterns differ between outpatient and inpatient care settings in terms of drug classes involved, severity, and contributing factors. This variation necessitates the implementation of setting-specific interventions [42,44,128]. Against this background, the aim of this study was to identify two sets of prioritised ADEs, one for the hospital admission setting and one for the inpatient setting, that could serve as a basis for defining medication safety measures for use in clinical practice (e.g. decision support), clinical surveillance, and research (e.g. outcome measures).

Methods: The study design was an expert consensus process based on the RAND®/UCLA Appropriateness Method (RAM) [157]. In consensus processes based on the RAM, clinical presentations (in this study: ADEs) are rated in two rounds while considering the scientific evidence that is currently available. Each clinical presentation is given an independent rating by experts in the first round. In the second round, after a panel meeting to examine and discuss the first-round ratings and update the initial list of presentations, the experts re-rate each clinical presentation separately, leading to the final results. In this study, we conducted two separate RAM consensus processes in order to prioritise ADEs for two clinical settings: at hospital admission to prioritise ADEs originating in ambulatory care (panel 1) and during hospital stay (panel 2). The panellists were asked to assess the overall importance of different ADEs, which were identified by a systematic review of studies investigating ADEs in Germany. For each ADE, panellists were asked to rate *"Imagine an average hospitalised patient with the following event during hospital stay: How important is it to conduct a medication review in the near future as a strategy to prevent further or repeated harm from this ADE?"* on a four-point Likert scale (1=not important to 4=very important). ADEs with a median rating of ≥ 3 without disagreement after round two were a priori defined as "prioritised". Disagreement was pre-defined to be present if at least 30% of expert ratings were 1 or 2 (for items with a median of ≥ 3, consistent with prioritisation), or 3 or 4 (for items with a median of < 3, consistent with non-prioritisation). In addition, we asked the panellists to rate the "seriousness" and "drug-relatedness" of

each ADE. These additional ratings were not used for prioritisation, but were intended to (a) encourage the panellists to consider these aspects in their overall importance ratings and (b) identify sources of disagreement between the panellists to inform discussions at the panel meeting.

Results: Panel 1 and panel 2 consisted of 13 and 12 members from 11 and 9 German university sites, respectively. The systematic literature search led to 63 ADEs (panel 1) and 61 ADEs (panel 2) being rated in round one, of which 31/63 ADEs (49%) and 25/61 ADEs (41%) were prioritised (median ≥ 3 without disagreement) after round one, respectively. During discussions, the experts decided to split two ADEs, resulting in 65 ADEs (panel 1) and 63 ADEs (panel 2) to be rated in round two. In panel 1, there was consensus after round two to prioritise 38/65 ADEs (58%) and to not prioritise 18/65 ADEs (28%). Disagreement was present for 9/65 ADEs (14%) (four on prioritisation and five on non-prioritisation). In panel 2, there was consensus after round two to prioritise 34/63 ADEs (54%) and not to prioritise 13/63 ADEs (21%). In this panel, disagreement was present for 16/63 ADEs (25%) (eight on prioritisation and eight on non-prioritisation). Comparing the overall importance ratings of both panels, 29 ADEs were prioritised in both, 9 ADEs were prioritised only in panel 1 and 4 ADEs only in panel 2. Acute kidney injury and hypoglycaemia were among the highest-rated ADEs in both panels, as well as Stevens-Johnson syndrome in panel 1 and rhabdomyolysis in panel 2. Comparing the overall importance ratings with the seriousness and drug-relatedness ratings, there were eight ADEs (12%) in panel 1 and one ADE (2%) in panel 2 where ratings for seriousness and drug-relatedness diverged from the overall importance rating (overall importance rating ≥ 3 and both other ratings < 3). A total of 9/65 ADEs (14%) in panel 1 and 13/63 ADEs (21%) in panel 2 had a median overall importance rating of < 3 but a median seriousness rating of ≥ 3, while there was no ADE with a median overall importance rating of < 3 and a median drug-relatedness rating of ≥ 3 in both panels.

Discussion: The expert consensus processes resulted in two sets of prioritised ADEs. A total of 13 ADEs were prioritised by only one panel, thus supporting our approach of two setting-specific consensus processes. The medications utilised in inpatient and outpatient settings differ, which could account for the disparity in prioritisation between the two panels. Aminoglycosides, for example, which predominantly cause toxic damage to the inner ear, are mainly used in the inpatient setting. This can explain why panel 2 (hospital stay) gave priority to this ADE, whereas panel 1 (hospital admission) did not [158]. Comparing the directions of the overall importance ratings with the seriousness ratings and drug-relatedness ratings gave insights into factors influencing the overall importance of ADEs. In both panels, the majority of the ADEs with median overall importance ratings of ≥ 3 also had median ratings of ≥ 3 for both seriousness and drug-relatedness. This shows that these factors seem to be substantial determinants of the overall importance. Nevertheless, as some ADEs had an overall importance

rating of ≥ 3, but the median drug-relatedness and seriousness ratings were both < 3, other factors (e.g. prevalence or preventability) may also be important drivers of overall importance. A similar expert survey conducted in the United States by Jeon and colleagues exclusively prioritised inpatient ADEs that were considered preventable by pharmacists [159]. Thrombosis, nausea and vomiting, hypothyroidism, hypertensive crisis, decompensated heart failure, anaemia and gastrointestinal ulcers were prioritised for preventive actions by pharmacists in their consensus process but were not prioritised in our expert consensus process. The disparities in prioritisation can be attributed to the distinct scopes of the two consensus processes. The study by Jeon et al. considered the preventability of ADEs and included the underuse of medications as a cause of ADEs (e.g. uncontrolled pain due to underuse of pain medication). In our process, by contrast, ratings were placed in relation to ADEs caused by drugs rather than their underuse. To conclude, the two sets of prioritised ADEs can provide a basis for further research and practice. In order to achieve our aim to detect adverse drug reactions, the next step was to create drug-event pairs by combining the prioritised ADEs with potentially causative drugs through a second RAM process (see chapter 4).

4. Drug-event pairs as indicators for the detection of adverse drug reactions during hospitalization in routinely collected electronic data sources

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Contribution: I designed and conducted the consensus process. This included (1) selecting experts, (2) conducting the pretest, (3) performing the systematic literature search and evaluating the extracted potentially causative drugs, (4) developing and preparing the assessment form, (5) writing the evidence report, and (6) managing the rating process. Finally, I analysed and visualised the rating results and wrote the manuscript.

Introduction: Conventional methods of adverse drug reaction (ADR) detection, such as voluntary incident reporting, retrospective chart review, and direct observation in prospective ADR surveillance, have limitations in terms of effectiveness and affordability [77]. In addition, establishing the causal relationship between the adverse drug event (ADE) and the drug requires a time-consuming and complex causality assessment by clinical professionals utilising validated algorithms or assessment criteria [76,147]. The development of screening instruments that can be used efficiently at the point of care to identify potential ADRs would therefore be an important step forward, as they could be used in clinical surveillance or research to repeatedly measure changes in the occurrence of potential ADRs on a large scale [40,110]. Electronic trigger tools are a promising approach to reach this goal (see chapter 1.3.1). Nevertheless, the triggers of existing tools, such as the several modified versions of the Institute for Healthcare Improvement's Global Trigger Tool for Measuring ADEs, are primarily based on a single variable (e.g. only digoxin level > 2 ng/mL or only usage of diphenhydramine), which limits their positive predictive values regardless of the data category [80,81,106,160–162]. This is underlined by a prospective observational study, which found that 52.4%, 40.3%, and 7.3% of ADRs required one, two, or three information items more than just the medication information to be detected [163]. Given that certain drugs are more likely to cause ADRs than others, and that the associated drugs differ by ADR category, combining clinically important and highly drug-related ADEs with potentially causative drugs could focus the detection of ADRs in electronic health record (EHR) data on those for which a drug-related cause is (at least) probable [41,154,159]. In order to provide a consensus-based list of drug-event pairs indicating ADRs in EHR data, hereafter referred to as "indicators of ADRs", we aimed to assess the likelihood of specific drugs contributing to clinically important inpatient ADEs.

Methods: We conducted a two-round expert consensus process based on the RAND®/UCLA Appropriateness Method (RAM), in which the experts were asked to rate the strength of the causal link between an ADE and potentially causative drugs (as individual drugs or grouped into drug classes) [157]. The 14 ADEs considered were selected through a different, previous consensus process (see chapter 3) [154]. For each ADE, a structured literature search was conducted to generate comprehensive lists of potentially causative drugs, resulting in the drug-event pairs which had to be rated in the consensus process. The experts were asked to rate the strength of the causal link between

the ADE and potentially causative drugs by answering the following question: *"How likely is it that the listed medication significantly contributed to the adverse event, so that you would assume an adverse drug reaction?"*. The four-point Likert scale for responding to this question was based on the causality categories from the WHO-UMC system for standardised case causality assessment [149]. If the experts couldn't assess a drug-event pair based on the evidence presented, they had the option to abstain (0 = no comment). To determine the threshold for the presence of an ADR, we also asked about the likelihood of an ADR being present if two drugs rated as possible or two drugs rated as probable would be listed together with the ADE in the EHR data (drug combination-event pairs). Based on the final ratings after round two, the drug-event pairs were categorised according to the likelihood of an ADR being present if this drug-event pair is present in routine healthcare data. Drug-event pairs with a median rating of 4 and 3 (or 3.5) without disagreement were predefined as indicators of certain and probable ADRs, respectively. Disagreement was predefined to be present if at least 30% of expert ratings were 1 or 2 (for drug-event pairs with a median of ≥ 3) or 3 or 4 (for drug-event pairs with a median of < 3). Drug-event pairs with a median rating of ≥ 3 with disagreement or with a median rating of 2 or 2.5 with and without disagreement were considered indicators of possible ADRs. All drug-event pairs with a median rating of < 2 were predefined as indicators of unlikely ADRs.

Results: The structured literature search yielded between 5 and 80 publications, depending on the event, which served as the basis for the assessment form. The extraction of potentially causative drugs from these publications and their subsequent grouping resulted in 233 drug classes to be rated in combination with certain ADEs in round one by five physicians and five pharmacists from nine German university hospitals. The rating of round one resulted in 1 drug-event pair considered as an indicator of a certain ADR (0.4%), 19 drug-event pairs considered as indicators of probable ADRs (8%), 130 drug-event pairs considered as indicators of possible ADRs (56%) and 83 drug-event pairs considered as indicators of unlikely ADRs (36%). In the second rating round, 255 drug-event pairs were assessed, as the experts decided during the panel meeting to add one drug-event pair, exclude two drug-event pairs and split 21 drug-event pairs into 44 drug-event pairs. Of these 255 drug-event pairs, 2 (1%) and 42 (16%) achieved consensus validation by the expert panel that they certainly and probably indicate an ADR. In addition, 137 (54%) drug-event pairs were considered as indicators of possible ADRs, and 74 (29%) drug-event pairs were considered as indicators of unlikely ADRs. For the events hyperkalaemia, delirium and serotonin syndrome, there was agreement after the second rating round that the concomitant use of two drugs classified as possibly indicating an ADR together with the presence of the related event (drug-event pair combination) probably indicates an ADR. This resulted in three additional indicators of probable ADRs, consisting of two drugs with a possible rating and the ADE.

Discussion: That more than half of the assessed drug-event pairs were confirmed as only possibly indicating an ADR reflects that causation in clinical practice and pharmacovigilance is hardly ever certain [151]. The uncertainty in assessing whether an ADR is present or not arises due to the complex interplay of triggering factors (e.g. drugs) and confounding factors (e.g. underlying diseases). Even in prospective observational studies, where confounding factors can be more effectively controlled, detecting ADRs with certainty remains challenging. For example, in the ADRED study, which assessed ADR cases in four German emergency departments, only 12.4% of suspected medications were deemed probably or definitely causative [164]. To account for the uncertainty in ADR assessments, we categorised the drug-event pairs into four ADR likelihood categories rather than using a binary categorisation, as a simple yes or no decision about the presence of ADRs does not represent their nature. The aetiology of the ADRs hyperkalaemia, serotonin syndrome and delirium can explain why for these events there was consensus that the concomitant use of two drugs classified as possibly indicating an ADR is probably indicating an ADR. Hyperkalaemia is rare in large clinical trials of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists but more common in clinical practice due to the combined use of these potassium-altering drugs [165–167]. Similarly, serotonin syndrome often results from multiple serotonergic drugs affecting serotonin levels differently [168–170]. The risk of delirium also rises with multiple predisposing factors, often involving more than one drug [171,172]. There are already two existing trigger lists consisting of causative drugs for specific ADRs [114,173]. These lists were primarily designed to detect ADR-related hospitalisations in the elderly and lack a categorisation of the potentially causative drugs. Most drug classes from the cited trigger lists were included in our consensus process, highlighting the comprehensiveness of our approach. Only angiotensin receptor blockers for hyponatraemia and monoamine oxidase inhibitors for hypoglycaemia were not included in our consensus process. Even if the main limitation of our developed indicators is that they lack validation, they are evidence-based and content-validated. In addition, their systematic categorisation into different ADR likelihood levels will facilitate their future application in clinical practice (e.g. decision support), clinical surveillance (e.g. quality indicators) and research (e.g. outcome measures).

5. Challenges in detecting and predicting adverse drug events via distributed analysis of electronic health record data from German university hospitals

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Contribution: I was responsible for the detailed design and execution of work package 1.5 of the POLAR_MI project. This included the participation in the evolution of overarching research goals and the development of the methodology within this work package. Furthermore, I participated in the data curation and plausibility checks of the data, formal analysis (e.g. application of statistical, mathematical, computational, or other formal techniques to analyse the data) and investigation as well as validation of the received local, aggregated results. Finally, I analysed and interpreted the meta-analysed results, participated in the visualisation of the results and wrote the manuscript.

Introduction: Through the establishment of a nationwide infrastructure for the secure and interoperable exchange of routine healthcare data by the Medical Informatics Initiative (MII), the investigation of adverse drug events (ADEs) in German routine healthcare data across multiple university hospitals became possible [16,17]. Within the overarching use case POLAR_MI, we aimed to develop models predicting specific inpatient ADEs, thereby testing the MII methods and processes [26]. ADE prediction models can help to facilitate the detection and prevention of ADEs, as they can guide the prioritisation of services like medication review or medication reconciliation for patients at high risk for ADEs, optimising resource use and enhancing medication safety [133,174–176]. Many ADE prediction models exist, but as these models are often based on prospective studies tailored to this research question, they may not fully reflect real-world inpatient care [133,134]. In contrast, our project utilised electronic health record (EHR) data from routine healthcare. Despite the unknown quality and completeness of EHR data, they can complement prospective study data to create predictive models based on real inpatient care [132,138]. This project presents our initial multicentre investigation on the detection and prediction of ADEs using a distributed analysis approach. We focused on two ADEs, gastrointestinal (GI) bleeding and drug-related hypoglycaemia, as examples and evaluated the feasibility and impact of incorporating laboratory values and considering the chronology of events in our analysis.

Methods: POLAR_MI was a multicentre, retrospective observational study at ten German university hospitals, which included patients aged 18 years and older who were admitted and discharged within the time interval 2018/01/01 and 2021/12/31. For data collection and processing, we applied the POLAR_MI ETL pipeline, a two-step distributed and privacy-preserving analysis approach without direct data access for the analyst. This approach consisted of a local statistical data analysis at all participating centres, followed by a mixed-effects meta-analysis [26]. Relevant encounter characteristics were summarised as median or relative frequency. They were assessed both as simply documented and considering the chronology of covariates and outcomes, i.e. the covariate value had to be documented on admission and the outcome only during the hospital stay. We used uni- and

multivariable logistic regression to examine associations between selected covariates and each binary outcome. Covariates were chosen based on their varying strengths of association with the respective outcome and the utilisation of different MII core dataset modules. Thereby, two multivariable logistic regression models were constructed for each outcome: (1) including only demographics, diagnoses and medications (referred to as base model), and (2) extended by laboratory values (referred to as extended model). As numerically stable estimations of both models were not possible at each centre, we constructed different centre subgroups for meta-analyses (see Table 2). These analyses allowed us to assess the impact of including (a) different numbers of centres, (b) laboratory values in multivariable models, and (c) the chronology of covariates and outcomes in the analysis.

Table 2. Definitions of the analyses for both outcomes [155].

Analysis	Inclusion criteria	
	multivariable model(s)	chronology
Outcome: GI bleeding		
(B1.a)	base	none
(B1.b)	base, extended	none
(B1.c)[*1]		yes
Outcome: Drug-related hypoglycaemia		
(H1.a)	base	none
(H1.b)	base, extended	none
(H1.c)[*1]		yes

For each analysis, all centres with stable results for the respective models were included, if not stated otherwise.

[*1] Same centres as in (B1.a) and (H1.a), respectively. Abbreviation: GI, gastrointestinal

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Results: For the outcome GI bleeding, 336,002 encounters from seven centres (analysis B1.a) and 242,755 encounters from five centres (analysis B1.b) could be included in the respective meta-analyses. For the outcome hypoglycaemia, 295,609 encounters from six centres (analysis H1.a) and 195,498 encounters from four centres (analysis H1.b) could be considered. Overall, for both outcomes, the requirement of laboratory values was a frequent limiting factor for receiving stable results from regression modelling, leading to the exclusion of centres. In addition, missing laboratory values were the most common reason for encounter exclusions within an included centre for both outcomes. The prevalence estimates were around 1.2% for GI bleeding and around 3.0% for drug-related hypoglycaemia when not considering the chronology of events. When considering the chronology of events, the prevalence estimates of both outcomes and all covariates decreased, making regression modelling considering this chronology not reasonable. However, numerically stable multivariable regression models with and without laboratory values not considering the chronology of events could be received from several centres. All selected diagnoses, laboratory values and medications, except non-steroidal anti-inflammatory drugs (NSAIDs), showed univariable associations with a higher chance

of exhibiting the respective outcome in the analyses (B1.a) and (H1.a). In the multivariable base models of these analyses, only selective serotonin reuptake inhibitors (SSRIs) and liver disease remained associated with a higher chance of exhibiting GI bleeding, and any insulin, heart failure and all types of DM remained associated with drug-related hypoglycaemia. Encounters with a documented NSAID showed a lower likelihood of exhibiting GI bleeding across all univariable and multivariable models. The effect directions in the base models did not differ between analyses requiring laboratory values and those without (comparisons: base model between the analyses (B1.a) and (B1.b) as well as between (H1.a) and (H1.b)). After the adjustment for laboratory values in the extended models, the associations of male gender with GI bleeding as well as of age and heart failure with drug-related hypoglycaemia were no longer observed. For all multivariable regression models, the median area under the receiver operating characteristic curve (ROC AUC) was above 0.70.

Discussion: Distributed regression modelling for detecting and predicting GI bleeding and drug-related hypoglycaemia using routine healthcare data from German university hospitals can be deemed possible, as we received plausible estimates for prevalence and regression modelling odds ratios. The distributions of age and gender in the study population were comparable to those in the German hospital statistics for the year 2022, and also the prevalences of considered diagnoses were comparable to those in the literature [177–179]. That all selected diagnoses, laboratory values, and drugs—aside from NSAIDs—were at least univariably associated with a higher likelihood of the respective outcome underlines the feasibility of regression modelling since all of the chosen covariates are discussed in the literature as risk factors for the respective outcome [180–188]. More contentious risk factors according to literature, e.g. SSRIs and bisphosphonates for GI bleeding or female gender for drug-related hypoglycaemia, only showed an association in the analyses with a larger sample size and therefore more statistical power [180,183,184,189]. The strengths and directions of the associations were mostly maintained when adjusting for laboratory values that caused a reduction in sample size and therefore a reduction in statistical power. This reduction in statistical power explains the observation that some associations could no longer be observed when adjusting for laboratory values. The finding that encounters with a documented NSAID were less likely to exhibit a documented GI bleeding can be explained by the fact that the majority of the GI bleedings were present at the time of admission. As NSAID use is contraindicated for patients with an acute or a history of GI bleeding, they may not have been administered or were stopped before hospital records were updated in patients admitted with GI bleeding [190,191]. Regression modelling considering timestamps was not pursued in this work, as the available timestamps were often imprecise, and their requirement led to a substantial reduction in sample size. Reasons were (1) retrospective coding for reimbursement reasons, often after discharge, leading to timestamps that are often delayed; (2) multiple coding of

the same event at different times, e.g. a GI bleeding was coded on admission and during hospital stay; and (3) setting the timestamps to unknown [3,192,193]. In addition, ambiguous filling of mandatory timestamps occurred. For example, in the case of laboratory values, identical timestamps were provided for sampling, ordering the service, sample receipt, analysis and result transmission. Still, we received multivariable regression models not considering the chronology of events with a median ROC AUC above 0.7, suggesting viability with respect to our initial goal of developing predictive models. When summarising the local ROC AUC values, a better predictive performance was indicated for the extended models considering laboratory values, but the Akaike-Information-Criterion and Bayesian-Information-Criterion for the meta-analysed regression models were better for the models without laboratory values, indicating that the penalty term for more variables dominated. In conclusion, our results suggest that the development of predictive models in a distributed setting is possible if the research question is tailored meaningfully to the infrastructure and available data.

6. Conclusions and future perspectives

The aim of this thesis was to develop and evaluate various methods for the detection and prediction of adverse drug events (ADEs) in German routine healthcare data within the Medical Informatics Initiative (MII). This effort was undertaken to characterise the current status and to improve the possibilities of ADE analyses in Germany. To reach these goals, both qualitative and quantitative research approaches were successfully applied. The expert consensus processes that resulted in content-validated indicators for detecting adverse drug reactions (ADRs) in routine healthcare data and the evaluation of the feasibility of building models for ADE detection and prediction using a distributed analysis approach should be seen as complementary. Together, they contribute to advancing the detection and prediction of ADEs, particularly within the framework of the MII. Going forward, the developed ADR indicators could be integrated as outcome measures in a distributed analysis approach, thereby promoting drug safety studies under real-world hospital conditions. For instance, the ADR indicators can be utilised as outcome measures to determine the prevalence of potential ADRs in electronic health record (EHR) data at a given time. This can yield insights into the quality of care and patient safety. Another application of the developed ADR indicators could be their integration in a clinical decision support system (CDSS). By implementing this CDSS directly in the EHRs of a hospital information system, the ADR indicators can be applied at the point of care for real-time and continuous monitoring of potential ADRs. Again, such applications can improve patient safety by preventing and ameliorating harm. In terms of predictive modelling, drug-event pairs probably and certainly indicating an ADR can serve as dependent variables (outcomes) in an ADE prediction model, while confounding factors can be integrated into the model as independent variables (covariates). This approach leads to a "causal prediction modelling framework" that facilitates causal interpretations and, consequently, ADR prediction without the necessity for a time-consuming causality assessment. The major results, conclusions, and future perspectives of the individual projects are described below.

Prioritisation of ADEs as a basis for medication safety screening tools

The first expert consensus process, based on the RAND®/UCLA Appropriateness Method (RAM), led to a set of 34 prioritised ADEs, for which there is consensus that they are of particular importance as presentations of acute medication-related harm during hospitalisation. We demonstrated that the set of prioritised ADEs depends on the setting considered and that the ADE's severity and likelihood of being drug-related are important drivers for their overall importance.

As this structured expert consensus process facilitated professional exchange on the importance of different ADEs, this project contributes to the development of a shared understanding of which ADEs warrant the greatest attention and provides a foundation for harmonised efforts in medication safety.

For instance, the set of prioritised ADEs could guide which ADEs to target first in clinical practice and medication safety research, including the development of ADR screening tools for the most important events. Thereby, the sensitivity and specificity of such ADR detection tools are crucial factors to consider [194,195]. While a lack of specificity may cause alert fatigue in a clinical setting and a restricted ability to adapt in a research setting, a lack of sensitivity may result in ADEs requiring treatment being missed. Although we have identified ADEs that are important presentations of medication-related harm with a high degree of drug-relatedness, many of these events can also result from other causes [121]. Therefore, taking into account only the prioritised ADEs limits the specificity in the context of ADR detection. To enhance specificity and achieve our aim to detect ADRs during hospital stays in routinely collected electronic data sources, combining the ADEs identified in this project as clinically important with potentially causative drugs is a promising approach for developing an ADR screening tool.

Combination of ADEs with potentially causative drugs (drug-event pairs) as indicators for the detection of ADRs during hospitalisation in routinely collected electronic data sources

Building on the set of prioritised ADEs derived from the first expert consensus process, this project proceeded towards the overall aim of developing an ADR screening tool. For the 14 clinically most important ADEs according to the first consensus process, 255 drug-event pairs (e.g. gastrointestinal bleeding with NSAID use) were constructed as indicators for the detection of ADRs in routine healthcare data. Through a second RAM process, these drug-event pairs were classified into one of four categories – certain, probable, possible or unlikely – based on the likelihood of an ADR being present if this drug-event pair is present in routine healthcare data.

This project fills an important gap in the existing literature, as the developed ADR indicators, unlike triggers of many existing tools, are not based on a single variable, which would limit their positive predictive values and specificity [80,81,106,160,161,163]. In addition, the developed ADR indicators are less complex than suboptimal medication use patterns (e.g. hospital admission for gastrointestinal bleeding preceded by at least one month of NSAID use without gastroprotection), which can also be used as triggers for ADRs [196,197]. While the utilisation of suboptimal medication use patterns attempts to increase specificity, it may reduce the sensitivity of ADR detection by failing to detect all non-preventable ADRs and even some preventable ADRs. The underlying reason for this is that it is not possible to compile a comprehensive list of all suboptimal medication use patterns due to their broad spectrum [196,197].

The systematic categorisation of our drug-event pairs into four ADR likelihood categories, a common omission in similar trigger tools, enables a risk-stratified application of our ADR indicators in clinical

practice (e.g. for clinical decision-making and resource allocation) and clinical research [114,173,198]. The selection of drug-event pairs for an ADR trigger tool can be based upon the prioritisation of sensitivity or specificity. When sensitivity is more important, indicators of possible, probable and certain ADRs can be used. If specificity is prioritised, only indicators of probable and certain ADRs can be utilised. For example, hospitals could prioritise monitoring certain/probable drug-event pairs (44 in total) while deprioritising unlikely ones (74 in total), optimising pharmacists' and physicians' workloads.

Even if our developed ADR indicators are content-validated and evidence-based, the overall applicability and performance (e.g. specificity, sensitivity, positive predictive values, negative predictive values) of the indicators in clinical practice and research remain a crucial aspect. Consequently, the implementation of our ADR indicators should be accompanied by a validation process involving actually using them to screen for ADRs in routine healthcare data. This includes developing reliable measurements for the events in EHR data. Thereby, determining an appropriate combination of data categories (e.g. LOINC® codes, ICD-10 codes) which represents the event with high accuracy is more or less challenging depending on the event. For example, the incidence and prevalence of delirium will be underestimated if determined by ICD-10-coded diagnoses alone [199,200]. In addition, the real-time availability of the selected data categories in EHRs must be considered, as there is a potential for delays in data access [3].

Overall, the developed ADR indicators offer a foundation for future research and implementation of automated ADR detection systems in clinical practice. In addition, this project provides a methodological blueprint for extending the developed indicator set to other ADRs through standardised consensus processes.

Utilisation of a distributed analysis approach: Challenges in detecting and predicting ADEs in EHR data from German university hospitals

In this project, inpatient treatment data from diverse German university hospitals with different infrastructures were made accessible and subsequently analysed. The analysis was conducted using a two-step distributed analysis approach based solely on the data interoperability standards of the MII at the data integration centres. As this analysis approach was undertaken without direct data access for the analysts, it ensured compliance with data protection regulations by avoiding direct data sharing, thus making it a privacy-preserving solution for multicentre studies.

During our analysis, the unavailability of laboratory values used to define the outcome "drug-related hypoglycaemia" and some potential risk factors, as well as the unavailability of reliable timestamps, were among our major challenges. Therefore, we tailored our research question by questioning the

integration of timestamps and by constructing regression models of varying complexity (a base model without laboratory values and an extended model with laboratory values). As we received plausible estimates for prevalence and regression modelling odds ratios from a broad dataset reflecting routine healthcare in German university hospitals, this project suggests that the development of predictive models in a distributed setting is possible within the framework of the MII. The prerequisite is that the research question is adapted to the infrastructure and the available data.

Based on EHR data from the beginning of 2018 to the end of 2021 and the related MII core dataset (CDS) specifications (version 1.0), this project revealed important challenges when analysing routine healthcare data. Our lessons learnt based on these challenges led to important insights which have guided and will continue to guide improvements of the MII CDS specifications, thereby enhancing interoperability in Germany. At the moment, the implementation of the CDS version 2.0 is spreading. The extent to which this will improve the potential of such analyses and eliminate the shown challenges is being investigated in the follow-up project of the POLAR_MI project, called INTERPOLAR (INTERventional POLypharmacy – drug interActions – Risks), and other use cases carried out in the ongoing consolidation and extension phase from 2023 to 2026 [201].

Further steps are needed to achieve one of the overarching goals of the MII and the POLAR_MI project: conducting multicentre studies to assess medication-related risks that will directly benefit patients, e.g. by leading to validated prediction models that can be used in clinical practice to screen for patients at high risk for ADEs. Firstly, the data quality and completeness must be improved, for example, by flagging diagnoses present on admission. Secondly, validations should be carried out to capture the extent of inaccuracies in EHR data, as this is a critical factor for the acceptance of results based on EHR data. One proposed approach is to use an electronic Case Report Form (eCRF) for documentation by trained professionals alongside EHR data in the same study, followed by a comparison of the results obtained from these two data collection methods [3]. This allows the accuracy of variable definitions and outcome measures to be assessed, enabling them to be refined based on the observations gathered through the eCRF. Thirdly, when aiming at developing applicable ADE prediction models for many different hospitals, an external validation of these models is needed. According to the data in the MII, there are generally two methods possible to acquire a validation dataset: (1) geographical validation and (2) temporal validation [131,202]. Geographical validation is carried out by only a selection of centres being utilised for model creation, while the remaining centres are designated for model validation. In contrast, using temporal validation, model creation and validation can occur at all centres, as the dataset is split at a specific point in time. Data available at the start of the study can be utilised for model creation, while data gathered during and after model development can be used for model validation. Both methodologies possess distinct advantages and disadvantages. Utilising a

single centre for model development while using all others for validation would enhance implementation in the context of distributed analysis. Splitting by time would likely yield more generalisable outcomes, as the development would take place across all centres, considering their heterogeneity [131,155,202].

7. Summary

The implementation of electronic health records (EHRs) in German university hospitals enables the analysis of large volumes of structured routine healthcare data. The analysis of such data offers new potential for detecting and predicting adverse drug events (ADEs). The Medical Informatics Initiative (MII) plays a pivotal role in making EHR data usable for research purposes in Germany, as this initiative facilitates interoperability and exchange of EHR data from all German university hospitals. As part of the MII, the use case POLAR_MI (POLypharmacy, drug interActions and Risks) was developed to retrospectively identify medication-related risks in hospitalised adult patients. Within this context, the aim of this work was to develop and evaluate various methods for the detection and prediction of ADEs using routine healthcare data from several German university hospitals involved in the POLAR_MI project. To ensure data protection and legal compliance, parts of this work applied a distributed analysis approach, the feasibility of which was also aimed to be assessed.

A set of 34 clinically relevant inpatient ADEs was identified through an expert consensus process based on the RAND®/UCLA Appropriateness Method. Key factors contributing to their overall importance were the seriousness of the ADE and its likelihood of being drug-related. In a second expert consensus process, the likelihood of specific drugs contributing to the 14 most clinically relevant inpatient ADEs was assessed in order to provide a consensus-based list of drug-event pairs indicating adverse drug reactions (ADRs). Of the 255 drug-event pairs evaluated, 2 were considered as indicators of certain ADRs, 42 as indicators of probable ADRs, 137 as indicators of possible ADRs and 74 as indicators of unlikely ADRs. Indicators of possible, probable, or certain ADRs can serve as electronic triggers for detecting ADRs in routine healthcare data, offering a basis for future research and the implementation of automated ADR detection systems. Moreover, this work provides a methodological framework for extending the developed indicator set to other ADRs through standardised consensus processes.

The feasibility of developing models for ADE detection and prediction using a distributed and privacy-preserving analysis approach built upon MII interoperability standards was assessed using two ADEs as examples: gastrointestinal bleeding and drug-related hypoglycaemia. Despite several challenges such as missing laboratory data, unreliable timestamps, and heterogeneous IT infrastructures, plausible estimates for the prevalence of ADEs and regression modelling odds ratios were received. This suggests that predictive models can be developed in a distributed setting if the research question is adapted to the infrastructure and available data. Furthermore, this work demonstrated the potential of analyses within the MII.

In conclusion, the expert consensus processes that resulted in content-validated ADR indicators and the evaluation of the feasibility of building models for ADE detection and prediction using a distributed

analysis approach should be regarded as complementary approaches. Together, they contribute to the advancement of ADE detection and prediction, particularly within the MII. The integration of the developed ADR indicators as outcome measures in a distributed analysis approach is a future prospect, with the potential to promote drug safety studies under real-world hospital conditions.

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Further information on assistance received and resources used

General

During the preparation of this work, I used DeepL Write, DeepL Translate and QuillBot Premium in order to improve the readability and language without altering the content. I reviewed and edited the suggestions of these tools as necessary, and I take full responsibility for the content of this work.

Chapter 3: Prioritisation of adverse drug events leading to hospital admission and occurring during hospitalisation: A RAND survey

Tobias Dreischulte provided an introduction to the RAND®/UCLA appropriateness method.

Annette Haerdtlein designed and conducted the expert consensus process for the hospital admission setting. This included (1) selecting experts, (2) conducting the pretest, (3) performing the systematic literature search, (4) developing and preparing the assessment form, (5) writing the evidence report, (6) managing the rating process, (7) analysing and visualising the rating results and (8) writing the manuscript.

Ulrich Jaehde and Tobias Dreischulte assisted in the design of the consensus process.

Katharina Karsten Dafonte was the second reviewer to decide which studies to include in the systematic review of in-hospital adverse drug events (ADEs) in Germany.

Marietta Rottenkolber provided support in the analysis of the rating results.

All co-authors contributed to writing the manuscript.

Chapter 4: Drug-event pairs as indicators for the detection of adverse drug reactions during hospitalization in routinely collected electronic data sources

Ulrich Jaehde, Tobias Dreischulte and Annette Haerdtlein contributed to the design of the consensus process.

Annette Haerdtlein, Wolfgang Fehrmann and Clara Weglage helped with the literature search, which was used to compile the lists of potentially causative drugs for assessed ADEs. They also participated in the writing of the evidence report. For instance:

- Annette Haerdtlein conducted the literature search and wrote the first draft of the evidence report for the following ADEs: Rhabdomyolysis, Serotonin syndrome and Stevens-Johnson syndrome.
- Clara Weglage conducted the literature search and wrote the first draft of the evidence report for the following ADEs: Bleeding outside the gastrointestinal tract and Gastrointestinal bleeding.

- Wolfgang Fehrmann conducted the literature search and wrote the first draft of the evidence report for the following ADEs: Acute kidney injury, Hyperkalaemia and Hyponatraemia.

All co-authors helped to interpret the results of the literature search and of the consensus process.

All co-authors contributed to writing the manuscript.

Chapter 5: Challenges in detecting and predicting adverse drug events via distributed analysis of electronic health record data from German university hospitals

Study data was provided by participating centres (Bonn, Erlangen, Freiburg/Breisgau, Gießen, Halle/Saale, Hamburg, Heidelberg, Jena, Kiel, and Leipzig).

All co-authors contributed to the design and conduction of the POLAR_MI project. Torsten Thalheim, Miriam Kesselmeier and Ulrich Jaehde assisted in the detailed design and execution of work package 1.5.

An introduction to the distributed analysis approach was provided by Miriam Kesselmeier, Torsten Thalheim and Florian Schmidt.

Torsten Thalheim, Florian Schmidt, Thomas Peschel, Alexander Strübing and Miriam Kesselmeier wrote the modules (i.e. a composition of several R scripts) for local data retrieval and analysis as well as for the centralised meta-analysis. André Medek assisted in the writing of the R scripts as well as in the plausibility checks of the local results.

All co-authors participated in the formal analysis of the results.

Miriam Kesselmeier contributed to the investigation and visualisation of the results and wrote the R scripts for building the graphs.

All co-authors contributed to writing the manuscript.

Appendix

Full-text publications and supplementary materials

Journal of
Clinical Medicine

MDPI

Article

Prioritisation of Adverse Drug Events Leading to Hospital Admission and Occurring during Hospitalisation: A RAND Survey

Annette Haerdtlein [1,2,†], Anna Maria Boehmer [3,†], Katharina Karsten Dafonte [4], Marietta Rottenkolber [1], Ulrich Jaehde [3,‡] and Tobias Dreischulte [1,*,‡]

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Abstract: (1) Adverse drug events (ADEs) are a common cause of emergency department visits and occur frequently during hospitalisation. Instruments that facilitate the detection of the most relevant ADEs could lead to a more targeted and efficient use of limited resources in research and practice. (2) We conducted two consensus processes based on the RAND/UCLA appropriateness method, in order to prioritise ADEs leading to hospital admission (panel 1) and occurring during hospital stay (panel 2) for inclusion in future ADE measurement instruments. In each panel, the experts were asked to assess the "overall importance" of each ADE on a four-point Likert scale (1 = not important to 4 = very important). ADEs with a median rating of ≥3 without disagreement were defined as "prioritised". (3) The 13 experts in panel 1 prioritised 38 out of 65 ADEs, while the 12 experts in panel 2 prioritised 34 out of 63 ADEs. The highest rated events were acute kidney injury and hypoglycaemia (both panels), as well as Stevens–Johnson syndrome in panel 1 and rhabdomyolysis in panel 2. (4) The survey led to a set of ADEs for which there was consensus that they were of particular importance as presentations of acute medication-related harm, thereby providing a focus for further medication safety research and clinical practice.

Keywords: adverse drug events; drug-related side effects; consensus; RAND survey; prioritisation; medication safety

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1. Introduction

Adverse drug events (ADEs) are a common cause of emergency department visits and also occur frequently during hospitalisation [1,2]. Recent prospective observational studies on acute emergency department or hospital admissions have shown that about five to 30% were attributable to ADEs, of which two thirds or more were assumed to be at least possibly preventable [3–6]. According to a systematic review and meta-analysis of in-hospital ADEs, 19% of inpatients suffer from an ADE and approximately one third of these ADEs are judged as preventable [2]. Such ADEs can impose a significant burden on patients [1,7–10]. For example, in a prospective study of patients that were admitted to four large hospital emergency departments due to suspected adverse drug reactions (ADRs), 4% of patients with ADRs died and 1% suffered permanent damage [1]. A systematic review and meta-analysis of the characteristics of ADRs revealed that 31% of ADRs occurring

in hospitalised older adults are severe [7]. Another meta-analysis reported an overall percentage of drug-related deaths among inpatients of around 6% [10]. ADEs are also associated with major economic challenges for health care systems [11,12]. In Germany, the estimated total costs for ADE-related emergency hospitalisations may amount to EUR 2.25B per year [12]. Inpatient ADEs were estimated to increase the average treatment costs per patient by EUR 970 [11].

Preventing harm from medication requires identification of the risks before harm occurs; existing risk detection tools range from software highlighting drug–drug interactions to lists of potentially inappropriate medication (PIM) [13–17]. Nevertheless, even in settings implementing the most sophisticated countermeasures, the continued occurrence of ADEs is inevitable. In this scenario, the detection of ADEs and their causes is crucial to ameliorate harm and to prevent recurrence [18]. ADE recognition is also a pre-requisite to avoiding unintended prescribing cascades (i.e., the prescription of new drugs to treat ADEs that are misinterpreted as new medical conditions) [19].

The gold standard of ADE detection is a causality assessment by clinical experts using validated algorithms, but this is time consuming and requires experience [20,21]. The development of screening instruments, which can be efficiently applied at the point of care to identify potential ADEs, would therefore be an important step forward. If implemented in routinely collected electronic data sources, such screening instruments could also be used in clinical surveillance or research to repeatedly measure changes in the occurrence of potential ADEs at scale [17,22].

The aim of the present study was to identify a set of prioritised ADEs as a basis for defining medication safety measures for applications in clinical practice (e.g., decision support), clinical surveillance and research (e.g., as outcome measures).

The research that is reported here is embedded in the Germany-wide POLAR (POLypharmacy, drug interActions, Risks) project, which is part of the Medical Informatics Initiative (MII). POLAR focusses on the use of routinely collected hospital inpatient data to detect and prevent medication-related problems including ADEs at hospital admission and during hospitalisation [23].

2. Materials and Methods

2.1. Study Design

We conducted two separate expert consensus processes based on the RAND/UCLA appropriateness method (RAM) [24], in order to prioritise adverse drug events (ADEs) for two clinical settings: (1) at hospital admission (to prioritise ADEs originating in ambulatory care); (2) during hospital stay (to prioritise ADEs originating in the hospital). Similar to the Delphi method, we developed an assessment form with candidate ADEs for each panel based on a literature search. Panellists then independently rated each ADE on two occasions, with the first-round ratings fed back to them before the second-round ratings were placed. In contrast to the Delphi method but consistent with the RAM, a moderated face-to-face meeting (one for each panel) was held in between rounds to enable the exchange of arguments between experts (Figure 1).

2.2. Selection of Experts

For both expert panels, we recruited physicians and pharmacists with an academic interest or clinical experience in the detection or treatment of ADEs at hospital admission or during hospital stay, respectively, aiming for a balanced distribution of the two professions and of self-reported (predominant) professional activity as scientists or clinicians in each panel. Aiming for approximately 12 experts in each panel, we initially invited a total of 36 physicians and pharmacists that were involved in the POLAR project, as well as 14 additional physicians and pharmacists who had either been involved in large German studies on inpatient or outpatient ADEs or were nominated by POLAR project experts. Those that were interested in participating completed a self-declaration form about their field of activity, and their professional and academic background.

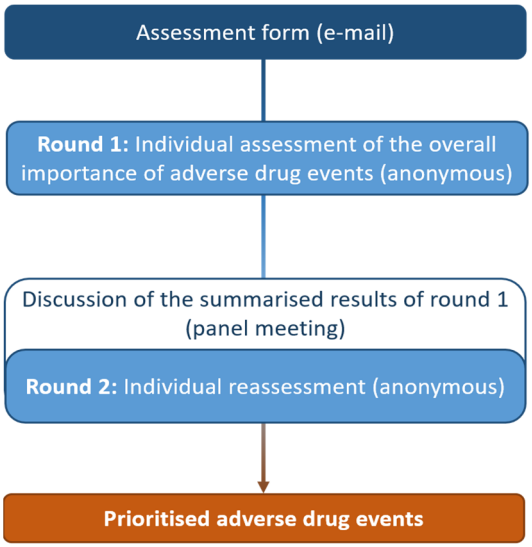

Figure 1. RAND consensus process followed by each of the two expert panels prioritising adverse drug events (ADEs) on admission (panel 1) and during inpatient stay (panel 2).

2.3. Design of the Assessment Forms

In order to generate a comprehensive list of candidate ADEs occurring at hospital admission or during inpatient stay, respectively, two systematic literature searches were performed. We searched MEDLINE for articles that were published between 01/2000 and 07/2020, combining search terms for the setting ('hospital' or 'hospital admission' in 'Germany') and the focus of the study ('ADEs'). All empirical studies reporting ADEs in the general population on admission or during inpatient stay were included, whereas studies targeting specific populations or ADEs were excluded. More details of the literature search are provided in Supplement S1.

From selected publications, we extracted all reported ADEs, classified them by organ system, and grouped them into superordinate categories, guided by the International Classification of Diseases, 10th Revision (ICD-10). Since the focus was on the detection of acute events at hospital admission or during hospital stay, ADEs that were unlikely to lead to hospital admission or worsen acutely (e.g., osteoporosis or obesity) were excluded. In addition, we excluded the following ADEs since they were out of scope: explicit consequences of surgical or medical procedures (e.g., infections after infusion, transfusion or injection) or drug poisoning (e.g., harmful use of non-addictive substances); events only involving children (e.g., neonatal icterus or laryngospasm) or pregnant women (e.g., liver diseases during pregnancy, childbirth and the postpartum period); and ADEs that were judged to be the consequences of medication underuse (e.g., uncontrolled pain). All exclusions were based on consensus discussions within the core research team (AH, TD, AMB, UJ). The studies that were used to generate the lists of ADEs to be rated by each panel were summarised in two different evidence reports, i.e., one for each setting-specific panel.

2.4. Pretest and Optimisation of the Assessment Forms

Based on the literature searches, drafts of the assessment forms (which were virtually identical for both panels) and the two different evidence reports were pretested and optimised in two stages. In the first stage, a convenience sample of three pharmacists and one physician (who were not part of the research team) were presented with the draft assessment form and the evidence document for panel 2 (hospital stay). In stage 2, another two pharmacists and two physicians were presented with a revised assessment form and the evidence document for panel 1 (hospital admission). Feedback from the pretest participants was obtained at each stage via semi-structured interviews (interview guide: Supplement S2) which focussed on the comprehensiveness of the ADEs that were listed in the assessment forms, the comprehensibility of the scales, rating instructions and ADE descriptions; on the

grouping of ADEs in superordinate categories; and the comprehensiveness and utility of the evidence reports. Expert feedback emerging from the first stage was implemented and a last round of amendments after the second feedback round yielded the final optimised versions of the first-round assessment forms.

2.5. Rating Process

2.5.1. Definitions and Pre-Specifications

"Overall importance" was the pre-specified key criterion that was used to prioritise the ADEs. Since we considered "overall importance" an insufficiently specific concept to be uniformly understood by the panellists, we asked them to rate for each ADE the importance to "conduct a medication review (in the near future) as a strategy to prevent further or repeated harm" in relation to an average patient (Figure 2). In addition, we asked the panellists to rate each ADE for "seriousness" (defined as the likelihood of the ADE leading to serious harm (prolonged hospital stay, permanent damage or life-threatening condition)) and "drug-relatedness" (defined as the likelihood that one or more drug(s) contributed to the adverse event). Although prioritisation was to be solely based on overall importance ratings, the additional rating scales served the dual purpose of (a) encouraging the panellists to consistently consider these aspects in their overall importance ratings; (2) identifying sources of disagreement between the panellists to inform discussions prior to the second-round ratings. Given that the same ADEs may be worded in ways that reflect different levels of severity (e.g., constipation and ileus), the panellists were instructed that all the ADEs to be rated would be assumed to be sufficiently severe to warrant hospital admission (panel 1) or medical treatment (panel 2). For laboratory parameters (e.g., hyperkalaemia), threshold values were provided to specify severity. For broader ADEs or those that were identified as potentially ambiguous during pretests, examples were provided for clarity. We also pre-specified that ADEs with a median overall importance rating of $\geq$3 without disagreement would be defined as "prioritised". Disagreement was pre-defined to be present if at least 30% of expert ratings were 1 or 2 (for items with a median of $\geq$3 consistent with prioritisation), or 3 or 4 (for items with a median of <2 consistent with non-prioritisation).

Overall Importance	Seriousness	Drug-relatedness
Panel 1: Imagine an average patient admitted to hospital due to the following event… Panel 2: Imagine an average hospitalised patient with the following event during hospital stay…		
How important is it to conduct a medication review *in the near future* as a strategy to prevent further or repeated harm from this AE ?*	How likely is it that this AE leads to serious harm (*prolonged hospital stay*, permanent damage or life-threatening condition)?*	How likely is it that one or more drug(s) contributed to this AE?
1 = Not important	1 = Unlikely	1 = Unlikely
2 = Somewhat important	2 = Somewhat likely	2 = Somewhat likely
3 = Important	3 = Likely	3 = Likely
4 = Very important	4 = Very likely	4 = Very likely

Figure 2. Assessment criteria and rating scales for panel 1 (hospital admission) and panel 2 (hospital stay); * *Italic* terms were only part of the assessment form of panel 2. *Abbreviations:* AE = adverse event.

2.5.2. Rating Rounds

The experts were sent the assessment form by e-mail, including rating instructions and the respective evidence report for each setting. Approximately two weeks after completion of the first round, a face-to-face expert meeting took place for each panel, moderated by

TD for panel 1 (hospital admission) and UJ for panel 2 (hospital stay), respectively. At the beginning and during discussions, important aspects to consider were highlighted, including clarification that all ratings should be placed in relation to the ADE being caused by a drug, rather than by underuse of drugs or drug withdrawal.

For each ADE, the first-round ratings were summarised (median and distributions of ratings for overall importance, seriousness and drug-relatedness, and whether there was disagreement) and fed back to the experts. To facilitate the discussion, ADEs were discussed in thematic blocks (e.g., cardiovascular ADEs, gastrointestinal ADEs). The focus of discussion was on ADEs with disagreement regarding their overall importance after the first rating round, while differences in seriousness and drug-relatedness were used to inform the discussion.

After discussion of a thematically related set of ADEs, the panellists directly placed their second-round ratings. The ADEs with a median overall importance rating of $\geq$3 without disagreement (defined as above) after the second-round rating were deemed "prioritised".

3. Results

3.1. Expert Panels

The expert panels comprised 13 members from 11 German university sites (panel 1) and 12 members from nine German university sites (panel 2), respectively. Table 1 shows that members of both panels were approximately balanced in terms of professional background and main field of professional activity. The majority of the recruited experts had additional research or clinical qualifications.

Table 1. Characteristics of participating experts in the two panels.

	Panel 1 (Hospital Admission) n = 13		Panel 2 (Hospital Stay) n = 12	
	Physicians (n = 6)	Pharmacists (n = 7)	Physicians (n = 6)	Pharmacists (n = 6)
Academic background				
Additional qualification (habilitation/doctc and/or clinical specialist qualification)	6 (100%)	4 (57%)	4 (67%)	5 (83%)
Main field of professional activity				
Scientific research	4 (67%)	2 (29%)	3 (50%)	1 (17%)
Clinical practice	0 (0%)	2 (29%)	1 (17%)	2 (33%)
Both	2 (33%)	3 (43%)	2 (33%)	3 (50%)

3.2. Literature Search and Design of Round 1 Assessment Forms

For panel 1 (hospital admission), the first-round assessment form was informed by nine publications and for panel 2 (hospital stay) by eight publications (a flow chart of identified, screened, included and excluded publications is provided in Supplement S1). The extracted ADEs of both literature searches led to the same 74 superordinate events within 13 organ classes to be included in the first drafts of the assessment forms for both panels, of which 57 ADEs satisfied our inclusion and exclusion criteria (excluded ADEs are listed in Supplement S3). The main changes that emerged from the experts' feedback were to include more detailed rating instructions and to split the ADEs that were considered too broad for assessment. For example, the ADE bone marrow suppression was split into anaemia, thrombocytopenia and neutropenia/agranulocytosis. Additionally, in order to optimally adapt the assessment forms to the respective setting, the ADEs myopathy (without rhabdomyolysis) and somnolence were only assessed in panel 1 (hospital admission). The resulting round 1 assessment forms contained 63 ADEs (panel 1) and 61 ADEs (panel 2), respectively (Figure 3).

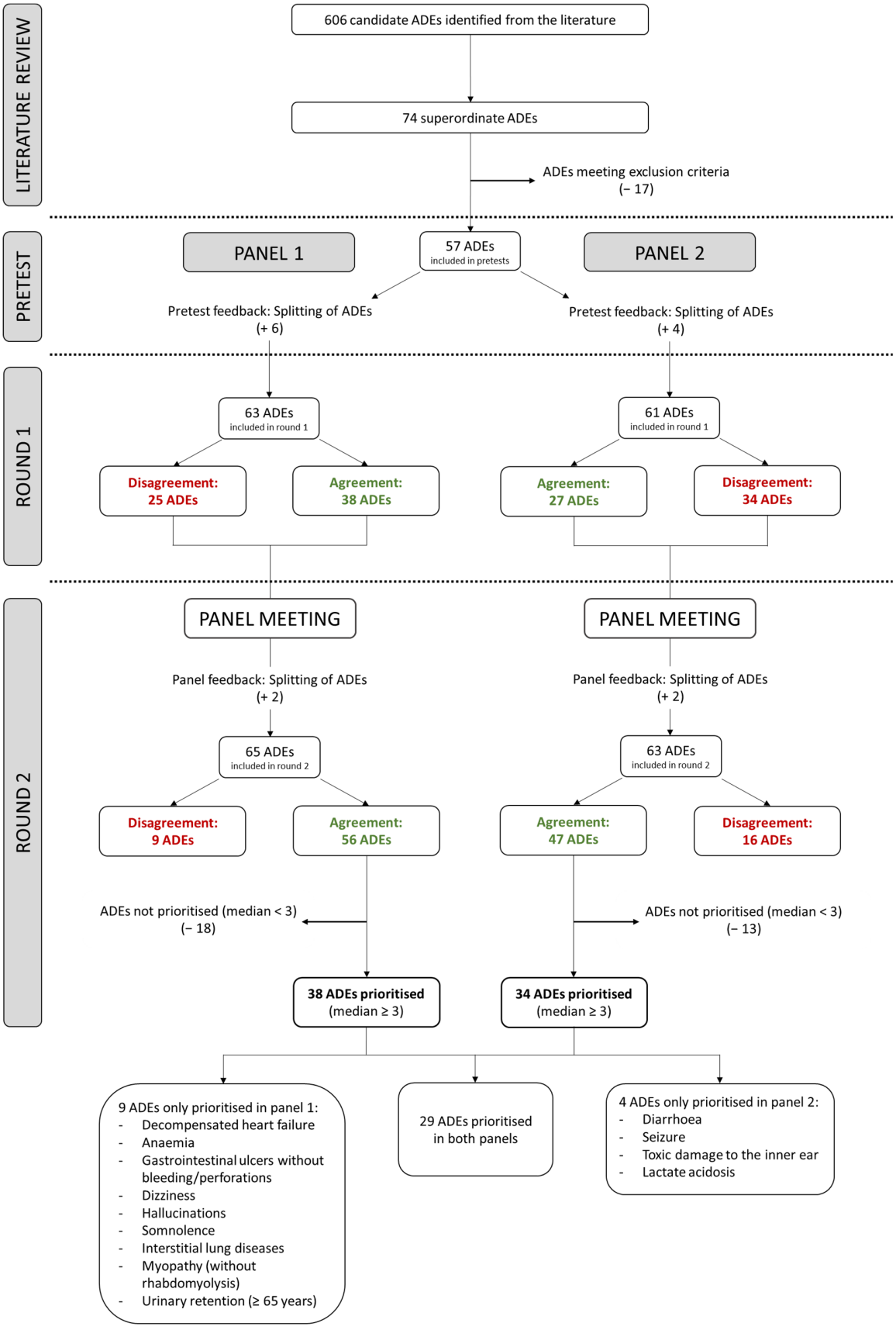

Figure 3. Flow chart showing the ADE prioritisation process in panel 1 (hospital admission) and panel 2 (hospital stay). *Abbreviations:* ADEs = adverse drug events.

3.3. Rating Process and Findings

For both panels, the ratings for round 1 are provided in Supplement S4 Table S1 and the results of round 2 are presented in Figures 4 and 5.

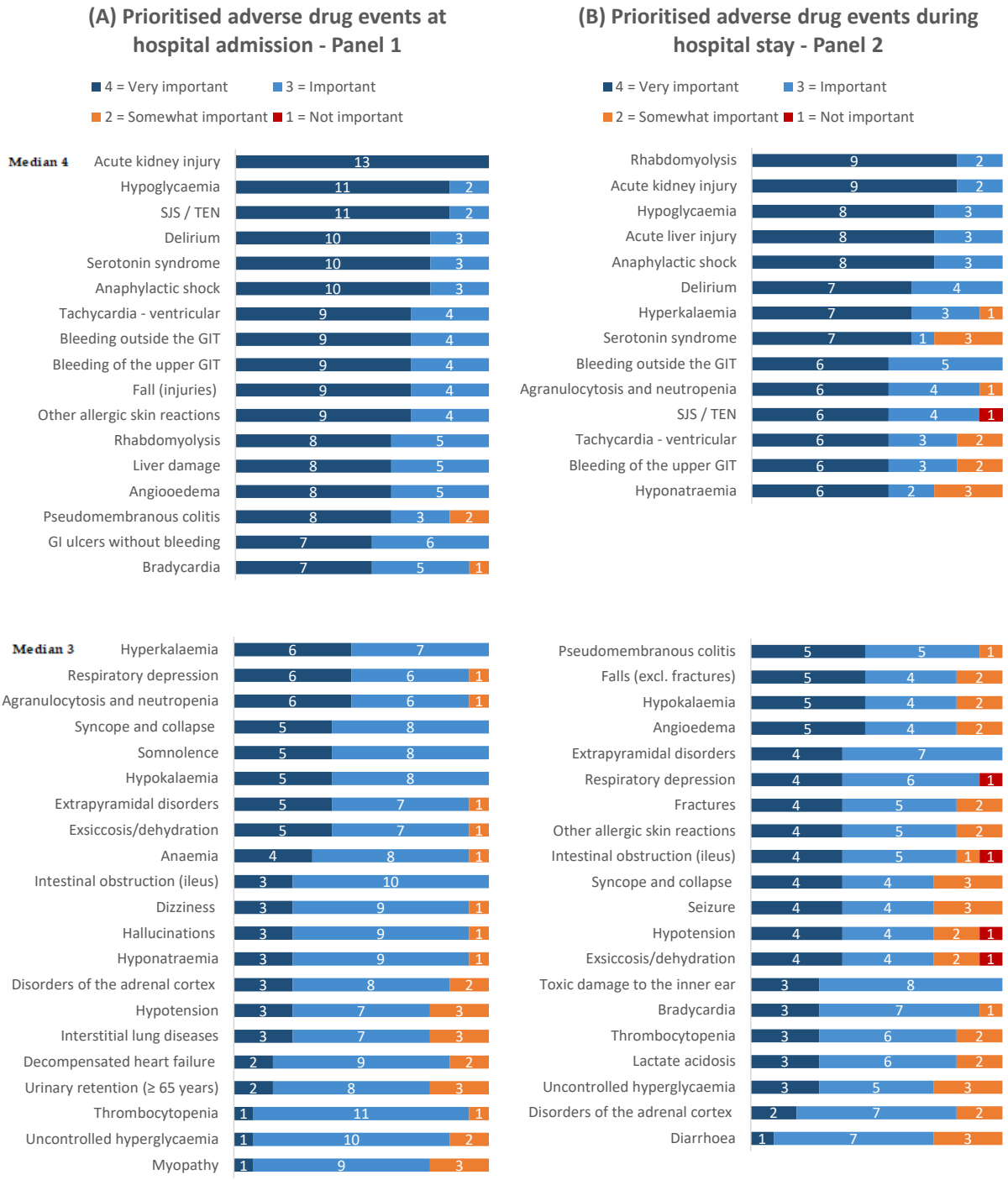

Figure 4. Distributions of overall importance ratings in (**A**) panel 1 (hospital admission) and (**B**) panel 2 (hospital stay) for the prioritised adverse drug events after completion of the second assessment round of the RAND consensus process. *Abbreviations:* SJS/TEN = Stevens–Johnson syndrome/toxic epidermal necrolysis; GIT = gastrointestinal tract.

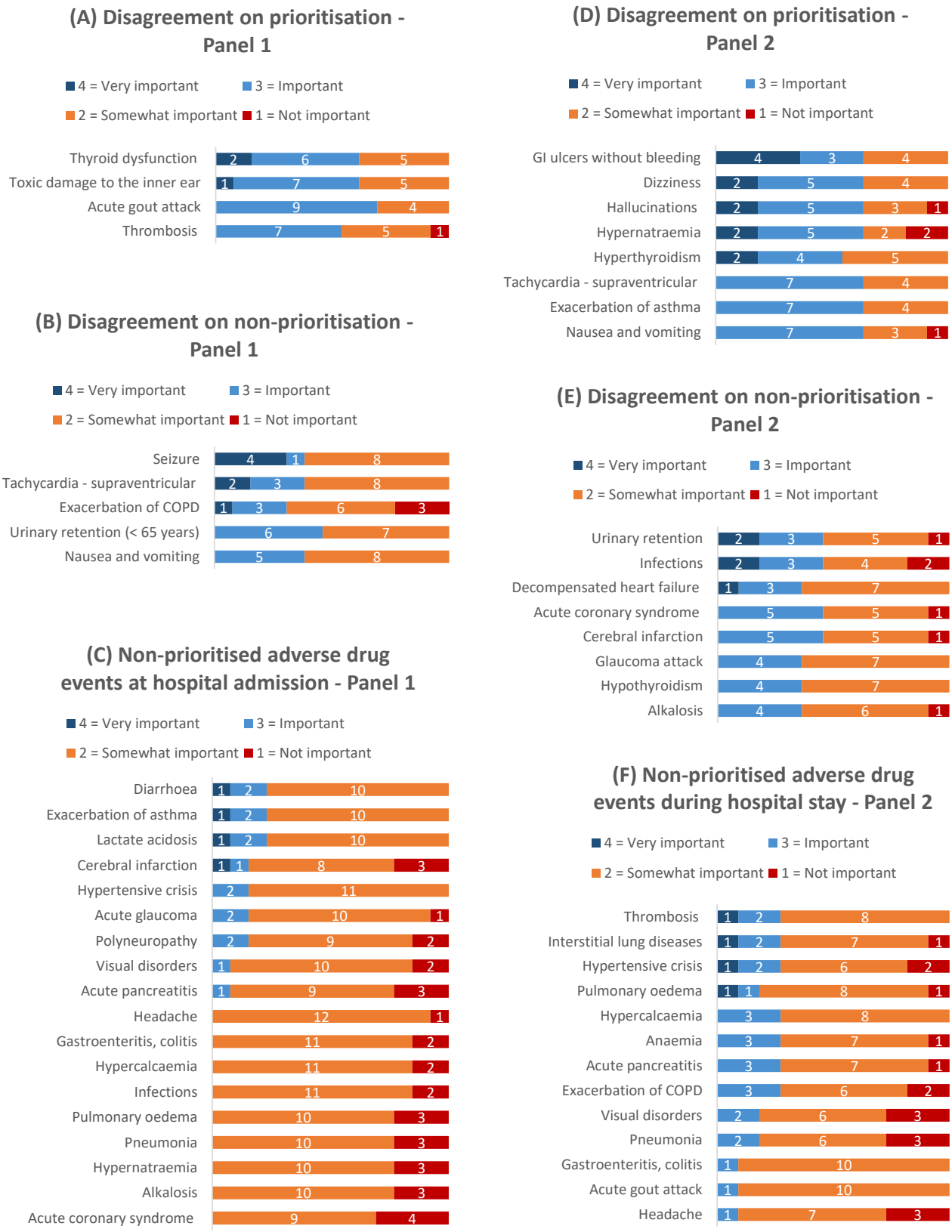

Figure 5. Distributions of overall importance ratings in (**A**–**C**) panel 1 and (**D**–**F**) panel 2 for ADEs that were not prioritised after the second assessment round, incl. those that reached no consensus. *Abbreviations:* COPD = chronic obstructive pulmonary disease; GI = gastrointestinal.

3.3.1. Panel 1: Prioritisation of ADEs on Admission

The round 1 assessment form was emailed to the panellists in January 2021 and the expert panel met, discussed the first-round findings and conducted the second-round ratings on 26 February 2021.

All 13 (100%) experts returned a fully completed round 1 assessment form, all took part in the moderated expert discussion and returned a fully completed round 2 assessment form. In round 1, of 63 ADEs assessed, there was consensus for 31 (49%) to be prioritised (median ≥ 3 without disagreement) and for seven (11%) not to be prioritised (median < 3 without disagreement). Disagreement was present for 25 ADEs (40%) (disagreement on prioritisation: 11 ADEs; disagreement on non-prioritisation: 14 ADEs, Figure 3). During the discussion, the experts decided to split the ADE gastroenteritis and colitis (into pseudomembranous colitis and gastroenteritis, and colitis excluding pseudomembranous colitis) and the ADE urinary retention (to be assessed for people aged <65 and $\geq$65 years separately). Therefore, a total of 65 ADEs were rated in round 2. Of these, there was consensus to prioritise 38 ADEs (58%) and not to prioritise 18 (28%). The second assessment round resolved first round disagreements for 16 ADEs (five of which were now prioritised and 11 not prioritised). However, after the second rating round, disagreement remained for 9 ADEs (14%) (four on prioritisation, five on non-prioritisation).

3.3.2. Panel 2: Prioritisation of ADEs during Inpatient Stay

The round 1 assessment form was emailed to the panellists in January 2021 and the expert panel met on 4 March 2021 to discuss the first-round findings and conduct the second-round ratings.

All 12 (100%) experts returned the round 1 assessment form, all took part in the moderated expert discussion and 11 experts (92%) returned a fully completed round 2 assessment form. Of 61 ADEs rated in round 1, there was consensus for 25 ADEs (41%) to be prioritised (median ≥ 3 without disagreement) and for 2 ADEs (3%) not to be prioritised (median < 3 without disagreement). Disagreement was present for 34 ADEs (56%) (disagreement on prioritisation: 19 ADEs; disagreement on non-prioritisation: 15 ADEs, Figure 3). As in panel 1 (hospital admission), the panel 2 (hospital stay) experts decided to split the ADE gastroenteritis and colitis as above and to additionally split the ADE thyroid dysfunction into the ADEs hyperthyroidism and hypothyroidism. After round 2, there was consensus to prioritise 34/63 ADEs (54%) and not to prioritise 13 (21%). The second rating round resolved disagreements for 19 ADEs (8 were now prioritised and 11 not prioritised). However, after the second rating round, disagreement remained for 16 ADEs (25%) (eight on prioritisation; eight on non-prioritisation).

3.4. Comparison of the Overall Importance Findings in Panels 1 and 2

A comparison of the panel findings (Figures 3 and 4) shows that 29 ADEs were prioritised in both panels, while nine ADEs were prioritised only in panel 1 (hospital admission), and four ADEs were prioritised only in panel 2 (hospital stay). In both panels, acute kidney injury and hypoglycaemia were among the three highest rated events, which also featured Stevens–Johnson syndrome in panel 1 (hospital admission) and rhabdomyolysis in panel 2 (hospital stay).

3.5. Relationship between Overall Importance, Seriousness and Drug-Relatedness

Supplement S4 Tables S2 and S3 show an overview of the assessment results for overall importance, seriousness and drug-relatedness after the second-round ratings of both panels. Of ADEs with median overall importance ratings of $\geq$3, 22/42 ADEs (52%) in panel 1 (hospital admission) and 26/42 ADEs (62%) in panel 2 (hospital stay) also had median ratings of $\geq$3 for both seriousness and drug-relatedness. Nevertheless, there were eight ADEs (12%) in panel 1 (hospital admission) and one ADE (2%) in panel 2 (hospital stay) where ratings for seriousness and drug-relatedness diverged from the overall importance rating (overall importance rating ≥ 3 and the other ratings < 3), namely other allergic skin

reactions, hallucinations, hypotension, uncontrolled hyperglycaemia, urinary retention (≥65 years), myopathy, thyroid dysfunction and acute gout attack in panel 1 (hospital admission) and hyperthyroidism in panel 2 (hospital stay). A total of nine ADEs (14%) in panel 1 (hospital admission) and 13 ADEs (21%) in panel 2 (hospital stay) had a median overall importance rating of <3, but a median seriousness rating of ≥3 (e.g., acute coronary syndrome and cerebral infarction in both panels), while there were no ADEs with a median overall importance rating of <3 and a median drug-relatedness rating of ≥3 in both panels.

4. Discussion

4.1. Summary of Findings

In this study, we identified a total of 38/65 (58%) ADEs at hospital admission and 34/63 (54%) ADEs during hospital stay, for which there was consensus on their high overall importance, thus classified as "prioritised". While the majority of prioritised ADEs after round 2 were common to both panels (n = 29), a total of 13 ADEs were selected only by one panel (nine ADEs only by panel 1 and four ADEs only by panel 2), which supports our approach of separate setting-specific consensus processes.

The median importance rating was ≥2 for all the ADEs in both panels, which may reflect that all the ADEs that were included in the assessment form had previously been empirically identified as potential presentations of medication-related harm and emphasises the relevance of the ADEs that were included in the assessment form. Despite this, our study indicates that by asking the panellists to rate the importance of conducting a medication review to prevent further or repeated harm from the ADE on a 4-point Likert scale, it is possible to discriminate between more and less relevant ADEs.

The ratings for overall importance on the one hand, and for seriousness and drug-relatedness on the other, generally pointed in the same directions. Of the ADEs with median overall importance ratings of ≥3, the majority (≈60%) also had median ratings of ≥3 for seriousness and drug-relatedness in both panels, which suggests that seriousness and drug-relatedness are important drivers for overall importance. However, the finding that among ADEs with lower overall importance ratings (<3), all had a lower drug-relatedness rating (<3)—whereas several had a higher seriousness rating (≥3)—suggests that drug-relatedness may be a more important driver of overall importance than seriousness.

There were several examples where the ratings for either seriousness or drug-relatedness diverged from the overall importance ratings, suggesting that other criteria may also play a role. For example, despite an overall importance rating of 3, the ADE myopathy had a median score of <3 for both seriousness and drug-relatedness. Myopathy is multi-causal (which may explain a lower drug-relatedness rating) and rhabdomyolysis was rated separately (so that lower seriousness ratings may be explained by myopathy being limited to less severe presentations). Nevertheless, myopathy is a common adverse reaction of frequently prescribed drugs (i.e., statins) and early recognition may prevent more serious events [25]. This suggests that the prevalence of ADEs and the preventability of further drug-related harm may be independent drivers of overall importance.

The different settings caused diverging prioritisation in the respective panels for some ADEs, partly due to differences between the drugs that are used in outpatient and inpatient settings. For example, the ADE toxic damage to the inner ear is predominantly caused by aminoglycosides, which are almost exclusively used in the inpatient setting [26]. This likely explains why this ADE was prioritised by panel 2 (hospital stay), but not by panel 1 (hospital admission).

4.2. Comparison with Literature

To the best of our knowledge, this is the first consensus process study to prioritise ADEs systematically at both hospital admission and inpatient stay. There is only one similar expert survey from the United States by Jeon et al., focussing on inpatient ADEs, which exclusively prioritised ADEs that were deemed as preventable by pharmacist intervention [27]. We included ADEs irrespective of their preventability because our focus was on

their detection to avert further harm, or to measure them in the context of clinical surveillance or research. The survey by Jeon et al. identified 21 ADEs as priorities for preventive action by pharmacists. Of the latter, the following comparable ADEs of our assessment form were not prioritised by panel 2 (which also focussed on ADEs originating in hospital): thrombosis, nausea and vomiting, hypothyroidism, hypertensive crisis, decompensated heart failure, anaemia and gastrointestinal ulcers (although gastrointestinal bleeding was prioritised in our set). These differences are likely explained by our exclusion of ADEs that are the consequence of the underuse of medication.

4.3. Strengths and Limitations

A strength of the present RAND consensus process is the heterogeneous composition of the two expert panels, with a balanced representation of physicians and pharmacists who are predominantly involved in scientific research or clinical practice and have expertise in studying or detecting ADEs at hospital admission or during inpatient stay. Also noteworthy is their distribution across numerous university sites throughout Germany, so that the expert panels covered a breadth of experience from a variety of perspectives. We systematically tested and optimised the assessment forms (two iterations) prior to their distribution. This meant that any ambiguities of rating constructs or wording of ADEs could be minimised. Any remaining misunderstandings were clarified during moderated discussions. The personal discussions during the panel meetings also enabled an exchange of arguments and experiences for the panellists to consider in their second-round ratings, which are key strengths of the RAND consensus process. Due to the simultaneous implementation of the consensus process for two different settings, a direct comparison of the results was possible, revealing commonalities and differences in the relevance of ADEs at hospital admission and during inpatient stay.

A limitation of our RAND consensus process was that for feasibility reasons, the large number of individual ADEs had to be combined into superordinate categories, partly resulting in broad ADE definitions. Nevertheless, we compensated for this by providing definitions and examples, thereby ensuring that all experts had the same basis for assessment. In addition, where ADEs appeared to be too heterogeneous to be rated collectively, the panellists had the opportunity (and made use of it) to suggest splitting ADEs during expert discussions, which were then rated separately in the second rating round.

4.4. Implications for Research and Practice

The two sets of prioritised ADEs that are developed here can provide a basis for a number of future applications.

In order to support clinical practice, the prioritised ADEs could be implemented in routine electronic data sources as decision support and/or case finding tools to prompt medication reviews and/or to efficiently direct staff resources, e.g., of clinical pharmacists or pharmacologists. The aim here would be to prevent further or repeated harm from detected ADEs (i.e., ADE management and secondary prevention). Our ADE lists therefore supplement the work by Jeon et al., who prioritised ADEs that could be prevented by clinical pharmacists (i.e., primary prevention of ADEs) [27].

In order to support clinical research, the prioritised ADEs could be implemented in routine electronic data sources to efficiently and repeatedly measure the prevalence or incidence of ADEs, both to inform and evaluate quality improvement interventions. Instruments to efficiently and specifically measure the clinical impact of medication safety initiatives are currently missing. While there are examples of interventional studies, which have measured drug-related hospital admissions (ascertained by expert assessment), most of them have been either limited to measuring processes (i.e., medication use) or unspecific outcomes, such as all-cause hospital admissions or the prolongation of inpatient stay [28–30]. Our prioritised lists of ADEs may therefore provide a basis to fill an important gap in the medication safety literature.

For applications in both clinical practice and research, the sensitivity and specificity of ADE detection instruments are important considerations. A lack of sensitivity could result in missing ADE cases that require management, while a lack of specificity may lead to alert fatigue in a clinical context and a limited responsiveness to change in a research context. Although we have identified adverse drug events that may be important presentations of medication-related harm, many of the events can also have other causes, which implies limitations in specificity.

In order to increase the specificity of ADE detection, previous authors have combined adverse events with preceding suboptimal medication use patterns (e.g., hospital admission for gastrointestinal bleeding preceded by the use of antiplatelets in patients aged ≥75 years without gastroprotection) [31,32]. This approach focusses on failures in the medication use process but limits the sensitivity of ADE detection because it misses all unpreventable ADEs and cannot identify all preventable ADEs (since the spectrum of suboptimal medication use patterns is too broad to be comprehensively pre-specified). A potentially more promising compromise between sensitivity and specificity is to combine the ADEs that are identified here with potentially causative drugs (e.g., hospital admission for gastrointestinal bleeding preceded by the use of antiplatelets), which would restrict detected adverse drug events to those where a drug-related cause is (at least) possible without a restriction to pre-specified medication use patterns.

5. Conclusions

By conducting a RAND survey for the two clinical settings 'hospital admission' and 'hospital stay', we have identified two sets of ADEs for which there is consensus that they are of particular importance as presentations of acute medication-related harm, thereby providing a focus for further medication safety research and clinical practice. As part of the POLAR project, we aim to further develop the prioritised items into indicators of potential ADRs by identifying potentially causative medication in a second consensus process. The indicators will be implemented in data that are routinely available in the data integration centres of German University hospitals.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11154254/s1, Supplement S1: Systematic literature search; Supplement S2: Interview guide; Supplement S3: Excluded adverse drug events (ADEs); Supplement S4 Table S1: Expert ratings in the first round of the RAND survey; Supplement S4 Table S2: Expert ratings in the second round of the RAND survey in panel 1 (hospital admission); Supplement S4 Table S3: Expert ratings in the second round of the RAND survey in panel 2 (hospital stay). Reference [33] is cited in the Supplementary Materials.

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Informed Consent Statement: Not applicable as no patients were involved in this study.

Data Availability Statement: The data presented in this study are available in Figures 4 and 5, Supplement S4 Tables S1–S3.

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Supplement S1: Systematic literature search

1.1 Search strategy

Adverse drug events (ADEs) during inpatient stay

Setting hospital (Hospital[mesh]) OR (Hospital Medicine[mesh])) OR (medication systems, hospital[mesh])) OR (pharmacy service, hospital[mesh])) OR (medical records department, hospital[mesh])) OR (hospital administration[mesh])) OR (hospital information systems[mesh])) OR (inpatients[mesh])) OR (hospitalization[mesh])) OR ("Hospital" [All Fields])) OR ("Hospitals" [All Fields])) OR ("inpatient" [All Fields])) OR ("inpatients" [All Fields])) OR ("hospitalized" [All Fields])) OR ("ward" [All Fields])) OR ("wards" [All Fields])) OR ("hospitalised" [All Fields])

AND

ADE/ADR (drug-related side effects and adverse reactions[mesh]) OR (medication errors[mesh])) OR ("adverse drug event*" [All Fields])) OR ("adverse drug reaction*" [All Fields])) OR ("medication error*" [All Fields])) OR ("adverse drug effect*" [All Fields])

AND

Germany (Germany [All Fields] OR german [All Fields] OR (germany[mesh])

NOT

emergency service, hospital[mesh] OR outpatient clinics, hospital[mesh] OR emergency service, psychiatric[mesh] OR psychiatric emergency service[mesh] OR outpatient[Title] OR ambulatory[Title] OR emergency[Title] OR systematic review[Title/Abstract] OR meta analysis [Title/Abstract]

Adverse drug events (ADEs) at hospital admission

Setting hospital admission (("emergency service, hospital"[MeSH Terms] OR "hospitalization"[MeSH Terms] OR "emergency medical services"[MeSH Terms] OR "patient admission"[MeSH Terms] OR "hospital admission"[All Fields] OR "emergency department"[All Fields]))

AND

ADE/ADR (drug-related side effects and adverse reactions[mesh]) OR (medication errors[mesh]) OR ("adverse drug event*" [All Fields]) OR ("adverse drug reaction*" [All Fields]) OR ("medication error*" [All Fields]) OR ("adverse drug effect*" [All Fields])

AND

Germany (Germany [All Fields] OR german [All Fields] OR (germany[mesh]))

1.2 Inclusion and exclusion criteria

ADEs during inpatient stay

Table S1. Inclusion and exclusion criteria for the literature search on inpatient ADEs

	Inclusion criteria	**Exclusion criteria**
E1: Study design	Retrospective or prospective intervention or observational study	○ Review ○ Meta-analysis ○ Simulation study ○ Survey ○ Clinical trial
E2: Study population	Patients ≥ 18 years with a drug prescription and a hospital stay	Focus on patients with a specific disease/drug intake
E3: Setting	Hospital in Germany	○ Psychiatry ○ Clinics for TCM or similar ○ Outpatient clinics
E4: Evaluation	**General analysis of ADEs/ADRs** All occurring ADEs/ADRs were considered and at least one of the following quantitative frequencies was described: (I) the frequencies of ADE-associated drug substances (II) the frequencies of the different types of ADEs, e.g. based on organ classes or ICD-10 codes	○ ADEs in the context of hospital admissions or in the emergency department ○ ADEs of specific drugs or classes of drugs ○ ADEs due to a single DRP, e.g. interactions, overdose

Abbreviations: DRP = drug-related problem; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th revision; TCM = traditional Chinese medicine; ADEs = adverse drug events; ADRs = adverse drug reactions.

ADEs at hospital admission

Table S2. Inclusion and exclusion criteria for the literature search on ADEs at hospital admission

	Inclusion criteria	**Exclusion criteria**
E1: Study design	Retrospective or prospective intervention or observational study	○ Review ○ Meta-analysis ○ Simulation study ○ Survey ○ Clinical trial
E2: Study population	Patients ≥ 18 years admitted to hospital or emergency department	Focus on inpatients or patients with specific disease/drug intake
E3: Setting	Hospital admission or emergency department visit in German hospitals	○ Admission to specific ward (e.g. ICU) ○ Inpatient setting only
E4: Evaluation	**General analysis of ADEs/ADRs** All occurring ADEs/ADRs were considered and at least one of the following quantitative frequencies was described: (I) the frequencies of ADE-associated drug substances, (II) the frequencies of the different types of ADEs, e.g. based on organ classes or ICD-10 codes	○ ADEs during hospital stay ○ ADEs of specific drugs or drug classes. ○ ADEs due to a single DRP, e.g. interactions, overdose

Abbreviations: DRP = drug-related problem; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th revision; TCM = traditional Chinese medicine; ADEs = adverse drug events; ADRs = adverse drug reactions.

1.3 Results

ADEs during inpatient stay

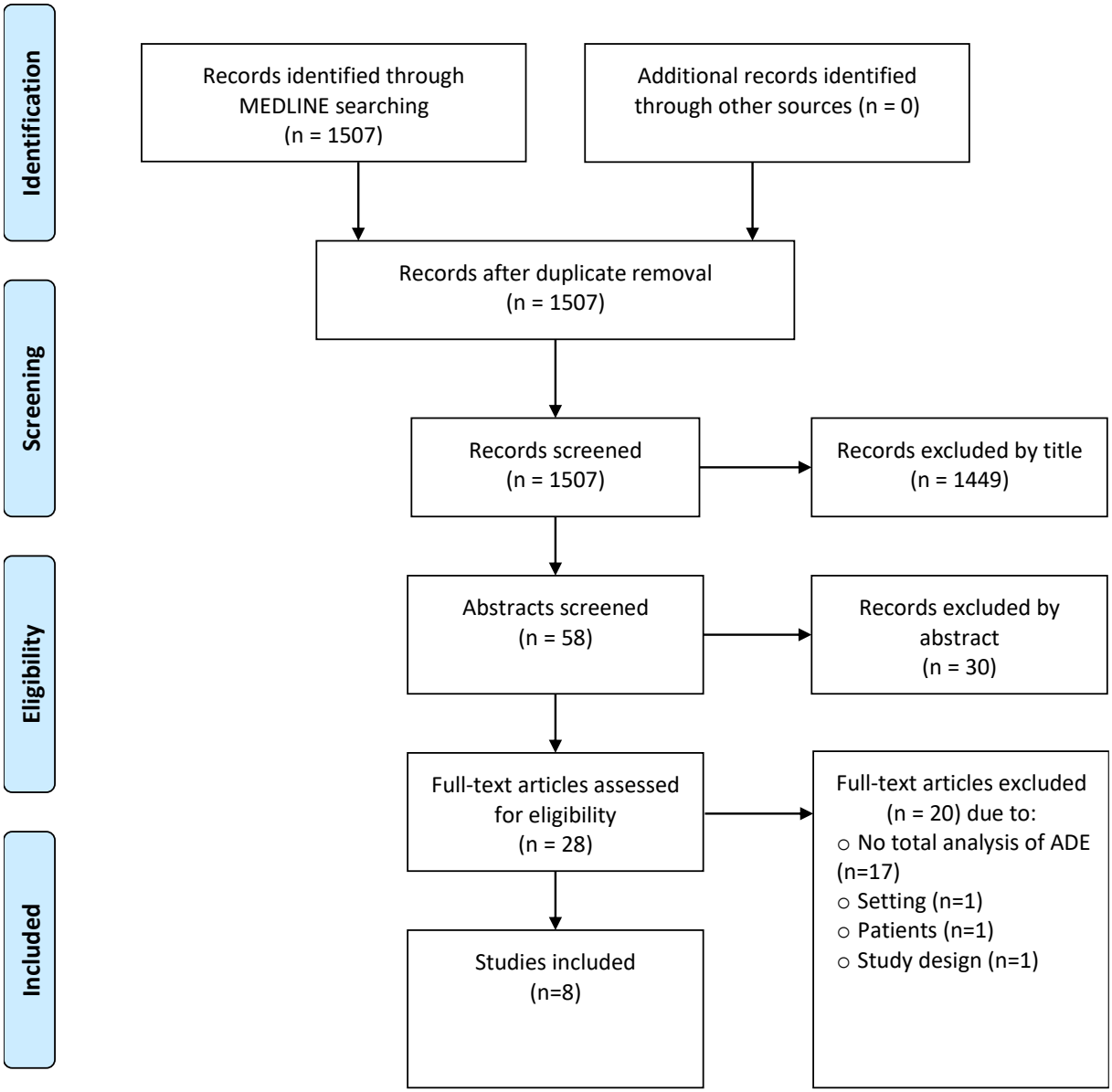

Figure S1. Results of the systematic literature search on in-hospital adverse drug events (ADEs) [1]

ADEs at hospital admission

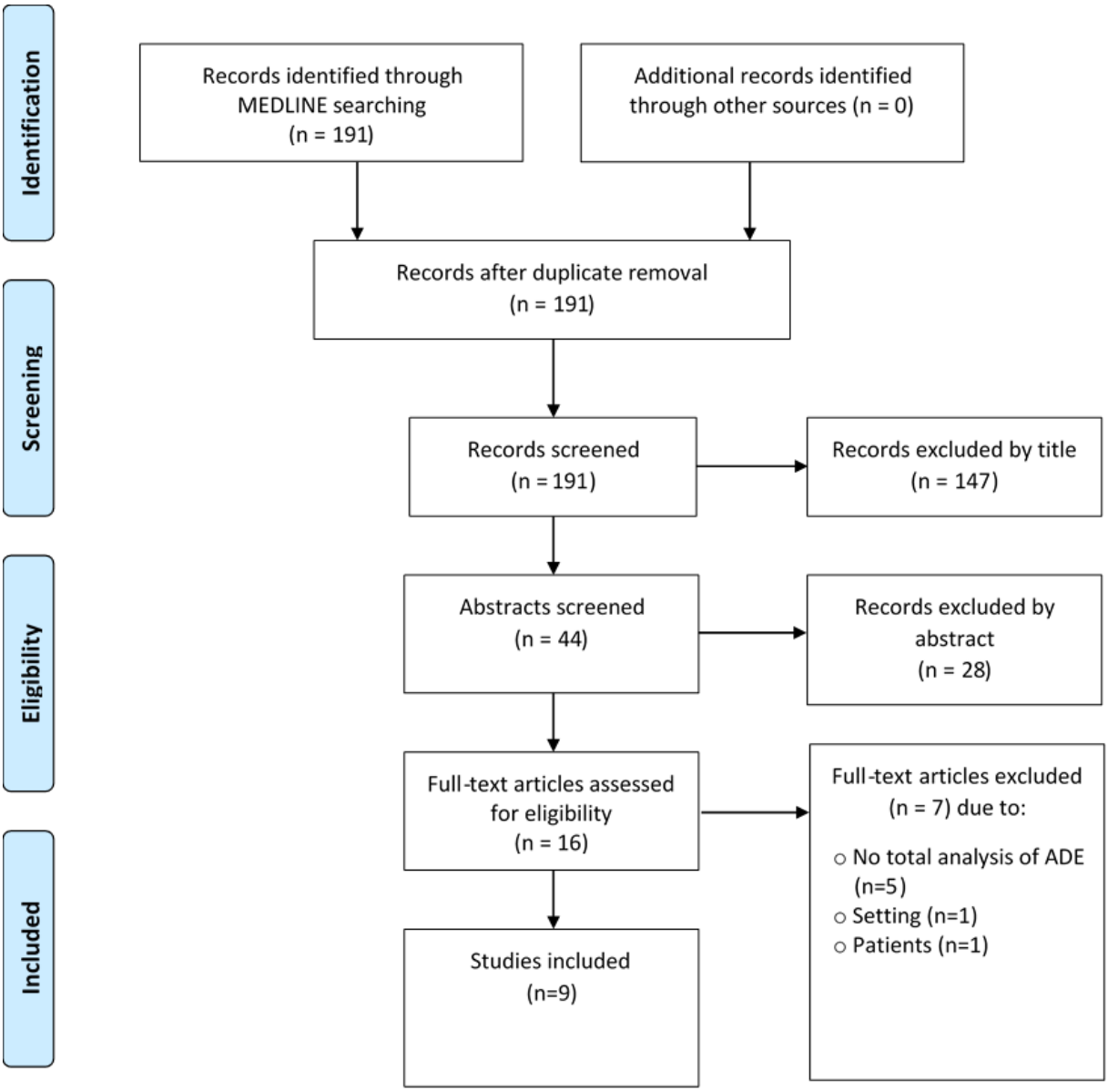

Figure S2. Results of the systematic literature search on adverse drug events (ADEs) at hospital admission [1]

[1] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7): e1000097

Supplement S2: Interview guide

Translated interview guide

Introduction

Thank you for taking the time to test our RAND procedure for identifying clinically relevant adverse drug events (ADEs) at hospital admission/during hospitalisation*.

Content start

Through the RAND process, we aim to combine the best available scientific evidence with the collective judgement of experts to identify the most important/relevant ADEs during hospital stay or on admission. Based on the results of the first two rounds, risk constellations for the most important ADEs will be assessed in rounds 3 and 4.

Comprehension of the assessment criteria

1. How did you generally deal with the assessment criteria? Did you understand them?
2. Did you have problems with “intermediate” levels 2 and 3? Did you use them?
3. Did the assessment of "seriousness" help you to assess "overall importance"?
4. Did the assessment of "drug-relatedness" help you to assess "overall importance"?

In the following, I would like to discuss each of the assessment criteria with you in detail.

5. What considerations did you make when assessing "overall importance"? What challenges did you face during the assessment?
6. What considerations did you make when assessing "seriousness"? What challenges did you face in the assessment?
7. What considerations did you make when assessing "drug-relatedness"? What challenges did you face in the assessment?

Comprehension of the adverse drug events:

1. Which events were unclear? Please name the corresponding events and the respective ambiguities.
   Could a fine-grained division of the event contribute to more clarity?
2. Did you base your evaluation on an exemplary event from the event category or did you use all events of a category for your evaluation?

Assessment of the evidence report

1. How helpful was the attached evidence report?
2. What further information would you like to see?

Final question

Do you have any further suggestions regarding our RAND process?

*dependent on panel

Supplement S3: Excluded adverse drug events (ADEs)

The following ADEs were excluded due to

(1) Complications from surgical or medical procedures, poisoning, ADEs involving only children or pregnant women, and ADEs resulting from underuse:

- Laryngospasm
- Damage to the embryo/fetus/newborn by medicines, drugs or toxins
- Other and unspecified disorders/diseases due to medicinal products
- Poisoning due to medicines
- Poisoning or harmful use of medicines or other substances
- Uncontrolled pain
- Complications due to anesthesia
- Complications of surgical procedures and medical treatment

(2) Unlikeliness to lead to hospital admission or worsen acutely or to occur during a hospital stay of average duration (7 days)

- Obstipation
- Polyneuropathy*
- Osteoporosis and other osteopathies
- Diseases of the connective tissue
- Obesity
- Hypofunction and other disorders of the pituitary gland
- Hypertrophy of the mammary gland
- Sexual dysfunction not caused by an organic disorder or disease
- Pruritus

* This event was only excluded in panel 2 (hospital stay)

Note: The ADEs ‘falls’ and ‘fractures’ were assessed separately in panel 2, whereas ‘fall (injuries)’ was rated as one ADE in panel 1.

Supplementary Table S1: Expert ratings in the first round of the RAND survey

Table S1 Expert ratings of the first round

	Panel 1: Adverse drug events at hospital admission							Panel 2: Adverse drug events during hospital stay						
	Overall Importance					Seriousness	Drug-relatedness	Overall Importance					Seriousness	Drug-relatedness
	Number of participants with score							Number of participants with score						
	1	2	3	4	Median	Median	Median	1	2	3	4	Median	Median	Median
Decompensated heart failure	2	1	5	5	3	3	2	0	7	3	2	2	3,5	2
Tachycardia - supraventricular	0	5	5	3	3	2	2	0	5	6	1	3	2	2
Tachycardia - ventricular	0	0	4	9	4	4	3	0	1	4	7	4	4	3
Bradycardia (requiring treatment)*	0	1	5	7	4	3	3	0	1	8	3	3	3	3
Hypertensive crisis	0	5	7	1	3	2	2	1	4	4	3	3	3	2
Hypotension (requiring treatment)*	0	2	8	3	3	2	2	1	2	4	5	3	2	3
Syncope and collapse	0	0	7	6	3	2	3	0	4	3	5	3	3	3
Acute coronary syndrome	2	6	4	1	2	4	1	3	5	1	3	2	4	1
Cerebral infarction	2	5	3	3	2	4	1	3	5	2	2	2	4	1
Thrombosis	0	5	7	1	3	3	2	1	6	1	4	2	3	2
Bleeding outside the gastrointestinal tract	0	0	6	7	4	4	3	0	1	4	7	4	4	3
Anaemia	1	2	6	4	3	2	2	0	7	3	2	2	2	2
Thrombocytopenia	0	3	8	2	3	3	2	0	4	5	3	3	2	2

Agranulocytosis and neutropenia	0	2	5	6	3	3	3	0	1	4	7	4	3,5	3,5
Bleeding/perforations of the upper gastrointestinal tract	0	0	4	9	4	3	3	0	2	3	7	4	3	3
Gastrointestinal ulcers without bleeding/perforations	0	1	5	7	4	2	3	0	5	3	4	3	2	3
Gastroenteritis, colitis	0	7	3	3	2	2	2	1	5	2	4	2,5	3	2
Acute pancreatitis	3	8	2	0	2	3	2	2	2	7	1	3	3,5	2
Nausea and vomiting (requiring treatment)*	0	7	5	1	2	1	2	1	5	2	4	2,5	2	3
Diarrhoea (requiring treatment)* (excl. gastroenteritis, colitis)	0	7	4	2	2	2	2	0	7	4	1	2	2	2,5
Intestinal obstruction (ileus)	0	4	7	2	3	3	2	0	3	4	5	3	3	2,5
Seizure	0	7	2	4	2	3	2	0	4	3	5	3	3,5	2
Extrapyramidal disorders	0	2	5	6	3	2	3	0	1	6	5	3	3	3,5
Polyneuropathy	2	8	2	1	2	2	2	-	-	-	-	-	-	-
Headache (requiring treatment)* (excl. migraine)	1	9	2	1	2	1	2	3	6	2	1	2	1,5	2
Delirium	0	0	4	9	4	3	3	0	0	4	8	4	3,5	3
Dizziness (requiring treatment)*	0	2	8	3	3	2	3	0	4	5	3	3	2	3
Hallucinations	0	4	4	5	3	2	2	2	2	5	3	3	3	2
Serotonin syndrome	0	0	4	9	4	3	4	1	2	1	8	4	3	4
Somnolence	0	2	5	6	3	2	3	-	-	-	-	-	-	-
Visual disorders (requiring treatment)* (excl. glaucoma)	3	7	3	0	2	2	2	3	6	2	1	2	2	2
Glaucoma attack	3	5	2	3	2	3	2	0	5	6	1	3	2,5	2,5

Toxic damage to the inner ear (excl. vertigo)	0	6	4	3	3	3	2	0	2	6	4	3	3	3
Exacerbation of asthma (excl. pneumonia)**	1	6	4	2	2	2	2	0	5	4	2	3	3	2
Exacerbation of chronic obstructive pulmonary disease (COPD) (excl. pneumonia)	4	3	4	2	2	2	2	2	5	4	1	2	3	2
Pulmonary oedema	1	8	3	1	2	3	2	1	6	2	3	2	3	2
Pneumonia (excl. exacerbation of asthma/COPD)**	3	7	3	0	2	3	1	3	4	3	1	2	3	2
Interstitial lung diseases	4	3	3	3	2	3	2	1	7	2	2	2	3	2
Respiratory depression	0	1	6	6	3	4	3	1	0	6	5	3	3,5	3,5
Fall (injuries) *(Panel 1)*/ Falls (requiring treatment)* (excl. fractures) *(Panel 2)*	0	0	5	8	4	3	3	0	2	4	6	3,5	3	3
Fractures	-	-	-	-	-	-	-	1	2	5	4	3	4	2,5
Acute gout attack	1	5	7	0	3	2	2	0	7	2	3	2	2	2
Rhabdomyolysis	0	2	4	7	4	3	3	0	1	2	9	4	4	3,5
Myopathy (excl. rhabdomyolysis)	0	4	8	1	3	2	2	-	-	-	-	-	-	-
Uncontrolled hyperglycaemia	1	2	7	3	3	2	2	0	4	3	5	3	3	2
Hypoglycaemia (requiring treatment)*	0	0	3	10	4	4	4	0	1	2	9	4	3	4
Thyroid dysfunction (requiring treatment)*	2	6	3	2	2	2	2	2	3	3	4	3	2	3
Disorders of the adrenal cortex	0	3	6	4	3	3	3	0	4	6	2	3	3	3
Exsiccosis/dehydration (requiring treatment)*	1	1	6	5	3	3	3	1	2	4	5	3	3	3
Hypernatraemia (requiring treatment)*	3	5	5	0	2	3	2	2	2	6	2	3	3	2

Hyponatraemia (requiring treatment)*	0	3	7	3	3	3	3	0	3	4	5	3	3	3
Lactate acidosis (requiring treatment)*	0	5	6	2	3	3	2	0	2	6	4	3	4	2
Alkalosis (requiring treatment)*	3	8	2	0	2	2	2	1	6	4	1	2	2	2
Hyperkalaemia (requiring treatment)*	0	0	7	6	3	3	3	0	1	3	8	4	3	3
Hypokalaemia (requiring treatment)*	0	0	8	5	3	3	3	0	2	4	6	3,5	3	3
Hypercalcaemia (requiring treatment)*	2	7	4	0	2	2	2	0	4	6	2	3	3	2
Acute kidney injury	0	0	0	13	4	3	3	0	0	2	10	4	3	3
Urinary retention	1	3	7	2	3	2	2	1	6	3	2	2	2	2
Liver damage	0	0	5	8	4	3	2	0	0	3	9	4	3	3
Stevens-Johnson syndrome/ toxic epidermolytic necrosis (TEN)	0	1	1	11	4	4	4	2	2	2	6	3,5	4	3
Other allergic skin reactions (requiring treatment)*	0	4	0	9	4	2	2	0	2	6	4	3	2	3
Anaphylactic shock	1	0	2	10	4	4	2	0	2	2	8	4	4	3
Angioedema	0	0	5	8	4	3	3	0	4	4	4	3	4	3
Infections (requiring treatment)* (excl. pseudomembranous colitis)	1	9	2	1	2	3	2	2	3	2	5	3	3,5	2

* Addition ‘requiring treatment’ only for adverse drug events during hospital stay (panel 2); in panel 1, all ADEs should be considered for assessment as sufficiently severe to warrant hospital admission; ** Missing values in panel 2

Supplementary Table S2: Expert ratings in the second round of the RAND survey panel 1 (hospital admission)

Table S2 Expert ratings in the second round (panel 1)

	Panel 1: Adverse drug events at hospital admission		
	Overall Importance Median	**Seriousness** Median	**Drug-relatedness** Median
Prioritised adverse drug events without disagreement			
Acute kidney injury	4	3	3
Hypoglycaemia	4	4	4
Stevens-Johnson syndrome / toxic epidermolytic necrosis (TEN)	4	4	4
Delirium	4	3	3
Serotonin syndrome	4	3	4
Anaphylactic shock	4	4	2
Tachycardia - ventricular	4	4	3
Bleeding outside the gastrointestinal tract	4	4	3
Bleeding/perforations of the upper gastrointestinal tract	4	3	3
Fall (injuries)	4	3	3
Other allergic skin reactions	4	2	2
Rhabdomyolysis	4	3	3
Liver damage	4	3	2
Angioedema	4	3	3
Gastrointestinal ulcers without bleeding/perforation	4	2	3
Bradycardia	4	3	3
Pseudomembranous colitis	4	3	4
Hyperkalaemia	3	3	3
Syncope and collapse	3	2	3
Agranulocytosis and neutropenia	3	3	3
Somnolence	3	2	3
Respiratory depression	3	4	3
Hypokalaemia	3	3	3
Extrapyramidal disorders	3	2	3
Exsiccosis/dehydration	3	3	3
Anaemia	3	3	3

Intestinal obstruction (ileus)	3	3	2
Dizziness	3	2	3
Hallucinations	3	2	2
Hyponatraemia	3	3	3
Disorders of the adrenal cortex	3	3	3
Decompensated heart failure	3	3	2
Hypotension	3	2	2
Thrombocytopenia	3	3	3
Interstitial lung diseases	3	3	2
Uncontrolled hyperglycaemia	3	2	2
Urinary retention (≥ 65 years)	3	2	2
Myopathy (without rhabdomyolysis)	3	2	2
Adverse drug events with disagreement on prioritisation			
Thyroid dysfunction	3	2	2
Toxic damage to the inner ear (excl. vertigo)	3	3	2
Acute gout attack	3	2	2
Thrombosis	3	3	2
Adverse drug events with disagreement on non-prioritisation			
Seizure	2	3	2
Tachycardia - supraventricular	2	2	2
Urinary retention (< 65 years)	2	2	2
Nausea and vomiting	2	1	2
Exacerbation of chronic obstructive pulmonary disease (COPD) (excl. pneumonia)	2	2	2
Non-prioritised adverse drug events without disagreement			
Diarrhoea (excl. gastroenteritis, colitis)	2	2	2
Exacerbation of asthma (excl. pneumonia)	2	2	2
Lactate acidosis	2	3	2
Hypertensive crisis	2	2	2
Glaucoma attack	2	3	2
Cerebral infarction	2	4	1
Polyneuropathy	2	2	2
Headache (excl. migraine)	2	2	2
Visual disorders (excl. glaucoma)	2	2	2
Gastroenteritis, colitis	2	2	2
Acute pancreatitis	2	3	2

Hypercalcaemia	2	2	2
Infections (excl. pseudomembranous colitis)	2	2	2
Pulmonary oedema	2	3	2
Pneumonia (excl. exacerbation of asthma/COPD)	2	3	1
Hypernatraemia	2	3	2
Alkalosis	2	2	2
Acute coronary syndrome	2	4	1

Median = 4 Median = 3 Median = 2 Median = 1

Frequency of assessment patterns:

Overall Importance	Seriousness	Drug-relatedness	Frequency
Prioritised	Prioritised	Prioritised	22
Prioritised	Non-prioritised	Prioritised	5
Prioritised	Prioritised	Non-prioritised	7
Prioritised	Non-prioritised	Non-prioritised	8
Non-prioritised	Prioritised	Prioritised	0
Non-prioritised	Non-prioritised	Prioritised	0
Non-prioritised	Prioritised	Non-prioritised	9
Non-prioritised	Non-prioritised	Non-prioritised	14

Supplementary Table S3: Expert ratings in the second round of the RAND survey panel 2 (hospital stay)

Table S3 Expert ratings in the second round (panel 2)

	Panel 2: Adverse drug events during hospital stay		
	Overall Importance Median	**Seriousness** Median	**Drug-relatedness** Median
Prioritised adverse drug events without disagreement			
Rhabdomyolysis	4	4	4
Acute kidney injury	4	3	3
Hypoglycaemia requiring treatment	4	3	4
Acute liver damage	4	3	3
Anaphylactic shock	4	4	3
Delirium	4	3	3
Bleeding outside the gastrointestinal tract	4	4	3
Hyperkalaemia requiring treatment	4	3	3
Agranulocytosis and neutropenia	4	4	4
Tachycardia - ventricular	4	4	3
Bleeding/perforations of the upper gastrointestinal tract	4	3	3
Pseudomembranous colitis	3	3	3
Extrapyramidal disorders	3	3	3
Serotonin syndrome	4	3	4
Stevens-Johnson-syndrome / toxic epidermolytic necrosis (TEN)	4	4	3
Toxic damage to the inner ear (excl. vertigo)	3	3	3
Falls requiring treatment (excl. fractures)	3	3	3
Hyponatraemia requiring treatment	4	3	3
Hypokalaemia requiring treatment	3	3	3
Angioedema	3	4	3
Bradycardia requiring treatment	3	2	3
Respiratory depression	3	4	3
Fractures	3	4	3
Other allergic skin reactions requiring treatment	3	2	3
Syncope and collapse	3	3	3

Thrombocytopenia	3	3	2
Intestinal obstruction (ileus)	3	3	3
Seizure	3	3	2
Lactate acidosis requiring treatment	3	4	2
Hypotension requiring treatment	3	2	3
Uncontrolled hyperglycaemia	3	3	2
Disorders of the adrenal cortex	3	3	3
Exsiccosis/dehydration requiring treatment	3	3	3
Diarrhoea requiring treatment (excl. gastroenteritis, colitis)	3	2	3
Adverse drug events with disagreement on prioritisation			
Gastrointestinal ulcers without bleeding/perforations	3	2	3
Dizziness requiring treatment	3	2	3
Hallucinations	3	3	2
Hyperthyroidism	3	2	2
Tachycardia - supraventricular	3	3	2
Exacerbation of asthma (excl. pneumonia)	3	3	2
Hypernatraemia requiring treatment	3	3	2
Nausea and vomiting requiring treatment	3	2	3
Adverse drug events with disagreement on non-prioritisation			
Urinary retention	2	2	2
Decompensated heart failure	2	4	2
Infections requiring treatment (excl. pseudomembranous colitis)	2	3	2
Acute coronary syndrome	2	4	1
Cerebral infarction	2	4	1
Glaucoma attack	2	3	2
Hypothyroidism	2	2	2
Alkalosis requiring treatment	2	2	2
Non-prioritised adverse drug events without disagreement			
Thrombosis	2	3	2
Interstitial lung diseases	2	3	2
Hypercalcaemia requiring treatment	2	3	2
Hypertensive crisis	2	3	2
Anaemia	2	2	2
Acute pancreatitis	2	3	1

Pulmonary oedema	2	3	2
Gastroenteritis, colitis	2	2	2
Exacerbation of chronic obstructive pulmonary disease (COPD) (excl. pneumonia)	2	3	2
Acute gout attack	2	2	2
Visual disorders requiring treatment (excl. glaucoma)	2	2	2
Pneumonia (excl. exacerbation of asthma/COPD)	2	3	1
Headache requiring treatment (excl. migraine)	2	2	2

Median = 4 Median = 3 Median = 2 Median = 1

Frequency of assessment patterns:

Overall Importance	Seriousness	Drug-relatedness	Frequency
Prioritised	Prioritised	Prioritised	26
Prioritised	Non-prioritised	Prioritised	7
Prioritised	Prioritised	Non-prioritised	8
Prioritised	Non-prioritised	Non-prioritised	1
Non-prioritised	Prioritised	Prioritised	0
Non-prioritised	Non-prioritised	Prioritised	0
Non-prioritised	Prioritised	Non-prioritised	13
Non-prioritised	Non-prioritised	Non-prioritised	8

Drug-Event Pairs as Indicators for the Detection of Adverse Drug Reactions during Hospitalization in Routinely Collected Electronic Data Sources

Anna Maria Wermund[1], Annette Haerdtlein[2], Wolfgang Fehrmann[1], Clara Weglage[2], Tobias Dreischulte[2] and Ulrich Jaehde[1,*]

Adverse drug reactions (ADRs) are a common cause of morbidity and mortality in hospitalized patients. Identification of ADRs in clinical practice, surveillance and research is essential to prevent further harm. The aim of this study was to assess the likelihood of drugs contributing to clinically important inpatient adverse events, in order to provide a list of drug-event pairs indicating ADRs in electronic health record (EHR) data, referred to as "indicators of ADRs". We conducted a consensus process based on the RAND/UCLA Appropriateness Method for 14 ADRs. Experts were asked to rate the strength of the causal link between adverse events and potentially causative drugs on a 4-point Likert scale. Based on the median rating, drug-event pairs were categorized according to the likelihood of an ADR being present. Drug-event pairs with a median rating of ≥3 without disagreement were defined as indicators of certain and probable ADRs. Of the 255 drug-event pairs evaluated, 2 (1%) and 42 (16%) achieved consensus validation that they certainly and probably indicate an ADR. In addition, 137 drug-event pairs were considered as indicators of possible (54%) and 74 drug-event pairs were considered as indicators of unlikely (29%) ADRs. The provided set of content-validated indicators of clinically important inpatient ADRs can be used in clinical practice (e.g., decision support), surveillance (e.g., quality indicators) and research (e.g., outcome measures). They will be implemented in EHR data from German university hospitals to determine the prevalence of ADRs, support efficient use of pharmacist resources, and develop models predicting ADRs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Conventional methods of detecting adverse drug reactions (ADRs), such as voluntary incident reporting, retrospective chart review, and direct observation in prospective ADR surveillance, have limitations in terms of effectiveness and affordability. Increasingly, these methods are supplemented by electronic triggers, mainly consisting of a single information item. As most ADRs require more than one information item to be identified and the associated drugs differ between ADR categories, combining adverse events with potentially causative drugs could facilitate ADR detection.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The experts were asked to rate the strength of the causal link between adverse events and potentially causative drugs by answering the question, "How likely is it that the listed medication significantly contributed to the adverse event, so that you would assume an adverse drug reaction?"

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ For 14 clinically important inpatient ADRs, content-validated drug-event pairs as indicators of ADRs are provided for implementation in routine electronic data sources. Categorized into 2 indicators of certain, 42 indicators of probable, 137 indicators of possible, and 74 indicators of unlikely ADRs, they inform about the likelihood of an ADR being present.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The content-validated indicators can be applied in clinical practice (e.g., decision support), clinical surveillance (e.g., as quality indicators) and research (e.g., as outcome measures) to detect ADRs and to promote drug safety studies under real-world hospital conditions.

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This work has previously been presented at the following conferences: [8th Congress for Drug Information], Cologne, 27.01.2023–28.01.2023; [DGKPha Annual meeting], Heidelberg, 11.11.2022–12.11.2022; [DPhG Annual meeting], Tübingen, 07.10.2023–10.10.2023; [29. GAA Annual meeting], Münster, 24.11.2022–25.11.2022.

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The detection, characterization and prevention of adverse drug reactions (ADRs) remains a major challenge for the World Health Organization (WHO) and other health agencies worldwide,[1,2] as they are a common cause of morbidity and mortality across all health care settings.[3] For the hospital setting, a prospective observational study showed that ADRs affected 15% of hospitalized patients and prolonged their hospital stay by an average of 0.25 days/patient admission episode.[4] An ADR is defined as "a response to a medicinal product which is noxious and unintended". According to this definition, the causal relationship between the drug and the adverse event (AE) is at least a reasonable possibility. Therefore, an ADR must be clearly distinguished from an AE, defined as "any untoward medical occurrence in a patient to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment." A causal relationship is therefore suspected for an ADR, but is not required for an AE.[5]

Detecting and quantifying ADRs and their causes is essential to prevent further harm, identify safety priorities, and improve the quality of care through the development of remedial action plans.[6–8] However, conventional methods of ADR detection, such as voluntary incident reporting, retrospective chart review, and direct observation in prospective ADR surveillance, have limitations in terms of effectiveness and affordability.[8] Increasingly, these methods have been complemented by the use of electronic trigger tools: computer-based algorithms that automatically screen routinely collected, readily available electronic data and flag simple patterns suggestive of a past, present, or future ADR.[8–10] Implemented in electronic health records (EHR), they can be used efficiently at the point of care to automatically screen for potential ADRs, assess the overall harm caused by medical care, and measure changes in the occurrence of potential ADRs on a large scale for clinical surveillance and research.[9,11,12] Several sets of triggers have been developed, ranging from global lists of triggers for a large number of AEs[13] to very specific lists that differ according to the specific type of AEs (e.g., ADR),[14] clinical setting (e.g., oncology) or target patient population (e.g., pediatric, elderly).[15–18] Electronic trigger tools are moderately effective, time-efficient to use, and have been shown to be less burdensome than conventional methods of ADR detection.[19–22] This makes them a suitable tool for the Germany-wide POLAR_MI (POLypharmacy, drug interActions and Risks) project of the Medical Informatics Initiative Germany, which aims to detect medication-related risks using EHR data from university hospitals, including inpatient ADRs.[23] However, triggers of existing tools are mainly based on a single variable (e.g., only blood glucose < 50 mg/dL, only digoxin level > 2 ng/mL, only use of diphenhydramine), which are rather suitable for the detection of AEs and limit their positive predictive values regardless of the data category.[9,10,24,25]

Given the variability in the likelihood of drugs causing specific ADRs and the differing levels of clinical importance of ADRs, the combination of clinically important and highly drug-related AEs with potentially causative drugs can focus the detection of ADRs in EHRs on those with (at least) probable drug-related causes, potentially enhancing the predictive performance and specificity of ADR detection.[3,26,27] To achieve this goal, we aimed to assess the likelihood of specific drugs contributing to clinically important inpatient AEs, in order to provide a consensus-based list of drug-event pairs indicating ADRs in EHR data, hereafter referred to as "indicators of ADRs". The drug-event pairs were categorized according to the likelihood of an ADR being present.

MATERIAL AND METHODS

Study design and selection of ADRs

We conducted an expert consensus process based on the RAND/UCLA Appropriateness Method (RAM), a variant of the Delphi method that combines scientific evidence and expert opinion.[28] In consensus processes based on the RAM method, the experts rate clinical presentations in a two-round rating process, taking into account the available evidence. In the first round, experts rate each clinical presentation independently. In the second round, after a panel meeting to review and discuss first-round ratings and revise the initial list of presentations, the experts re-rate each clinical presentation individually. In the consensus process presented here, we followed this procedure (**Figure 1**). The experts were asked to rate the strength of the causal link between an AE and potentially causative drugs (as individual drugs or grouped into drug classes) in order to identify drug-event pairs indicating inpatient ADRs in EHR data.

The AEs considered were selected through a different, previous consensus process in which experts were asked to rate the clinical importance of AEs in the context of drug safety on a 4-point Likert scale (1 = not important to 4 = very important).[26] In this consensus process, 14 AEs had a median importance rating of 4 (=very important) and were therefore included in the consensus process presented here: rhabdomyolysis, acute kidney injury (AKI), hypoglycemia, liver damage, anaphylaxis, delirium, hyperkalemia, serotonin syndrome, bleeding outside the gastrointestinal tract (GIT), agranulocytosis and neutropenia, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), ventricular tachycardia, bleeding of the upper GIT and hyponatremia. The AE "ventricular tachycardia" was changed to "torsade de

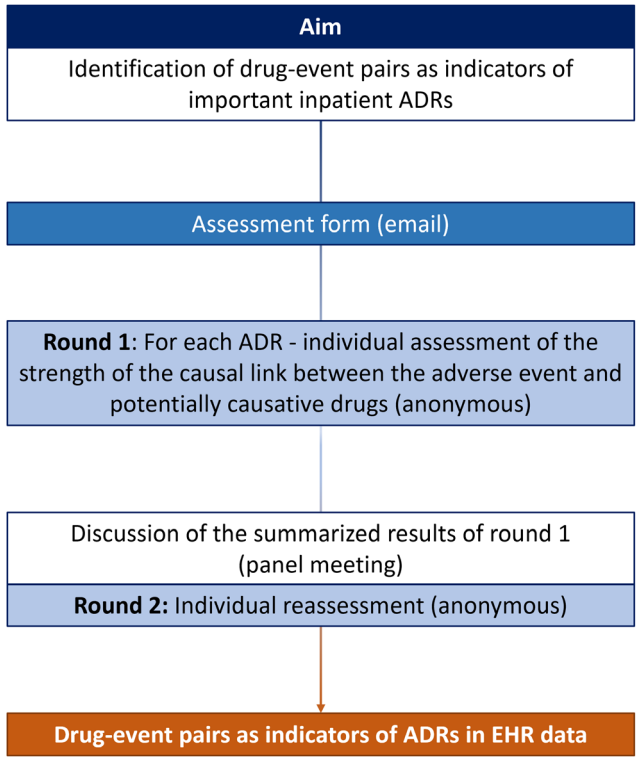

Figure 1 RAM consensus process (ADRs, adverse drug reactions; EHR, electronic health record).

pointes (TdP) tachycardia", as this specific type of tachycardia is more commonly caused by drugs.[29]

The Ethics Committee of the Medical Faculty of the University of Bonn, Germany (AZ 2021–502) exempted the study from institutional review board review.

Selection of experts

We attempted to re-recruit all the experts who participated in the previous consensus process by which the AEs considered here were selected.[26] Aiming for a minimum of nine experts, we sought a new expert if one was no longer available. In general, we recruited pharmacists and physicians with an academic interest or clinical experience in the detection or management of inpatient ADRs, aiming for a balanced distribution of the two professions and of self-reported (predominant) professional activity as scientist or clinician. We used the mailing list of the POLAR_MI project and asked involved experts to nominate further experts for recruiting.

Literature search on potentially causative drugs

A structured literature search was conducted to generate comprehensive lists of potentially causative drugs for each ADR. A standard operating procedure was developed, defining the search strategy, *Medical Subject Headings*, keywords, inclusion criteria, and extraction method (**Supplement 1**). We searched MEDLINE® for articles published between 2010 and 2021 or 2000 and 2021, depending on the amount of literature found in the 2010–2021 period. The search strategy consisted of one part describing the specific AE, combined with another part establishing the drug association. As reviews have been published for most AEs, we focused on this type of article and also included a reference book by Anne Lee.[30] We did not include information from summary of product characteristics (SmPCs) as we wanted to rely on scientific evidence rather than regulatory information, which is often insufficient to assess the strength of the causal link and varies between manufacturers. As the literature on liver damage and TdP tachycardia mainly refers to the databases Livertox® and CredibleMeds®, the potential causative drugs for these AEs were extracted from these databases.[29,31]

Extraction and grouping of potentially causative drugs

From selected publications, we extracted all drugs and drug classes for which a causal relationship with the AE was described and grouped them into superordinate drug classes, as it was not feasible to assess all individual drugs. If a specific drug class was mentioned in the literature, the experts were asked to consider the whole group. If only certain substances from a drug class were mentioned, but not the class itself, we investigated whether there was a group effect. If there was sufficient evidence, the individual drugs were combined into a drug class to be considered as a whole group. If there was insufficient evidence but the strength of the causal relationship was considered to be similar, the drugs were grouped together, and the experts were asked to assess only these certain drugs (e.g., certain antiepileptics: phenytoin, carbamazepine). All drugs that could not be assigned to a drug class were grouped as "miscellaneous drugs" In order to reduce the number of drugs in the miscellaneous groups and the number of other drug classes to be rated, drugs and drug classes with less evidence of causing the AE were excluded. Evidence was considered weak if only one reference was found in the literature search and no further evidence could be identified from other sources (e.g., summary of product characteristics). For the AEs liver damage and TdP tachycardia, the categories from LiverTox® and CredibleMeds® were used as drug classes, respectively (e.g., 1 drug from category A according to LiverTox®).[29,31]

RAM procedure

Design of the assessment form. The assessment form was a Microsoft Excel™ document with an instruction sheet and separate sheets for each AE. A sample of the round one assessment form is provided in **Supplement 2**.[32–36] The sheets listed the potentially causative drug classes, with specifications of individual drugs, where only certain drugs within each class were to be considered. In addition to the columns for ratings and comments, there was a separate column for the evidence report that the experts were asked to consider in their assessment. The evidence report included a description of the mechanism of action causing the ADR and the empirical evidence summarized from the publications from which the drugs were extracted.

Assessment criterion and pre-specifications. The experts were asked to rate the strength of the causal link between the AE and potentially causative drugs (drug-event pairs) by answering the question "How likely is it that the listed medication significantly contributed to the adverse event, so that you would assume an adverse drug reaction?" in relation to an average patient and assuming the drug exposure at the time of the AE. It was also pre-specified that all AEs should be assessed in relation to ADRs that occur acutely during hospitalization, require treatment and are not due to underuse or discontinuation of a drug. The 4-point Likert scale was based on the causality terms from the WHO-UMC system for standardized causality assessment.[37] The experts were given the opportunity to abstain (0 = no comment) if they were unable to assess a drug class despite the evidence provided. In addition, they could make comments on the composition of the drug classes (**Figure 2**).

To determine the threshold for the presence of an ADR, we also asked about the likelihood of an ADR being present if two drugs rated as possible or two drugs rated as probable were listed together with the AE in the EHR data (drug combination-event pairs).

The drugs and drug classes that were excluded due to insufficient evidence were listed below the drug classes to be rated, so that the experts could indicate whether they wanted to include one of these drugs in the assessment form. In a free text field, experts could add other drugs that were not included in the assessment form based on their own clinical experience.

Analysis of the ratings. Drug-event pairs with a median rating of 4 and 3 without disagreement were predefined as indicators of certain and probable ADRs, respectively. Disagreement was predefined to be present if at least 30% of expert ratings were < 3 (for drug-event pairs with a median of ≥ 3), or 3 or higher (for drug-event pairs with a median of < 3). Drug-event pairs with a median rating of ≥ 3 with disagreement or with a median rating of 2 or 2.5 with and without disagreement were considered indicators of possible ADRs. All drug-event pairs with a median rating of < 2 were predefined as indicators of unlikely ADRs.

Rating rounds. The assessment form was sent to the experts by email. Six weeks after the first round, an expert meeting took place, moderated by UJ. For each drug-event pair, the first-round ratings were summarized and fed back to the experts. To facilitate discussion, each ADR was discussed separately. The focus of the discussion was on drug-event pairs with disagreement and on drug classes where experts recommended splitting. Discussions were also held for all

Rating scale	Comments
ADR Indicator	**Adjustment of drug classes (optional)**
Imagine an average patient during hospital stay developing hyperkalemia:	
How likely is it that the listed medication significantly contributed to the adverse event, so that you would **assume** an **adverse drug reaction**? 0 = No comment 1 = Unlikely 2 = Possible 3 = Probable 4 = Certain	In my opinion, there are drugs in this group that differ from the others in a meaningful way, so they should be assessed separately. These drugs are:

Figure 2 Assessment criterion and rating scale using hyperkalemia as an example (ADR, adverse drug reaction).

Table 1 Composition of the expert panel

Characteristics	Physicians (*n* = 5)	Pharmacists (*n* = 5)
Academic background		
Additional qualification (habilitation/doctorate and/or clinical specialist qualification)	5 (100%)	5 (100%)
Main field of professional activity		
Scientific research	4 (80%)	1 (20%)
Clinical practice	0 (0%)	1 (20%)
Both	1 (20%)	3 (60%)

low-evidence drugs recommended for inclusion. The same applied to all other substances added by the experts. After discussion of all potentially causative drugs for an ADR, the panelists directly placed their second-round ratings.

Pre-test and optimization

The assessment form was pre-tested and optimized in two steps. Each step involved a pharmacist and a physician (who were not part of the research team or the expert panel). In the first step, the draft of the assessment form was presented to the experts. In the second step, another two experts were presented with a revised assessment form. In both steps, feedback was obtained through semi-structured interviews (interview guide: **Supplement 3**), focusing on the formulation and definition of the assessment criterion, the comprehensibility and completeness of the drug classes, the instructions, the evidence report, and the design of the assessment form. Implementing modifications based on the second step of feedback yielded the final assessment form.

RESULTS

Expert panel

The expert panel consisted of five physicians and five pharmacists from nine German university hospitals. Eight experts from the preliminary consensus process also participated in the consensus process presented here. As shown in **Table 1**, all experts had additional research or clinical qualifications.

Literature search and design of the assessment form

Depending on the ADR, the literature search yielded between 5 and 80 publications, used as the basis for each assessment sheet

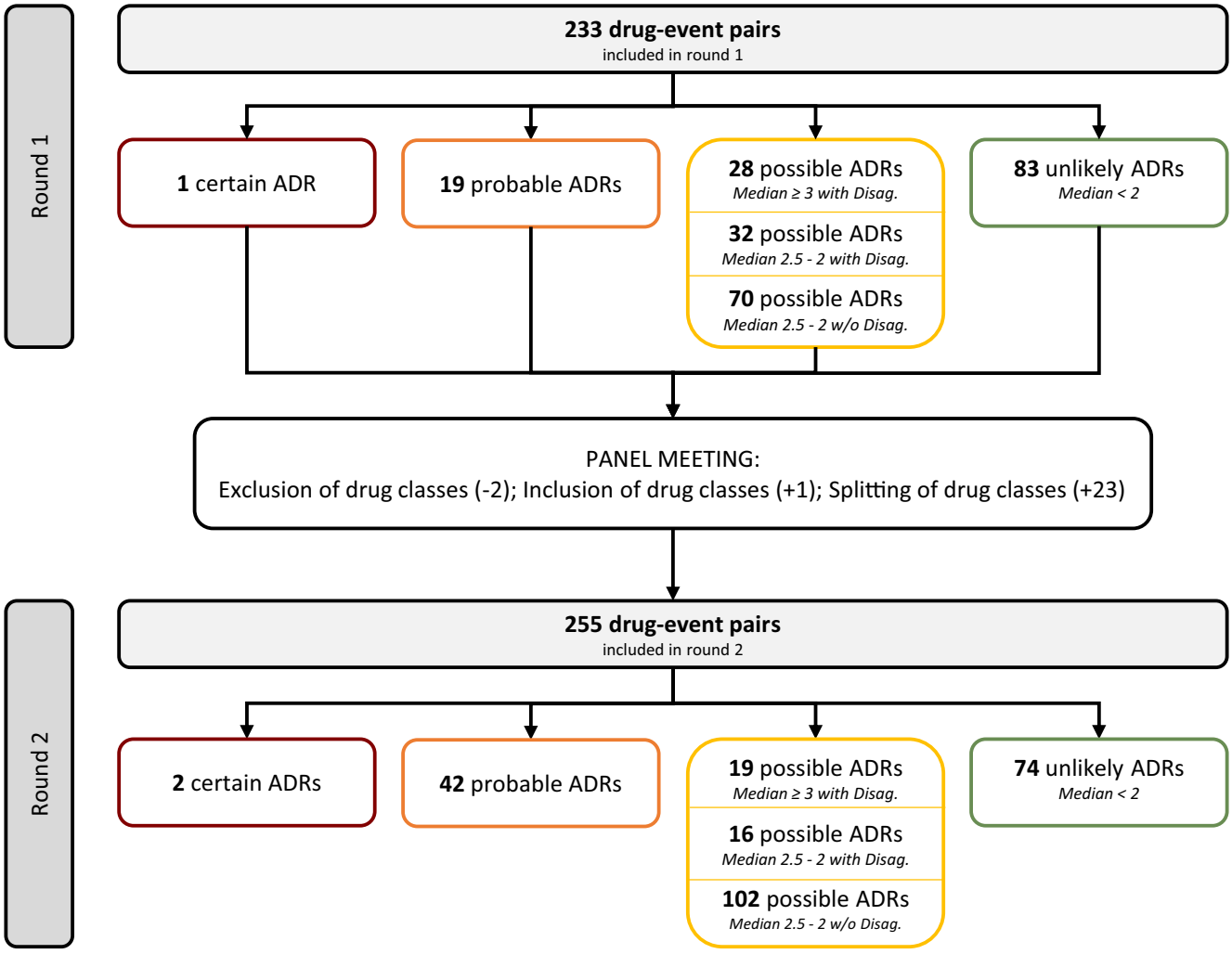

Figure 3 Flowchart showing the results of the rating process of the drug-event pairs considered in the consensus process (ADRs, adverse drug reactions; Disag., disagreement; w/o, without).

(details: **Supplement 1**). In total, the extraction and grouping of potentially causative drugs resulted in 279 superordinate drug classes after the pre-test. Due to insufficient evidence, 46 drug classes and 105 drugs from the miscellaneous groups were excluded, resulting in 233 drug classes to be rated in combination with certain AEs in round one. The excluded drugs and drug classes are listed in **Supplement 4**. As the literature search for rhabdomyolysis identified the drug-induced rhabdomyolysis atlas (DIRA), a database that contains a classification scheme for drugs causing rhabdomyolysis based on drug labeling information, the risk categories of this database were included as drug classes.[38] For delirium, the ACB score by Kiesel et al. was used to map the anticholinergic drugs.[39]

Rating process and findings

The round one assessment form was emailed to panelists in February 2022, and the panel of experts met on 30 March 2022. All 10 experts returned a fully completed round one assessment form, while nine experts took part in the moderated expert discussion and returned a fully completed round two assessment form. All drug-event pairs rated, as well as detailed first-round and second-round ratings, are provided in **Supplement 5**.

Drug-event pairs as indicators of ADRs. In round one, of the 233 drug-event pairs rated, disagreement was present for 60 drug-event pairs (26%). This resulted in 1 drug-event pair considered as an indicator of a certain ADR (0.4%), 19 drug-event pairs considered as indicators of probable ADRs (8%), 130 drug-event pairs considered as indicators of possible ADRs (56%) and 83 drug-event pairs considered as indicators of unlikely ADRs (36%) after round one (see **Figure 3**).

Of the excluded drugs due to low evidence, 17 were considered by the experts in round one and were therefore discussed during the panel meeting. It was decided to add the drug class "fibrinolytics" for the AE "bleeding outside the GIT". During the discussion, the experts also decided to split 21 drug classes into 44 drug classes (e.g., "contrast media" was split into "iodinated contrast media" and "other contrast media" for the AE "anaphylaxis"), to change the definition of four drug classes (e.g., for "AKI", the class "polymyxins" was changed to "polymyxins (i.v.)") and to exclude two drug classes because they cause a different ADR that can lead to the ADR being assessed (details of the adjustments are provided in **Supplement 6**). Therefore, 255 drug-event pairs were rated in round two. The second assessment round resolved first-round disagreements for 24 drug-event pairs without any adjustment of the drug class (14 of which were now indicators of probable and 9 were indicators of possible ADRs; one pair was excluded). Disagreement could also be resolved for 8 drug-event pairs through splitting into 17 drug-event pairs (7 of which were now indicators of probable and 10 were indicators of possible ADRs). However, disagreement remained for 28 pre-existing drug-event pairs and 7 new drug-event pairs. Finally, this resulted in 2 drug-event pairs considered as indicators of certain ADRs (1%), 42 drug-event pairs considered as indicators of probable ADRs (16%), 137 drug-event pairs considered as indicators of possible ADRs (54%) and 74 drug-event pairs considered as indicators of unlikely ADRs (29%) after round two (see **Figure 3**). The distribution of ADR categories after round two is shown in **Table 2**.

Drug combination-event pairs as indicators of ADRs. Regarding the combinations of two drugs rated as possible and two drugs rated as probable, for hyperkalemia, delirium and serotonin syndrome there was agreement after round two that the concomitant use of two drugs rated as possible together with the presence of the related AE (drug combination-event pair) is probable indicating an ADR. The concomitant use of two drugs rated as "3 = probable" never had a median rating of "4 = certain". This resulted

Table 2 Distribution of drug-event pairs across the ADR categories after round two

Adverse drug reaction	N Drug classes	N certain (%)	N probable (%)	N possible (%)	N unlikely (%)
Rhabdomyolysis	22	0 (0.0%)	2 (9.1%)	10 (45.5%)	10 (45.5%)
Acute kidney injury	32	0 (0.0%)	7 (21.9%)	18 (56.3%)	7 (21.9%)
Hypoglycemia	20	2 (10.0%)	0 (0.0%)	5 (25.0%)	13 (65.0%)
Liver damage	6	0 (0.0%)	1 (16.7%)	3 (50.0%)	2 (33.3%)
Anaphylaxis	27	0 (0.0%)	4 (14.8%)	19 (70.4%)	4 (14.8%)
Delirium	17	0 (0.0%)	2 (11.8%)	8 (47.1%)	7 (41.2%)
Bleeding outside the GIT	17	0 (0.0%)	7 (41.2%)	6 (35.3%)	4 (23.5%)
Hyperkalemia	16	0 (0.0%)	1 (6.3%)	13 (81.3%)	2 (12.5%)
Agranulocytosis/ Neutropenia	33	0 (0.0%)	4 (12.1%)	12 (36.4%)	17 (51.5%)
TdP tachycardia	8	0 (0.0%)	3 (37.5%)	5 (62.5%)	0 (0.0%)
Bleeding of the upper GIT	10	0 (0.0%)	4 (40.0%)	4 (40.0%)	2 (20.0%)
Serotonin syndrome	15	0 (0.0%)	3 (20.0%)	11 (73.3%)	1 (6.7%)
SJS/TEN	14	0 (0.0%)	0 (0.0%)	14 (100.0%)	0 (0.0%)
Hyponatremia	18	0 (0.0%)	4 (22.2%)	9 (50.0%)	5 (27.8%)

GIT, Gastrointestinal tract; N, Number; SJS/TEN, Stevens-Johnson syndrome and toxic epidermal necrolysis; TdP, Torsade de pointes.

Table 3 Ready-to-use list of all indicators of certain and probable ADRs

Adverse event	Drug class
Rhabdomyolysis	
Rhabdomyolysis	• Statins
Rhabdomyolysis	• Trabectedin
Acute kidney injury	
Acute kidney injury	• NSAIDs
Acute kidney injury	• Aminoglycosides
Acute kidney injury	• Vancomycin
Acute kidney injury	• Methotrexate/Cisplatin/Ifosfamide
Acute kidney injury	• Certain antivirals (Nucleoside analogues, Cidofovir, Foscarnet)
Acute kidney injury	• Contrast agents (i.v.)
Acute kidney injury	• Calcineurin inhibitors
Hypoglycemia	
Hypoglycemia	• Insulin
Hypoglycemia	• Sulfonylureas
Liver damage	
Liver damage	• 1 drug from category A according to LiverTox®
Anaphylaxis	
Anaphylaxis	• Beta-lactams
Anaphylaxis	• Vancomycin
Anaphylaxis	• Iodinated contrast media
Anaphylaxis	• Biologicals with immunological target
Delirium	
Delirium	• Total ACB score: ≥3 points
Delirium	• Narcotics
	• Two drugs rated as possible: Total ACB Score: ≥1 point; SSRI (excl. Paroxetine), Anticonvulsants (excl. Pheno-barbitals and Carbamazepine), Dopamine agonists, GABA-receptor agonists, Opiates, Miscellaneous drugs
Bleeding outside the GIT	
Bleeding outside the GIT	• ASA
Bleeding outside the GIT	• Heparins
Bleeding outside the GIT	• Vitamin K antagonists
Bleeding outside the GIT	• Direct oral anticoagulants
Bleeding outside the GIT	• Certain other anticoagulants (Fondaparinux, Argatroban, Bivalirudin)
Bleeding outside the GIT	• Other antiplatelet drugs (excl. ASA, Dipyridamole, Cilostazol)
Bleeding outside the GIT	• Fibrinolytics
Hyperkalemia	
Hyperkalemia	• Agents containing a high amount of potassium
	• Two drugs rated as possible: ACE inhibitors, ARBs, Direct renin inhibitors, Aldosterone antagonists, ENaC blockers, NSAIDs, Heparin and derivatives, Tacrolimus, Other calcineurin inhibitors, Pentamidine, Cotrimoxazole, Miscellaneous drugs, Suxamethonium
Agranulocytosis/Neutropenia	
Agranulocytosis/Neutropenia	• Cytotoxic anticancer drugs
Agranulocytosis/Neutropenia	• Clozapine
Agranulocytosis/Neutropenia	• Pyrazolones
Agranulocytosis/Neutropenia	• Mycophenolate mofetil/Azathioprine
Torsade de pointes tachycardia (CredibleMeds® categories)[a]	
Torsade de pointes tachycardia	• 1 drug with known risk
Bleeding of the upper GIT	
Bleeding of the upper GIT	• NSAIDs (non-selective COX inhibitors)
Bleeding of the upper GIT	• Direct oral anticoagulants
Bleeding of the upper GIT	• Vitamin K antagonists
Bleeding of the upper GIT	• Antiplatelet drugs
Serotonin syndrome	
Serotonin syndrome	• SSRI
Serotonin syndrome	• SSNRI
Serotonin syndrome	• MAO inhibitors
	• Two drugs rated as possible: Clomipramine, Imipramine and other TCA, Tetracyclic antidepressants, 5-HT2A antagonists, Certain atypical antipsychotics, Triptans, Certain antiemetics, Certain opioids, Certain antibiotics with MAO-inhibiting activity, Amphetamines and derivatives, Miscellaneous drugs
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	
No drug-event pair had a median rating of ≥3 without disagreement	
Hyponatremia	
Hyponatremia	• SSNRI/SSRI
Hyponatremia	• Thiazides
Hyponatremia	• Other diuretics
Hyponatremia	• Vasopressin und analogues

5-HT2A, 5-hydroxytryptamine 2A receptor; ACB score, Anticholinergic burden score by Kiesel et al.; ACE, Angiotensin-converting enzyme; ARBs, Angiotensin receptor blockers; ASA, Acetylsalicylic acid; COX, Cyclooxygenase; ENaC, Epithelial sodium channel; Excl., Exclusive; GABA, Gamma-aminobutyric acid; GIT, Gastrointestinal tract; MAO, Monoamine oxidase; NSAIDs, Non-steroidal anti-inflammatory drugs; SSNRI, Selective serotonin and norepinephrine reuptake inhibitors; SSRI, Selective serotonin reuptake inhibitors; TCA, Tricyclic antidepressants.

[a]Please note: Initially, "1 drug with known risk", "2 drugs taken simultaneously with known risk" and "1 drug with known risk + 1 drug with possible risk taken simultaneously" had a median rating of 3 without disagreement and were therefore categorized as indicators of probable ADRs. As "1 drug with known risk" is part of all these combinations, we collapsed these three indicators into one indicator for the ready-to-use list.

in 3 additional indicators of probable ADRs, consisting of two drugs with a possible rating and the AE. A list of all indicators of certain and probable ADRs can be found in in **Table 3**.

DISCUSSION

Summary of findings

This study provides a set of content-validated drug-event pairs as indicators of clinically important inpatient ADRs in EHR data. Of the 255 drug-event pairs evaluated, 2 (1%) and 42 (16%) achieved consensus validation that they certainly and probably indicate an ADR, respectively. In contrast, more than half of the evaluated drug-event pairs were confirmed as only possibly indicating an ADR. This reflects the complex interplay of triggering factors (e.g., drugs) and confounding factors (e.g., underlying disease), leading to uncertainty in assessing whether an ADR is present or not. This remains a challenge even in prospective observational studies, where confounding factors can be better addressed. In the ADRED study, which investigated ADR cases in four emergency departments in Germany, 87.6% of suspected drugs were classified as possibly causal and only 12.4% as probably or definitely causal.[40] This shows that a simple yes or no decision regarding the presence of ADRs does not capture their nature, supporting our approach to categorize the drug-event pairs into different probability levels instead of a binary categorization (yes/no). With our approach, drugs with a lower probability of causing a specific ADR could be distinguished from those with a higher probability.

Concomitant use of drugs and the probability of an ADR

To account for the complex relationship between ADR-triggering factors, we also asked whether the combination of two drugs is more likely to indicate an ADR than one drug alone. For all AEs, the concomitant use of two drugs, both with a rating of "3 = probable", never had a median rating of "4 = certain". This highlights again the uncertainty in ADR assessment, as even when two drugs with a strong causal relationship to the AE were used together, the experts were not certain of an ADR.

For hyperkalemia, delirium, and serotonin syndrome, there was consensus that the concomitant use of two drugs classified as possibly indicating an ADR is probably indicating an ADR, highlighting their stronger multidrug etiology compared to other ADRs such as anaphylaxis and SJS/TEN, being hypersensitivity reactions where usually one causative drug is sufficient to trigger the ADR. In general, all drugs that cause the same ADR can be expected to have a potentiating effect. However, for some ADRs, this is intrinsic to their etiology. Regarding hyperkalemia, it has been reported that the risk increases with each potassium-altering drug taken.[32–34] The incidence of hyperkalemia is low in large controlled clinical trials of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists, whereas a higher incidence is observed in clinical practice due to the co-administration of these potassium-altering drugs.[32–34] There is also a common perception of a multidrug etiology for serotonin syndrome, as serotonin toxicity usually occurs with the co-administration of two or more serotonergic drugs, especially if they increase the serotonin level in the synaptic cleft in different ways.[41–43] Similarly, the likelihood of developing delirium increases with the number of predisposing factors, which often include more than one drug.[44,45]

Comparison with other trigger tools

There are already two trigger lists consisting of causative drugs for specific ADRs. However, both were developed to detect ADR-related hospital admissions in the elderly and do not include a probability categorization of the drugs listed.[17,46] Delirium, AKI, bleeding (not separated into GIT and non-GIT bleeding), hypoglycemia, hyperkalemia, and hyponatremia are also covered by these trigger lists. Noorda et al. mostly considered 2 to 4 drug classes, while Thevelin et al. included between 4 and 18 drug classes per event.[17,46] With between 6 and 33 drug classes per event, we listed even more, but the categorization resulted in a more manageable number of one to seven indicators of at least probable ADRs per event. Almost all drug classes on the trigger lists cited were part of our consensus process, underlining the comprehensiveness of our list of potentially causative drugs. Only angiotensin receptor blockers for hyponatremia and monoamine oxidase inhibitors for hypoglycemia were not included in our consensus process.[17,46] The drug classes considered in our consensus process, but not on the trigger lists cited, mostly had a median rating of one, emphasizing that these drugs are unlikely to cause the ADR and are thus not required on a trigger list for this ADR. With the exception of fluoroquinolones and digoxin for delirium, all drug classes on the cited trigger lists had a median rating of ≥2, demonstrating that our consensus process was able to discriminate well between drug-event pairs unlikely to indicate an ADR and those indicating at least possible ADRs.

Strengths and limitations

A strength of the developed indicators is that they link clinically important AEs to causative drugs, leading to ADR indicators categorized into different probability levels. Pre-testing the assessment form in two steps minimized ambiguities in rating constructs and in the composition of drug classes. Any remaining misunderstandings could be clarified during the panel meeting, which also allowed for an exchange of arguments and experiences for the panelists to consider in their second-round ratings, which is a key strength of RAM. Specific strengths of our consensus process are the heterogeneous composition of the expert panel, with diverse knowledge and experience in ADR detection, as well as the categorization of a wide range of causative drugs, as it was based on a broad literature search leading to extensive lists of potentially causative drugs. Additionally, the experts were able to indicate when a drug was missing (used for only one AE).

A limitation of our consensus process was that, for feasibility reasons, potentially causative drugs had to be grouped into superordinate and miscellaneous drug classes, partly resulting in a heterogeneous composition. Although we tried to limit this by reviewing the evidence during grouping and by pre-testing the assessment form twice, there was still some ambiguity about the composition, especially during the first round. As the assessment form included the option of commenting if a drug class was too broad, these problems could be collected and discussed during the panel meeting.

This led to the splitting of drug classes for the second rating round, resolving prior ambiguities. Our main limitation is that although the indicators developed are evidence-based, further validation is needed by actually using them to screen for ADRs in EHR data. This includes developing reliable measures of AEs in EHR data, which is more or less challenging depending on the AE. Data categories that can be used to determine AEs are, for example, laboratory values defined by Logical Observation Identifiers Names and Codes (LOINC) or diagnoses defined by the International Statistical Classification of Diseases and Related Health Problems (10th Revision).[47,48] However, determining an appropriate combination of these data categories to represent the AE with high accuracy is challenging. For example, the incidence and prevalence of delirium will be underestimated if determined by ICD-10-coded diagnoses alone.[49,50] In addition, the real-time availability of the selected data category in the EHR must be considered. In a parallel project, we are also working on these challenges of AE detection.

Conclusions

The systematic categorization of the provided set of content-validated drug-event pairs as indicators of clinically important inpatient ADRs facilitates their future application in clinical practice (e.g., decision support), clinical surveillance (e.g., quality indicators) and research (e.g., outcome measures). Depending on whether sensitivity or specificity is more important, drug-event pairs at least possible or only at least probable indicating an ADR can be used. As this consensus process is embedded in the POLAR_MI project, the developed indicators will be operationalized and implemented in EHR data of university hospitals throughout Germany to determine the prevalence of potential ADRs, support the efficient use of pharmacist resources, and develop risk models predicting ADRs.[23]

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

AUTHOR CONTRIBUTIONS

A.M.W. wrote the manuscript; A.M.W., A.H., T.D., and U.J. designed the research; A.M.W., A.H., W.F., C.W., T.D., and U.J. performed the research; A.M.W. and U.J. analyzed the data.

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Drug-Event Pairs as Indicators for the Detection of Adverse Drug Reactions during Hospitalization in Routinely Collected Electronic Data Sources

SUPPLEMENT S1: Comprehensive literature search

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Literature search procedure

The literature search was carried out by four different researchers (AMW, AH, CW, WF) from two different centers.

For each adverse drug reaction, we searched for systematic reviews published between 2000 and the search date in 2021. In addition, we looked for any type of review published in a peer-reviewed journal between 2010 and 2021. If there was insufficient evidence, we searched for all types of reviews published since 2000. The literature search was supplemented by the second edition of Anne Lee's book 'Adverse drug reactions' [30].

Inclusion and exclusion criteria

Table S1-1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
E1: Study design	Any kind of review in a peer reviewed journal	○ Simulation studies ○ Surveys ○ Experimental and observational studies
E2: Study population	Patients ≥ 18 years	○ Focus on patients with a specific disease/drug intake ○ Focus on neonates and children
E3: Setting	Any setting	○ Clinics for Traditional Chinese Medicine or similar health care services
E4: Evaluation*	**General description of potentially causative drugs for the specific event.** A broad overview of potentially causative drugs for the specific event is provided.	○ Focus on a specific drug or class of drugs (e.g. review on paracetamol causing upper gastrointestinal bleeding) ○ Focus on herbal medicines or dietary supplements ○ Focus on medical devices and other aids (e.g. latex gloves)

* For the events "bleeding of the upper gastrointestinal tract (GIT)" and "bleeding outside the GIT", insufficient evidence was found in reviews that gave a broad overview of potentially causative drugs. For these events, reviews focusing on a specific drug or class of drugs were also included.

Search strategy and results

ADE/ADR drug related side effects and adverse reactions [MeSH Terms] OR drug-induced[All Fields] OR drug-related[All Fields] OR "adverse drug reaction"[All Fields] OR "adverse drug reactions"[All Fields] OR "adverse drug event"[All Fields] OR "adverse drug events"[All Fields] OR "adverse drug effect"[All Fields] OR "adverse drug effects"[All Fields]

AND

Specific term for each adverse event (see Table 2)

AND

Review [Filter] OR systematic review [Filter]

Language: English and German

Database: MEDLINE® (PubMed)

Table S1-2 Search strategies and results for each adverse drug reaction (Abbreviations: GIT = Gastrointestinal tract, R = Review; SR = Systematic review)

Adverse drug reaction	Search term	Time period	Number of results (number included)	Further literature considered
Rhabdomyolysis	rhabdomyolysis[MeSH] OR rhabdomyolysis [All Fields]	SR: 2000 – 05/2021 R: 2000 – 05/2021	SR: 10 (0) R: 106 (7)	Search rhabdomyolysis AND review [Filter]: 629 (2)
Acute kidney injury*	Systematic review: acute kidney injury[MeSH] OR “acute kidney injury” OR “acute kidney injuries” OR “acute renal injury” OR “acute renal injuries” OR “acute renal insufficiency” OR” acute renal insufficiencies” OR “acute kidney insufficiency” OR “acute kidney insufficiencies” OR “acute kidney failure” OR “acute kidney failures” OR “acute renal failure” OR “acute renal failures” NOT COVID-19[MeSH] Review: acute kidney injury [MeSH] NOT COVID-19[MeSH]	SR: 2010 – 06/2021 R: 2010 – 07/2021	SR: 804 (0) R: 151 (16)	
Hypoglycemia	“hypoglycemia” OR "low blood sugar" OR “hypoglycaemia” OR “hypoglycemic” OR “hypoglycaemic” OR "hypoglycemic drugs" OR "hypoglycemic drug" OR "hypoglycemic agent" OR "hypoglycemic agents" OR “hypoglycemics” OR “hypoglycaemics” OR "hypoglycemic effect" OR "hypoglycemic effects" OR "hypoglycaemic drugs" OR "hypoglycaemic drug" OR "hypoglycaemic agent" OR "hypoglycaemic agents" OR "hypoglycaemic effect" OR "hypoglycaemic effects" OR hypoglycemia[MeSH] OR agents, hypoglycemic[MeSH]	SR: 2000 – 04/2021 R: 2007 – 04/2021	SR: 37 (2) R: 284 (6)	
Anaphylaxis	"anaphylactic shock" OR "anaphylaxis" OR "anaphylactic reaction" OR "anaphylactic reactions" OR "anaphylactoid reaction" OR "anaphylactoid reactions" OR anaphylaxis[MeSH]	SR: 2000 – 05/2021 R: 2010 – 05/2021	SR: 34 (1) R: 385 (37)	Hand search of selected publications: + 1 publication

Adverse drug reaction	Search term	Time period	Number of results (number included)	Further literature considered
Delirium	delirium OR deliriums OR delirium[MeSH]	SR: 2000 – 05/2021 R: 2000 – 05/2021	SR: 13 (2) R: 108 (10)	Hand search of selected publications: + 2 publications
Hyperkalemia	hyperkalemia[MeSH] OR hypoaldosteronism[MeSH] OR hyperkalemia OR hyperpotassemia OR hyperkalaemias OR hyperkalaemia OR hyperpotassaemia OR hypoaldosteronisms OR hypoaldosteronism OR hyperkalemias OR hyperpotassemias	SR: 2000 – 04/2021 R: 2000 – 04/2021	SR: 2 (0) R: 41 (5)	
Serotonin syndrome	serotonin syndrome[MeSH] OR „serotonin syndrome“ OR „serotonin toxicity“	SR: 2000 – 07/2021 R: 2010 – 07/2021	SR: 12 (1) R: 99 (6)	
Bleeding outside the GIT	hemorrhage[MeSH] OR hematoma[MeSH] OR “hemorrhage” OR "haemorrhage" OR "bleeding" OR "hematoma" OR "haematoma" NOT gastrointestinal hemorrhage[MeSH] NOT "Gastrointestinal hemorrhage" NOT "Gastrointestinal bleeding"	SR: 2000 – 08/2021 R: 2010 – 08/2021	SR: 62 (12) R: 352 (44)	
Agranulocytosis and neutropenia	neutropenia[MeSH] OR agranulocytosis[MeSH] OR acquired agranulocytosis [Supplementary Concept] OR neutropenia OR agranulocytosis OR granulocytopenia OR agranulosis	SR: 2000 – 07/2021 SR: 2010 – 07/2021	SR: 70 (1) R: 172 (13)	Hand search of selected publications: + 3 publications
Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)	stevens-johnson syndrome[MeSH] OR stevens-johnson syndrome OR scalded skin syndrome OR toxic epidermal necrolysis OR lyell syndrome OR lyell’s syndrome	SR: 2000 – 04/2021 R: 2010 – 04/2021	SR: 41 (1) R: 431 (14)	
Bleeding of the upper GIT **	upper gastrointestinal tract/drug effects [MeSH Major Topic] OR gastrointestinal hemorrhage[MeSH] OR "gastrointestinal hemorrhage” OR "gastrointestinal hemorrhages" OR "gastrointestinal bleeding"	SR: 2000 – 07/2021 R: 2010 – 07/2021	SR: 119 (33) R: 446 (47)	

Adverse drug reaction	Search term	Time period	Number of results (number included)	Further literature considered
Hyponatremia	hyponatremia[MeSH] OR hyponatremia OR hyponatraemia OR hyponatraemias OR hyponatremias	SR: 2000 – 04/2021 R: 2000 – 04/2021	SR: 6 (0) R: 58 (9)	

If no search field is specified, the default is [All Fields].
***** In order to keep the number of hits to a manageable level, the search strategy for ADRs was adapted**:** ("drug related side effects and adverse reactions"[MeSH Terms] OR "drug-induced"[Title/Abstract] OR "drug-related"[Title/Abstract] OR "adverse drug reaction"[Title/Abstract] OR "adverse drug reactions" [Title/Abstract] OR "adverse drug event"[Title/Abstract] OR "adverse drug events"[Title/Abstract] OR "adverse drug effect"[Title/Abstract] OR "adverse drug effects"[Title/Abstract])
** The following MeSH Terms were added to the ADE/ADR search term: Risk Factors, Risk Assessment

Table S1-3 Summary of included reviews

Adverse drug reaction	Number of publications	Book from Anne Lee	Systematic reviews	Reviews	Further literature
Rhabdomyolysis	9	yes	1	8	Drug-induced Rhabdomyolysis Atlas (DIRA) [38]
Acute kidney injury	16	yes	0	16	
Hypoglycemia	8	yes	2	6	
Anaphylaxis	39	no	1	38	
Delirium	14	yes	3	11	Anticholinergic burden (ACB) score by Kiesel et al. [39]
Hyperkalemia	5	no	0	5	
Serotonin syndrome	7	yes	1	6	
Bleeding outside the GIT	56	no	12	44	
Agranulocytosis and neutropenia	17	yes	1	16	
SJS/TEN	15	yes	1	14	
Bleeding of the upper GIT	80	yes	33	47	
Hyponatremia	9	no	0	9	

Abbreviations: GIT: Gastrointestinal tract; SJS/TEN: Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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Drug-Event Pairs as Indicators for the Detection of Adverse Drug Reactions during Hospitalization in Routinely Collected Electronic Data Sources

SUPPLEMENT S2: Example of the assessment form

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Adverse event	Drug class	Drugs mentioned in the literature	Rating scale	Comments	Evidence
			ADR Indicator	**Adjustment of drug classes (optional)**	
			Imagine an average patient during hospital stay developing hyperkalemia: How likely is it that the listed medication significantly contributed to the adverse event, so that you would **assume** an **adverse drug reaction**? 0 = No comment 1 = Unlikely 2 = Possible 3 = Probable 4 = Certain	In my opinion, there are drugs in this group that differ from the others in a meaningful way, so they should be assessed separately. These drugs are:	**Please note:** The precise risk of hyperkalemia with the listed drugs and drug classes is difficult to calculate because the risk for developing hyperkalemia increases with declining renal function. In addition, many of the listed drugs are commonly encountered in patients with various medical conditions that potentially contribute to hyperkalemia (e.g. renal failure, diabetes, heart failure, cirrhosis, hypoaldosteronism), making it difficult to calculate precise drug-induced incidences [5]. **The following applies to all drug classes: The risk is higher in the presence of a predisposing condition [1-5].**
Hyperkalemia	ACE Inhibitors	**Whole group**			**Mechanism of action** *Reduced aldosterone secretion [1,3-5] / Impaired renal potassium excretion [4]* Blockade of angiotensin II synthesis with decrease of aldosterone secretion. Impaired delivery of sodium to the distal nephron [1,4,5]. Reduced renal perfusion [3,4]. **Empirical evidence** Reported percentage of hyperkalemia resulting from the medication: 8-37 % [1,3,4]. In a retrospective study investigating drug-associated life-threatening hyperkalemia, 47.1 % of cases were associated with an ACE inhibitor [1]. The incidence seems to be relatively low in patients with normal renal function/without predisposing factors. Serum potassium rarely increases by more than 0.5 mmol/L [1]. The risk appears to be proportional to the degree of renal insufficiency, but the serum potassium level can also increase significantly in patients with only moderate renal insufficiency [4]. In clinical trials, the risk of hyperkalemia with ACE inhibitor monotherapy in patients without predisposing factors is low (circa 2%-6%) and the absolute increases in serum levels are small [1,5]. However, the rates of hyperkalemia reported in clinical trials may not represent the risk in clinical practice, because most patients targeted for renovascular benefits of these drugs (such as those with diabetes, renal failure, or heart failure) are at high risk of developing hyperkalemia [1,3]. Hyperkalemia may occur in up to 10 % of outpatients within a year of commencing treatment with an ACE inhibitor [1].
Hyperkalemia	Angiotensin II Receptor Blockers (ARBs)	**Whole group**			**Mechanism of action** *Reduced aldosterone secretion [1,3-5] / Impaired renal potassium excretion [4]* Competitive binding to the angiotensin II receptor with decrease of aldosterone synthesis [1,5]; Reduced renal perfusion [3,4]. **Empirical evidence** Reported percentage of patients who develop hyperkalemia: 2-7 % [4]. The incidence of hyperkalemia seems to not differ between ACE inhibitors and ARB (1.3 % with ACE inhibitors vs. 1.5 % with losartan) [1,3]. Although hyperkalemia associated with ARBs is rare in patients without risk factors, it is estimated to be 2–31 % in high-risk patients [1].
Hyperkalemia	Direct Renin Inhibitors	**Whole group** Especially named in literature: Aliskiren			**Mechanism of action** *Reduced aldosterone secretion [1,5]* Inhibition of the conversion of angiotensinogen to angiotensin I with decrease of aldosterone formation [1,5]. **Empirical evidence** In a clinical trial, the proportion of patients with hyperkalemia was significantly higher in the aliskiren group than in the placebo group (11.2 vs. 7.2 %). In addition, hyperkalemia was the most common adverse event leading to the discontinuation of this study drug [1]. However, in a pooled analysis of seven randomized, double-blind studies including patients with hypertension treated with aliskiren, the incidence of hyperkalemia was similar to placebo [1]. The incidence of hyperkalemia is similar to that with ARB monotherapy (3.6 vs. 3.3 %, respectively) [1].
Hyperkalemia	Aldosteron Antagonists	**Whole group** Especially named in literature: Spironolactone, Eplerenone			**Mechanism of action** *Tubular resistance to the action of aldosterone [1,3-5] / Impaired renal potassium excretion [4]* Blockade of mineralocorticoid receptors [1,3-5]. In addition, the mechanism probably also involves extrarenal compensatory mechanisms: Decreased translocation of extracellular K+ to intracellular environments, decreased gastrointestinal secretion of potassium [1]. **Empirical evidence (Spironolactone, Eplerenone)** Average raise of plasma potassium: 0.2–0.3 mmol/L (therapeutic dose) [1]. Spironolactone may also induce life-threatening hyperkalemia even in the presence of a normal glomerular filtration rate [1]. Similar to ACE inhibitors and ARBs, hyperkalemia occurrence is low in large controlled clinical trials, whereas in clinical practice a higher incidence was observed because of simultaneous use of potassium-altering medications and multiple diseases [1,3]. Aldosterone antagonists are frequently administered in combination to treat arterial hypertension or heart failure [1]. In the randomized Aldactone Evaluation Study, serious hyperkalaemia occurred in only 2 % of patients. By contrast, population based time-series analyses have demonstrated significant increases in rates of hospitalisation and mortality from hyperkalaemia after the use of aldosterone antagonists was recommended whenever possible to RAAS blockade and beta blockers [1, 3]. **Additional information** Dose dependent [1,5].
Hyperkalemia	ENaC Blockers	**Whole group** Especially named in literature: Amiloride, Triamterene			**Mechanism of action** *Tubular resistance to the action of aldosterone [1] / Impaired renal potassium excretion [4]* Blockade of luminal sodium channels [1,3-5] with reduced mineralocorticoid activity due to resistance to the action of aldosterone action in the kidney [3]. **Empirical evidence** Reported percentage of patients who develop hyperkalemia: 2-19 % [4]. Reported percentage of hyperkalemia resulting from the medication: 9-21 % [4]. Moderate to severe hyerkalemia has been reported in 4 % to 19 % of patients treated with ENaC Blockers [4]. Case reports about severe hyperkalemia can be found. [1]. **Additional information** Dose dependent [5].
Hyperkalemia	Beta-blocking Agents	**Whole group**			**Mechanism of action** *Inducing of transmembrane potassium movement [1,3,4]* Decrease activity of Na^+/K^+-ATPase pump and renin release [1,4]. **Empirical evidence** Reported percentage of patients who develop hyperkalemia: 1-5 % [4,5]. Reported percentage of hyperkalemia resulting from the medication (with other contributing factors): 4-17 % [1,4]. Moderate increases in serum potassium concentrations (circa 0.3 mmol/L), rarely severe [1,4]. In patients undergoing cardiopulmonary bypass procedure or with end-stage renal disease serum potassium values can increase by 1 mmol/L or more [1]. Hyperkalemia was mainly seen with nonselective rather than with cardio-selective beta-blockers [1,5].

Hyperkalemia	Calcium Channel Blockers	**Whole group** Especially named in literature: Verapamil, Diltiazem, Amlodipine, Nifedipine			**Mechanism of action** Remains uncertain [1]. Inhibition of adrenal aldosterone biosynthesis; Reduction in aldosterone secretion [5]. *Verapamil:* May decrease potassium movement from the extracellular to the intracellular space by blocking calcium channels [1]. **Empirical evidence** Very sporadic reports [1,5]. Chronic kidney disease, hypoaldosteronism and other concomitant hyperkalemia-inducing drugs are usually present. Majority of cases associated with verapamil [1,5].
Hyperkalemia	NSAIDs	**Whole group** incl. COX2-Inhibitors			**Mechanism of action** *Reduced aldosterone secretion [1,3,4] / Impaired renal potassium excretion [3,4]* Decrease of prostaglandin-mediated renin release, renal blood flow and glomerular filtration rate [1,4,5] leading to hyporeninaemic hypoaldosteronism [3,4,5]. May cause direct renal toxicity [5]. **Empirical evidence** Reported percentage of patients who develop hyperkalemia: 10-46 % [4]. Reported percentage of hyperkalemia resulting from the medication: 9-18 % [4]. NSAIDs have been reported to cause hyperkalemia in patients with or without renal insufficiency [1]. May be more common in cardiac patients [5]. In patients with normal kidney function, the mean increase in plasma potassium is typically around 0.2 mmol/L [1]. In patients with CKD, elevations in plasma potassium can exceed 1 mmol/L. Although the degree of hyperkalemia is often mild, it can be sufficiently severe to cause cardiac arrest and death [1]. The risk of hyperkalemia varies among individual NSAIDs, ranging from high risk for indomethacin to low risks for salicylates and the other NSAID groups [1,4]. Up to 46 % of hospital patients treated with indomethacin develop an increase in serum potassium levels or hyperkalemia [4]. A retrospective cohort study performed by Aljadhey et al. suggested that selective cyclooxygenase (COX)-2 inhibitors may pose a greater risk of hyperkalemia than nonselective NSAIDs (increase in serum potassium of 0.15 mmol/l versus nonselective NSAIDs). [1] **Additional information** The decrease in potassium secretion begins to occur with the first dose of NSAID [1].
Hyperkalemia	Heparin and Derivatives	**Whole group** Especially named in literature: Unfractionated heparin (UFH), Low molecular weight heparin (LMWH)			**Mechanism of action** *Reduced aldosterone secretion [1,3,5] / Impaired renal potassium excretion [4]* Inhibition of aldosterone production by reduction in both the number and affinity of the angiotensin II receptors [1,2,4,5]. Inhibition of the final enzymatic steps of aldosterone formation [4]. Excess anticoagulation may also, in rare circumstances, precipitate adrenal hemorrhage and induce adrenal insufficiency [1]. **Empirical evidence** Reported percentage of patients who develop hyperkalemia: 8-17 % [4]. Reported percentage of hyperkalemia resulting from the medication: 1-20 % [4]. Heparin-induced hyperkalemia (HIH) might occur in approximately 7–8 % of heparin-treated patients [1]. Elevations in serum potassium have ranged from 0.2 to 1.7 mmol/L [1,4]. It may be seen after either i.v. or s.c. administration. Most patients remain asymptomatic [1]. However, patients with preexisting defects in potassium homeostatis or patients receiving prolonged heparin therapy are especially predisposed to HIH [1,4]. Hyperkalemia is not common but there are many case reports [5]. **Additional information** Dose dependent, occurs rapidly following initiation of therapy [1].
Hyperkalemia	Calcineurin Inhibitors	**Whole group** Especially named in literature: Tacrolimus, Ciclosporin			**Mechanism of action** *Reduced aldosterone secretion [1,3-5] / Impaired renal potassium excretion [4]* Decrease aldosterone synthesis and Na^+/K^+-ATPase pump activity [1,4,5]. An aldosterone resistance secondary to decreased transcription of human mineralocorticoid receptors on peripheral blood leukocytes is also reported [1]. *Ciclosporin* may also induce a chloride channel shunt that impairs the electrochemical driving force for potassium secretion [4]. It also inhibits apical secretory potassium channel activity in principal cells. Further it can cause acute, transient hyperkalemia by increasing potassium efflux from cells [4]. **Empirical evidence** Reported percentage of patients who develop hyperkalemia: 11-44 % (C.), 15-53 % (T.) [4]. Reported percentage of hyperkalemia resulting from the medication: 5-28 % (C.), 8-28 % (T.) [4]. Mild and uncomplicated hyperkalemia is commonly observed in patients treated with calcineurin inhibitors, especially transplant recipients (mainly renal transplant patients) [1,4]. 44-73 % of transplant recipients develop hyperkalemia [1]. The increased incidence may also be due the development of impaired kidney function in individuals chronically treated with these medications. However, hyperkalemia may occur despite adequate kidney function [1].
Hyperkalemia	**Certain** Antiinfectives	**Certain Antiinfectives:** Pentamidine, Cotrimoxazole (Trimethoprim/Sulfamethoxazole)			**Mechanism of action** Pentamidine: Blockade of luminal sodium channels [1,3-5]. Trimethoprim: Blockade of luminal sodium channels [1,3-5] and inhibition of Na+/K+-ATPase [1]. **Empirical evidence** *Pentamidine:* Pentamidine administration appears to be causally related to life-threatening hyperkalemia in the presence of a mild to severe renal insufficiency [1,2,4]. Reported percentage of patients who develop hyperkalemia: 5-24 % [4]; Reported percentage of hyperkalemia resulting from the medication 0-5 % [4]. *Trimethoprim:* An increase in serum potassium level, which ranges from 0.36 to 1.21 mmol/L or greater, occurs in most patients who receive trimethoprim [1]. Reported percentage of patients who develop hyperkalemia: 6-21 % [4]; Reported percentage of hyperkalemia resulting from the mediaction 14-29 % [4].
Hyperkalemia	Potassium-Containing Agents	**Whole group** For example: Penicillin G, Potassium Citrate, Potassium supplements (oral or i.v.), Salt substitutes			**Mechanism of action** *Potassium Input* **Empirical evidence** Percentage of patients who develop hyperkalemia 3-24 % [4]. Reported percentage of hyperkalemia resulting from the medication 11-58 % [4]. Potassium administration alone rarely induces hyperkalemia in the absence of an underlying defect in potassium homeostasis [1,2,4]. Incidence is quite high in patients with renal dysfunction [5]. The Boston Collaborative Drug Surveillance Program demonstrated a 3.6 % incidence of hyperkalemia among 4,921 patients taking physician-prescribed potassium supplements [1,4]. Other studies revealed that potassium supplements cause or contribute to hyperkalemia in approximately 15 % to 40 % of hospitalized patients [4]. Prolonged or excessive ingestion of potassium citrate may lead to severe hyperkalemia [1]. Penicillin G is usually administered as potassium salt (contains 1.7 mmol of potassium per million units). It can significantly alter potassium balance when given in very high doses. Severe hyperkalemia with cardiac arrest caused by penicillin is reported. Rapid intravenous infusion or oral administration of large amounts of semisynthetic penicillin derivatives may be potentially dangerous in patients with diabetes and renal insufficiency [1].
Hyperkalemia	Miscellaneous Drugs	Digoxin Mannitol Suxamethonium Propofol Ketoconazole Drospirenone Magnesiumsulfates			**Mechanism of action** ***Digoxin, Mannitol, Suxamethonium, Propofol*** : Drugs inducing transmembrane potassium movement [1,3-5]. ***Drospirenone, Ketoconazole:*** Tubular resistance to the action of aldosterone [1-5]. ***Magnesiumsulfates:*** Unknown mechanism. **Empirical evidence** ***Digoxin:*** Resulting from both acute and chronic toxicity. Therapeutic digoxin levels do not lead to hyperkalemia unless there are other predisposing factors [1,4,5]. Overdose may cause hyperkalemia that can be fatal [4]. Rarely, hyperkalemia develops in patients who have therapeutic or mildly increased digoxin levels if other risk factors for impaired potassium handling are present [4]. ***Suxamethonium:*** It causes an increase in serum potassium up to 1 mmol/L [1]. In normal subjects, the mean plasma potassium level increased by 0.5 mEq/liter within 3 to 5 minutes after i.v. application [1,4]. Marked hyperkalemia has been reported in patients with burns, occult myopathies, muscle injury, trauma, neuromuscular disease and severe infection [1,4,5]. ***Ketoconazole, Drospirenone, Propofol, Magnesiumsulfates, Mannitol:*** Very sporadic reports [1,5].

Hyperkalemia	Combination of two drugs you rated as possible (=2)				**Empirical evidence** Drug interactions are a common problem in the setting of hyperkalemia. **For all drug classes, it has been stated in the literature that the risk is greater when they are used concomitantly with other potassium-altering medications [1-5].** Many of the listed drugs are commonly combined, and those combinations may potentiate the risk of hyperkalemia [1,5]. An important example includes combining an ACE inhibitor or an ARB with a NSAID. Both of these drug classes have been shown to potentiate the risk of hyperkalemia separately. In addition, both drug classes potentiate the risk of developing renal dysfunction [5]. Several listed drugs are combined for the treatment of congestive heart failure or hypertension [1,3].
Hyperkalemia	Combination of two drugs you rated as probable (=3)				**Empirical evidence** Drug interactions are a common problem in the setting of hyperkalemia. **For all drug classes, it has been stated in the literature that the risk is greater when they are used concomitantly with other potassium-altering medicatons [1-5].** Many of the listed drugs are commonly combined, and those combinations may potentiate the risk of hyperkalemia [1,5]. An important example includes combining an ACE inhibitor or an ARB with a NSAID. Both of these drug classes have been shown to potentiate the risk of hyperkalemia separately. In addition, both drug classes potentiate the risk of developing renal dysfunction [5]. Several listed drugs are combined for the treatment of congestive heart failure or hypertension [1,3].

Further questions		
Inclusion of medicines not previously considered		
Consider the drugs listed in the next column: If you want to add one or more drugs as an indicator, please tick them.	Azole Antifungals	☐
	Amphotericin B	☐
	Dabigatran	☐
	Ethinyl estradiole	☐
	Hydroxycarbamide	☐
	Insulin	☐
	Nafarelin	☐
	Octreotide	☐
	Omeprazole	☐
	Thalidomid	☐
	Zoledronic acid	☐
	Other	☐
	Please define here which drug you want to add	

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SUPPLEMENT S3: Pre-test interview guide

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Interview guide

Translated interview guide. Interviews were held in German.

Introduction and getting started

Thank you for taking the time to test our RAM process.

Using the RAM methodology, we aim to combine evidence and expert opinion to identify drug-event pairs as indicators to capture potential adverse drug reactions (ADRs) in routine hospital data. Building on the first stage of our RAM process [the previous consensus process], which identified clinically important adverse events with a high drug-relatedness, we will now identify indicators for ADRs consisting of a drug or drug class and the adverse event (drug-event pairs). For this purpose, the assessment form consists of potentially causative drugs for each ADR, collected through a comprehensive literature search.

Question: How long did it take you to complete the assessment form?

Comprehension and suitability of the assessment criteria for identifying indicators for the detection of ADRs

Step 1: Participants were presented with three different options

Validity (How do you rate the validity of the combination (adverse event + drug) as an indicator for an adverse drug reaction? 1 = Not valid; 2; 3; 4 = Valid)

1. How did you deal with this assessment criterion in general? Did you understand what is meant by a valid indicator?
2. Did you have problems with levels 2 and 3? Have you used them? Should the intermediate levels be specifically labelled or can you get by with just the „endpoint label“?
3. What **considerations** did you make when assessing "validity"? What **challenges** did you face during the assessment?

Causality (How do you estimate the strength of the causal link between the adverse event and the listed drug class? 1 = Very weak; 2 = Weak; 3 = Strong; 4 = Very strong)

1. How did you deal with this assessment criterion in general? Did you understand it?
2. Did you have problems with levels 2 and 3? Have you used them?
3. What **considerations** did you make when assessing "causality"? What **challenges** did you face during the assessment?

Clinical context (How important is it to discontinue the medication or to reduce the dose as a strategy to prevent further or repeated harm from this adverse event? 1 = Not important; 2 = Somewhat important; 3 = Important; 4 = Very important)

1. How did you generally deal with this assessment criterion embedded in a clinical context? Did you understand it?
2. Did you have problems with levels 2 and 3? Have you used them?
3. What **considerations** did you make when assessing the causal relationship within the clinical context? What **challenges** did you face during the assessment?

To conclude: Which of the three assessment criteria do you think is most appropriate for assessing the drug-event pairs as indicators of ADRs?

Step 2: Participants were presented with a modified criterion

ADR indicator

1. How did you deal with this assessment criterion in general? Did you understand what was to be assessed?
2. Did you use the intermediate levels 2 and 3? Did you have problems with them?
3. What **considerations** did you make during the assessment? What **challenges** did you face during the assessment?

Comprehension and suitability of drug classes

1. How did you deal with the drug classes in general? Were you able to cope with the grouping of the drug classes?
2. Which drug classes were unclear or difficult for you to assess? Please tell me the relevant drug classes and the ambiguities/difficulties you experienced.
   Could a more detailed categorisation contribute to greater clarity?
3. Did you base your assessment on a specific drug in the class or did you use all drugs in a class for your assessment?

Comprehension and suitability of additional questions

1. In general, how did you deal with the two questions regarding the inclusion of other drugs? Did you understand them?

Assessment of the evidence report

1. How helpful was the (attached) evidence report?
2. What other information would you like to have?
3. How did you incorporate the evidence into your evaluation?
4. What did you think of the position of the evidence in the assessment form? Would you have preferred a separate document?

Final question

Do you have any further suggestions regarding our RAM process?

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SUPPLEMENT S4: Excluded drugs and drug classes

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Table S4 Excluded drugs and drug classes, listed below the drug classes to be assessed

Adverse drug reaction	Excluded drugs and drug classes
Hyperkalemia	• Azole antifungals • Amphotericin B • Dabigatran • Ethinylestradiol • Hydroxycarbamide • Insulin • Nafarelin • Octreotide • Omeprazole • Thalidomide • Zoledronic acid
Hyponatremia	• Antiarrhythmics • Antibiotics • Benzodiazepines • Barbiturates • Calcium channel blockers • Everolimus • Temsirolimus • Insulin • Pentamidine • Miconazole • Metformin • Metoclopramide
Hypoglycemia	• Tyrosine kinase inhibitors • Narcotics and other sedatives (Fentanyl) • Monoamine oxidase inhibitors • Terbutaline • Adrenaline • Atosiban • Brimonidine tartrate • Bupivacaine • Darbepoetin alfa • Heparin • Latanoprost • Methimazole (Thiamazole)

	• Naltrexone • Pantoprazole • Prednisolone • Varenicline • Infliximab • Penicillamine • Doxorubicin • Busulfan • Gemcitabine • L-Asparaginase • Methotrexate • Paclitaxel • Pemetrexed • Irinotecan • Rituximab • Topotecan • Carboplatin • Olanzapine • Zuclopenthixol • Buprenorphine • Tiopronin
Bleeding of the upper gastrointestinal tract	• Mirtazapine • Bupropion
Bleeding outside the gastrointestinal tract	• Amphotericin B • Propranolol • Paracetamol • Interferon-alfa • Phenothiazine • Thioxanthene • Amiodarone • Propafenone • Penicillamine • Ranitidine • Fibrinolytics • Corticosteroids (intranasal)
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	• Fexofenadine • Antimalarials (Quinine) • Pyrazolones (Metamizole) • Antiemetics (Domperidone, Ondansetron) • Protease inhibitors • Thiazide diuretics • Ranitidine • Sulfonylurea antidiabetics • Insulin • Phenothiazines • Calcium channel blockers • Angiotensin-converting enzyme inhibitors • Beta blockers
Anaphylaxis	• Angiotensin-converting enzyme inhibitors • Anticonvulsants • Fibrin sealants • Epinephrine

	• Ranitidine • Amphotericin B • Cyclosporine • Iron supplements • Hydroxychloroquine
Serotonin syndrome	• Ergot alkaloids (Ergotamine, Methylergometrine) • Clonazepam • Alprazolam • Levodopa • Atomoxetine • Hydroxyzine • Propofol • Haloperidol • Promethazine
Agranulocytosis and neutropenia	• Pirenzepine • Octreotide • Torsemide
Acute kidney injury	• Anaesthetics • Opioids (Methadone) • Sodium glucose linked transporter 2 inhibitors • Conjugated estrogens • Tumour necrosis factor blockers • Anticoagulants • Uricosuric drugs • Iron chelating agents • Sodium phosphate purgatives • Methyldopa • Colchicine • Heparin
Rhabdomyolysis	• Narcotics/Anaesthetics (Ketamine) • Laxatives • Serotonin antagonists • Monoamine oxidase inhibitors • Antimalarials • Glycopyrrolate • Trospium • Pantoprazole • Rabeprazole • Interferon beta-1a • Avelumab • Urokinase • Tenecteplase • Methylphenidate • Atomoxetine • Mifepristone • Metoclopramide • Tolvaptan • Chloral hydrate • Tetrabenazine • Cobicistat • Albendazole • Levodopa

	• Pramipexole • Aliskiren • Trientin-HCl • Eprosartan • Valsartan • Telmisartan • Irbesartan • Candesartan
Delirium	• Alpha-blocking agents • Calcium channel clockers (dihydropyridine type) • Angiotensin-converting enzyme inhibitors • Sympathomimetic agents

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SUPPLEMENT S5: Rating results

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Table S5-1 Expert ratings of the first round

		Number of participants with rating							
Drug-event pairs sorted by event	Certain drugs	1	2	3	4	0	Median	Disagreement	Category
Hyperkalemia									
ACE inhibitors		0	3	6	1	0	3	yes	possible
ARBs		0	5	5	0	0	2.5	yes	possible
Direct renin inhibitors		0	4	5	0	1	3	yes	possible
Aldosterone antagonists		0	2	7	1	0	3	no	probable
ENaC blockers		1	4	5	0	0	2.5	yes	possible
Beta-blocking agents		7	1	1	0	1	1	no	unlikely
CCBs		10	0	0	0	0	1	no	unlikely
NSAIDs		2	7	1	0	0	2	no	possible
Heparin and derivatives		6	4	0	0	0	1	no	unlikely

Calcineurin inhibitors		2	6	2	0	0	2	no	possible
Certain anti-infectives	Pentamidine, Sulfamethoxazole/Trimethoprim (Cotrimoxazole)	2	6	1	0	1	2	no	possible
Potassium-containing agents		1	3	5	1	0	3	yes	possible
Miscellaneous drugs	Digoxin, Mannitol, Propofol, Ketoconazole, Drospirenone, Magnesium sulfate, Suxamethonium	5	3	0	1	1	1	no	unlikely
Two drugs rated as possible (=2)		0	2	7	0	1	3	no	probable
Two drugs rated as probable (=3)		0	0	8	1	1	3	no	probable
Hyponatremia									
Oncologicals		1	5	3	0	1	2	yes	possible
MAO inhibitors		4	4	1	0	1	2	no	possible
SSNRI / SSRI		0	3	7	0	0	3	yes	possible
Tricyclic and tetracyclic antidepressants		0	7	3	0	0	2	yes	possible
Antipsychotics		1	7	2	0	0	2	no	possible
Thiazides		0	1	8	1	0	3	no	probable
Other diuretics		0	2	8	0	0	3	no	probable
ACE inhibitors		5	4	1	0	0	1.5	no	unlikely
Anticonvulsants		1	6	3	0	0	2	yes	possible
Vasopressin and analogues		0	4	3	1	2	2.5	yes	possible
Certain laxatives	Macrogol, Sodium picosulfate	3	7	0	0	0	2	no	possible
NSAIDs		9	0	1	0	0	1	no	unlikely
Opiates		8	1	1	0	0	1	no	unlikely

Proton pump inhibitors		8	2	0	0	0	1	no	unlikely
Certain antibiotics	Ciprofloxacin, Linezolid, Rifabutin, Sulfamethoxazole/Trimethoprim	9	1	0	0	0	1	no	unlikely
Miscellaneous drugs	Amiodarone, Amlodipine, Bromocriptine, Bupropion, Immunoglobulin, Paracetamol, Propafenone, Theophylline, Tolbutamide, Voriconazole	8	2	0	0	0	1	no	unlikely
Two drugs rated as possible (=2)		0	5	5	0	0	2.5	yes	possible
Two drugs rated as probable (=3)		0	1	7	2	0	3	no	probable
Hypoglycemia									
Incretin therapy		4	4	2	0	0	2	no	possible
Classic insulin secretagogues (Sulfonylureas and Glinides)		0	0	6	3	1	3	no	probable
Non-insulinotropic antidiabetics		6	3	1	0	0	1	no	unlikely
Insulin		0	1	3	6	0	4	no	certain
ACE inhibitors		8	1	1	0	0	1	no	unlikely
Beta-blocking agents		5	5	0	0	0	1.5	no	unlikely
Certain ARBs	Losartan, Telmisartan, Valsartan	8	2	0	0	0	1	no	unlikely
Certain α2-receptor agonists	Clonidine, Dexmedetomidine	9	1	0	0	0	1	no	unlikely
Certain CCBs (Dihydropyridine type)	Nifedipine, Felodipine	10	0	0	0	0	1	no	unlikely
Certain serotonergic antidepressants	Venlafaxine, Sertraline, Fluoxetine, Imipramine, Maprotiline, Nortriptyline, Doxepin	10	0	0	0	0	1	no	unlikely
Certain anticonvulsants	Gabapentin, Phenytoin, Topiramate, Valproate	8	2	0	0	0	1	no	unlikely
Anti-malaria drugs		3	5	0	0	2	2	no	possible
Quinolones		5	5	0	0	0	1.5	no	unlikely

Certain other antibiotics	Ceftriaxone, Clarithromycin, Doxycycline, Tetracycline, Oxytetracycline, Isoniazid, Para-aminosalicylic acid, Pentamidine, Piperacillin-tazobactam, Sulfadiazine, Sulfamethoxazole/ Trimethoprim	8	2	0	0	0	1	no	unlikely
Azole antimycotics		9	1	0	0	0	1	no	unlikely
Certain NSAIDs	Ibuprofen, Indomethacin, Phenylbutazone, Salicylates, Piroxicam	6	4	0	0	0	1	no	unlikely
Certain antivirals	Amprenavir, Entecavir, Ganciclovir, Saquinavir, Stavudine, Zidovudine	7	3	0	0	0	1	no	unlikely
Certain growth hormones	IGF-I (Mecasermin), Somatotropin	3	5	1	0	1	2	no	possible
Miscellaneous drugs	Amiodarone, Atorvastatin, Bortezomib, Chlormadinone, Clonazepam Propoxyphene/Dextropropoxyphene, Donepezil, Imatinib, Haloperidol, Etanercept, Ethacrynic acid, Etomidate, Hydralazine, Lidocaine, IL-2, Interferons, Lenalidomide, Lithium, Levothyroxine, 6-Mercaptopurine, Mifepristone, Octreotide, Paracetamol, Ranitidine, Salbutamol, Selegiline, Tramadol	9	0	0	0	1	1	no	unlikely
Two drugs rated as possible (=2)		0	5	5	0	0	2.5	yes	possible
Two drugs rated as probable (=3)		0	0	7	2	1	3	no	probable
Bleeding of the upper GIT									
NSAIDs (non-selective)		0	3	6	1	0	3	yes	possible
Selective COX-2 inhibitors		1	6	3	0	0	2	yes	possible
Paracetamol		7	2	0	0	1	1	no	unlikely
Direct oral anticoagulants		0	2	6	2	0	3	no	probable
Vitamin K antagonists		0	3	5	2	0	3	yes	possible
Antiplatelet drugs		0	2	6	2	0	3	no	probable

CCBs		10	0	0	0	0	1	no	unlikely
SSRI		2	6	2	0	0	2	no	possible
Glucocorticoids		2	6	2	0	0	2	no	possible
Certain angiogenesis inhibitors	Bevacizumab, Erlotinib, Axitinib, Aflibercept	2	2	5	0	1	3	yes	possible
Two drugs rated as possible (=2)		0	5	4	1	0	2.5	yes	possible
Two drugs rated as probable (=3)		0	0	8	2	0	3	no	probable
Bleeding outside the GIT									
NSAIDs (non-selective)		2	3	4	0	1	2	yes	possible
Heparins		1	2	5	2	0	3	yes	possible
Vitamin K antagonists		0	1	7	2	0	3	no	probable
Direct oral anticoagulants		0	1	7	2	0	3	no	probable
Certain other anticoagulants	Fondaparinux, Argatroban, Bivalirudin	0	2	6	2	0	3	no	probable
Antiplatelet drugs (excl. Dipyridamole, Cilostazol)		1	2	6	1	0	3	yes	possible
Certain phosphodiesterase inhibitors	Dipyridamole, Cilostazol	2	4	2	0	2	2	no	possible
SSRI / SSNRI		4	6	0	0	0	2	no	possible
Certain angiogenesis inhibitors	Ranibizumab, Bevacizumab, Sorafenib	1	5	3	0	1	2	yes	possible
Certain anticancer drugs	Fludarabine, Cytarabine, Cyclophosphamide, Ifosfamide, Oxaliplatin, Ramucirumab, Ibrutinib, Acalabrutinib, Zanubrutinib, Gefitinib, Azathioprine/Mercaptopurine	1	6	3	0	0	2	yes	possible
Certain beta-lactams	*Penicillin's:* Penicillin, Ampicillin, Piperacillin *Cephalosporins:* Ceftriaxone	6	2	0	0	2	1	no	unlikely
Certain other antibiotics	Trimethoprim/Sulfamethoxazole, Vancomycin, Rifampicin, Mitomycin, Nitrofurantoine	7	2	0	0	1	1	no	unlikely

Certain antiepileptics	Phenytoin, Carbamazepine, Valproic acid	7	2	0	0	1	1	no	unlikely
Miscellaneous drugs	Amlodipine, Mirtazapine, Quinine	9	0	0	0	1	1	no	unlikely
Two drugs rated as possible (=2)		0	3	6	0	1	3	yes	possible
Two drugs rated as probable (=3)		0	1	6	3	0	3	no	probable
Stevens-Johnson syndrome and toxic epidermal necrolysis									
Certain antiepileptics	Carbamazepine, Phenytoin, Phenobarbital, Valproate, Lamotrigine, Oxcarbazepine, Levetiracetam	0	4	4	2	0	3	yes	possible
Antibiotics (excl. Sulphonamides and Antituberculotics)		0	7	3	0	0	2	yes	possible
Sulphonamides		0	3	7	0	0	3	yes	possible
Antituberculotics		2	7	1	0	0	2	no	possible
Nevirapine		0	3	5	0	2	3	yes	possible
Antiretroviral therapy		2	5	2	0	1	2	no	possible
Certain antimycotics	Fluconazole, Nystatin, Terbinafine	5	3	2	0	0	1.5	no	unlikely
NSAIDs + Paracetamol		2	7	1	0	0	2	no	possible
Certain diuretics	Furosemide, Acetazolamide	4	6	0	0	0	2	no	possible
Glucocorticoids		7	3	0	0	0	1	no	unlikely
Allopurinol		0	4	5	0	1	3	yes	possible
Certain antidepressants	Sertraline, Mirtazapine, Duloxetine	3	6	1	0	0	2	no	possible
Certain anticancer drugs	*Taxanes:* Docetaxel, Paclitaxel *TKIs:* Afatinib, Imatinib, Sunitinib, Vandetanib, *Checkpoint inhibitors:* Ipilimumab, Nivolumab, Pembrolizumab	4	6	0	0	0	2	no	possible

	Other: Cetuximab, Leflunomide, Lenalidomide, Tamoxifen, Thalidomide, Vemurafenib								
Miscellaneous drugs	Amlodipine, Chloroquine, Famotidine, Isotretinoin, Oseltamivir, Pantoprazole, Ramipril, Tramadol	5	3	1	0	1	1	no	unlikely
Two drugs rated as possible (=2)		1	7	1	1	0	2	no	possible
Two drugs rated as probable (=3)		1	1	4	3	1	3	no	probable
Anaphylaxis									
Beta-lactams		0	2	5	3	0	3	no	probable
Fluoroquinolones		2	5	2	1	0	2	yes	possible
Sulphonamides		0	6	2	2	0	2	yes	possible
Macrolides		3	5	1	1	0	2	no	possible
Tetracyclines		1	7	0	1	1	2	no	possible
Glycopeptide antibiotics		1	4	3	2	0	2.5	yes	possible
Certain other antibiotics	Clindamycin, Metronidazole, Rifampicin, Bacitracin, Gentamicin, Tobramycin	3	6	1	0	0	2	no	possible
Anaesthetic agents		3	6	1	0	0	2	no	possible
Local anaesthetics		1	5	4	0	0	2	yes	possible
Glucocorticoids		7	3	0	0	0	1	no	unlikely
Certain chemotherapy agents	*Taxanes:* Docetaxel, Paclitaxel *Platinum compounds:* Carboplatin, Cisplatin, Oxaliplatin *Topoisomerase II inhibitors:* Podophyllotoxins (Etoposide, Teniposid), Doxorubicin *Other:* L-Asparaginase, Procarbazine, Cyclophosphamide, Cytarabine, Methotrexate, Leflunomide	1	7	2	0	0	2	no	possible

Contrast media		0	4	5	1	0	3	yes	possible
Neuromuscular blocking agents		0	3	5	1	1	3	yes	possible
NSAIDs		2	5	3	0	0	2	yes	possible
Opioids		1	9	0	0	0	2	no	possible
Certain other analgesics	Paracetamol, Metamizole (i.v.)	1	7	1	1	0	2	no	possible
Proton pump inhibitors		7	2	1	0	0	1	no	unlikely
Certain 5-HT3 antagonists	Ondansetron, Palonosetron	6	4	0	0	0	1	no	unlikely
Certain uterotonic drugs	Oxytocin, Dinoprostone	4	5	0	0	1	2	no	possible
Biologicals		1	4	3	2	0	2.5	yes	possible
Miscellaneous drugs	Abacavir, Atropine, Cetirizine, Heparin, Hyaluronidase, Mannitol, Neostigmine, Sugammadex, Tranexamic acid, Protamine	4	5	0	0	1	2	no	possible
Two drugs rated as possible (=2)		1	6	2	1	0	2	yes	possible
Two drugs rated as probable (=3)		1	1	4	3	1	3	no	probable
Serotonin syndrome									
SSRI		0	1	6	3	0	3	no	probable
SSNRI		0	1	7	2	0	3	no	probable
MAO inhibitors		0	1	7	1	1	3	no	probable
Tricyclic and tetracyclic antidepressants		0	6	3	1	0	2	yes	possible
5-HT2A antagonists		2	5	1	0	2	2	no	possible
Certain atypical antipsychotics	Risperidone, Clozapine, Olanzapine, Quetiapine, Amisulpride, Aripiprazole	3	6	1	0	0	2	no	possible
Triptans		5	4	0	1	0	1.5	no	unlikely

Certain antiemetics	Ondansetron, Granisetron, Metoclopramide	3	7	0	0	0	2	no	possible
Certain opioids	Tramadol, Fentanyl, Methadone, Tapentadol, Buprenorphine, Pethidine, Oxycodone, Codeine, Dextromethorphan	1	7	1	1	0	2	no	possible
Certain antibiotics with MAO-inhibiting activity	Linezolid, Tedizolid, Isoniazid	2	3	4	1	0	2.5	yes	possible
Amphetamines and derivatives		4	4	0	0	2	1.5	no	unlikely
Certain antiepileptics	Carbamazepine, Oxcarbazepine, Valproic acid	5	4	0	1	0	1.5	no	unlikely
Miscellaneous drugs	Bupropion, Buspirone, Chlorphenamine, Lithium, Procarbazine, St John's wort, Thioridazine	3	5	1	0	1	2	no	possible
Two drugs rated as possible (=2)		1	1	8	0	0	3	no	probable
Two drugs rated as probable (=3)		0	0	6	4	0	3	no	probable
Agranulocytosis / Neutropenia									
Cytotoxic anticancer drugs		0	0	7	3	0	3	no	probable
Certain antivirals	*Antiretroviral therapy:* Indinavir, Abacavir, Zidovudine *Other:* Acyclovir, Valacyclovir, Oseltamivir, Ganciclovir, Valganciclovir	1	3	6	0	0	3	yes	possible
ACE inhibitors		8	2	0	0	0	1	no	unlikely
Antiplatelet drugs (excl. ASA)		7	3	0	0	0	1	no	unlikely
Vitamin K antagonists		10	0	0	0	0	1	no	unlikely
Certain antiarrhythmics (excl. Cardiac glycosides)	Class Ia: Ajmaline Class Ib: Tocainide Class Ic: Flecainide, Propafenone Class III: Amiodarone	7	1	1	0	1	1	no	unlikely
Cardiac glycosides		8	2	0	0	0	1	no	unlikely
Thiazides		6	4	0	0	0	1	no	unlikely

Certain anticonvulsants	Phenobarbital, Carbamazepine, Ethosuximide, Lamotrigine, Levetiracetam, Phenytoin, Valproate	3	4	3	0	0	2	yes	possible
Certain H1-receptor blockers (first generation)	Chlorpheniramine, Tripelenamine	5	2	0	0	3	1	no	unlikely
H2-receptor blockers		6	4	0	0	0	1	no	unlikely
Phenothiazines		4	6	0	0	0	2	no	possible
Clozapine		0	4	3	3	0	3	yes	possible
Certain other neuroleptics (excl. Clozapine and Phenothiazines)	Olanzapine, Quetiapine, Ziprasidone, Haloperidol, Tiapride, Risperidone	3	6	1	0	0	2	no	possible
Retinoids		3	7	0	0	0	2	no	possible
Tricyclic and tetracyclic antidepressants		5	5	0	0	0	1.5	no	unlikely
NSAIDs (excl. Pyrazolones)		7	3	0	0	0	1	no	unlikely
Pyrazolones		0	2	6	2	0	3	no	probable
Beta-lactams		3	6	1	0	0	2	no	possible
Macrolides		7	3	0	0	0	1	no	unlikely
Tetracyclines		6	3	0	0	1	1	no	unlikely
Sulphonamides		2	4	4	0	0	2	yes	possible
Certain other antibiotics	*Lincosamide:* Clindamycin, Lincomycin *Glycopeptide antibiotics:* Teicoplanin, Vancomycin *Fluoroquinolones:* Norfloxacin, Ciprofloxacin *Aminoglycosides:* Streptomycin, Gentamycin, Tobramycin *Antituberculotics:* Rifampicin, Isoniazid, Ethambutol *Other:* Fusidic acid, Chlorampenicol, Nifuroxazid, Nitrofurantoin, Metonidazole, Linezolid, Dapsone	3	5	1	0	1	2	no	possible

Anti-malaria drugs		4	3	2	0	1	2	no	possible
Certain antimycotics	Ketoconazole, Fluconazole, Amphotericin B, 5-Flucytosine, Terbinafine	5	4	1	0	0	1.5	no	unlikely
Sulfonylureas		7	2	1	0	0	1	no	unlikely
Glucocorticoids		9	1	0	0	0	1	no	unlikely
Thionamides		1	7	2	0	0	2	no	possible
Certain immunosuppressants (excl. Biologicals)	*mTor inhibitors:* Sirolimus, Everolimus *Other:* Tacrolimus, Lenalidomide, Tofacitinib, Leflunomide, Azathioprine, MMF	0	5	5	0	0	2.5	yes	possible
Biologicals		1	6	3	0	0	2	yes	possible
Miscellaneous drugs	Acetylcysteine, Allopurinol, Bezafibrate, Chloralhydrat, Chlordiazepoxide, Colchicine, Deferiprone, Diazepam, Diflunisal, Fluoxetine, Flutamide, Furosemide, Hydralazine, Imatinib, Levodopa, Mebendazole, Methyldopa, Metoclopramide, Mesalazine, Nifedipine, Omeprazole, Paracetamol, Penicillamine, Propranolol, Riluzole, Spironolactone, Tamoxifen, Venlafaxine	4	5	0	0	1	2	no	possible
Two drugs rated as possible (=2)		1	5	4	0	0	2	yes	possible
Two drugs rated as probable (=3)		1	1	6	1	1	3	no	probable
Acute kidney injury									
NSAIDs		0	3	6	1	0	3	yes	possible
Anti-angiogenesis drugs		1	7	1	0	1	2	no	possible
Aminoglycosides		0	0	7	3	0	3	no	probable
Beta-lactams		5	4	1	0	0	1.5	no	unlikely

Fluoroquinolones/Quinolones		3	6	1	0	0	2	no	possible
Macrolides		6	4	0	0	0	1	no	unlikely
Polymyxins		0	4	4	1	1	3	yes	possible
Sulphonamides		3	7	0	0	0	2	no	possible
Tetracylines		5	5	0	0	0	1.5	no	unlikely
Certain other antibiotics	Clindamycin, Chloramphenicol, Ethambutol, Nitrofurantoin, Rifampicin, Vancomycin	2	3	4	0	1	2	yes	possible
Amphotericin B		0	3	5	2	0	3	yes	possible
Certain antiepileptic drugs	Carbamazepine, Phenobarbital, Phenytoin, Topiramate, Valproate, Zonisamide	5	5	0	0	0	1.5	no	unlikely
ARBs		2	6	2	0	0	2	no	possible
ACE inhibitors		1	6	3	0	0	2	yes	possible
Certain antineoplastic agents	*Platin compounds:* Carboplatin, Cisplatin, Oxaliplatin *Checkpoint inhibitors:* Ipilimumab, Nivolumab, Pembrolizumab *Antimetabolites:* Gemcitabine, Pemetrexed *Other:* Mitomycin C, Doxorubicin, Methotrexate, Ifosfamide	0	3	6	0	1	3	yes	possible
Bisphosphonates		4	5	1	0	0	2	no	possible
Certain antiplatelet drugs	Clopidogrel, Ticlopidine	10	0	0	0	0	1	no	unlikely
Certain antivirals	*Protease inhibitors:* Indinavir, Atazanavir *NRTIs*: Abacavir, Adefovir, Tenofovir *Nucleoside analogues:* Acyclovir, Ganciclovir, Valacyclovir, Valganciclovir *Other:* Cidofovir, Foscarnet	0	6	3	0	1	2	yes	possible
Contraceptive agents		9	0	1	0	0	1	no	unlikely
Contrast agents (i.v.)		0	2	8	0	0	3	no	probable

Thiazides		4	6	0	0	0	2	no	possible
Loop diuretics		4	4	2	0	0	2	no	possible
Potassium-sparing diuretics		6	4	0	0	0	1	no	unlikely
Certain H2-receptor blockers	Cimetidine, Ranitidine	9	1	0	0	0	1	no	unlikely
Proton pump inhibitors		5	4	1	0	0	1.5	no	unlikely
Calcineurin inhibitors / mTor inhibitors		0	3	7	0	0	3	yes	possible
5-Aminosalicylates		2	7	0	0	1	2	no	possible
Rhabdomyolysis-inducing drugs		3	4	3	0	0	2	yes	possible
Miscellaneous drugs	Allopurinol, Deferasirox, Ephedrine, Guaifenesin, Hydralazine, Infliximab, Interferons, Intravenous human globulins, Lithium, Paracetamol, Penicillamine, Pentamidine, Propylthiouracil, Quinine, Warfarin	1	8	0	0	1	2	no	possible
Two drugs rated as possible (=2)		0	5	5	0	0	2.5	yes	possible
Two drugs rated as probable (=3)		0	1	5	4	0	3	no	probable
Rhabdomyolysis									
Certain antibiotics	*Fluoroquinolones:* Levofloxacin, Ofloxacin *Macrolides:* Erythromycin, Clarithromycin *Other:* Daptomycin, Cotrimoxazole, Penicillin-Benzathine, Isoniazid, Pyrazinamide	3	6	0	0	1	2	no	possible
Certain antimycotics	Amphotericin B, Fluconazole, Itraconazole (+ Statin), Ketoconazole (+Statin), Voriconazole, Posaconazole, Terbinafine	3	6	1	0	0	2	no	possible
Certain antivirals	Tenofovir, Ritonavir, Ganciclovir, Letermovir, Simeprevir, Etravirin, Didanosine, Darunavir, Atazanavir, Tipranavir, Saquinavir, Raltegravir, Fosamprenavir, Indinavir, Lamivudine, Maraviroc, Nevirapin, Zidovudine	1	8	0	0	1	2	no	possible

Certain antihistamines	Diphenhydramine, Doxylamine, Cimetidine, Famotidine, Hydroxyzine	7	3	0	0	0	1	no	unlikely
Antipsychotics (typical/atypical)		2	7	0	0	1	2	no	possible
Antidepressants		3	6	0	0	1	2	no	possible
Statins		0	0	5	5	0	3.5	no	probable
Fibrates		0	4	4	2	0	3	yes	possible
Certain cytostatic drugs	Cytarabine, Nelarabine, Azacytidine, Oxaliplatin, Cyclophosphamide (+ Mitoxantrone), Ifosfamide, Trabectedin	2	8	0	0	0	2	no	possible
Certain hypnotics	*Barbiturates:* Phenobarbital *Benzodiazepines:* Diazepam, Lorazepam, Nitrazepam, Flunitrazepam, Triazolam	4	5	0	0	1	2	no	possible
Certain anticonvulsants	Phenytoin, Felbamate, Lamotrigine, Zonisamide, Pregabalin, Gabapentin	6	4	0	0	0	1	no	unlikely
Thiazides		9	1	0	0	0	1	no	unlikely
Opioids		9	1	0	0	0	1	no	unlikely
NSAIDs		10	0	0	0	0	1	no	unlikely
Corticosteroids		8	1	0	0	1	1	no	unlikely
Retinoids		5	3	0	0	2	1	no	unlikely
Certain iodinated contrast media	Iodixanol, Iohexol, Iopamidol, Iopromid, Ioversol	4	5	0	0	1	2	no	possible
Miscellaneous drugs with most concern according to DIRA	Certain drugs with most concern according to DIRA: Alteplase, Baclofen, Ciclosporin, Interferon-alfa-2b, Nivolumab, Succinylcholine, Sunitinib, Tolcapone, Ziconotide	2	5	2	0	1	2	no	possible
Miscellaneous drugs with possible concern according to DIRA	Certain drugs with possible concern according to DIRA: Aldesleukin, Diltiazem, Quinine, Cobimetinib, Colchicine, Everolimus, Lithium, Rotigotine, Sirolimus, Vasopressin, Verapamil	3	6	1	0	0	2	no	possible
Miscellaneous drugs with less concern according to DIRA	Certain drugs with less concern according to DIRA: Abirateronacetate, Amiodarone,	6	4	0	0	0	1	no	unlikely

	Dasatinib, Desflurane, Donezepil, Entacapone, Erlotinib, Ezetimibe, Febuxostat, Imatinib, Losartan, Olmesartan, Peginterferon alfa-2b, Propofol, Sonidegib, Sorafenib Sulfasalazine, Tacrolimus, Temsirolimus, Theophyllline, Trametinib								
Miscellaneous drugs not listed in DIRA	Certain drugs not listed in DIRA: Azathioprine, Leflunomide, Paracetamol	8	1	0	0	1	1	no	unlikely
Two drugs rated as possible (=2)		0	7	3	0	0	2	yes	possible
Two drugs rated as probable (=3)		0	1	6	3	0	3	no	probable
Delirium									
Total ACB-Score: 1 point		5	5	0	0	0	1.5	no	unlikely
Total ACB-Score: 2 points		4	6	0	0	0	2	no	possible
Total ACB-Score: ≥ 3 points		0	3	6	1	0	3	yes	possible
SSRI		1	9	0	0	0	2	no	possible
Anticonvulsants (excl. Phenobarbitals)		1	8	0	0	1	2	no	possible
Dopamine agonists		1	6	1	0	2	2	no	possible
Narcotics		0	3	5	1	1	3	yes	possible
GABA-receptor agonists		0	7	3	0	0	2	yes	possible
Antiarrhythmics (excl. Digitalis glycosides and Beta-blocking agents)		8	2	0	0	0	1	no	unlikely
Digitalis glycosides		5	4	1	0	0	1.5	no	unlikely
Beta-blocking agents		8	2	0	0	0	1	no	unlikely
Certain antibiotics	Beta-lactams/Cephalosporins, Quinolone/Fluoroquinolone, Macrolides, Antituberculotics	6	2	1	0	1	1	no	unlikely

Diuretics		5	3	2	0	0	1.5	no	unlikely
Antidiabetics		5	4	1	0	0	1.5	no	unlikely
Glucocorticoids (systemic)		6	2	2	0	0	1	no	unlikely
NSAIDs		7	3	0	0	0	1	no	unlikely
Opiates		2	4	4	0	0	2	yes	possible
Miscellaneous drugs	Bupropion, Disulfiram, Interferon Lithium, Methyldopa, Theophylline	2	6	1	0	1	2	no	possible
Two drugs rated as possible (=2)		0	4	6	0	0	3	yes	possible
Two drugs rated as probable (=3)		0	0	7	2	1	3	no	probable
Liver damage									
1 drug from category A according to LiverTox®		0	2	6	2	0	3	no	probable
1 drug from category B according to LiverTox®		0	5	5	0	0	2.5	yes	possible
1 drug from category C according to LiverTox®		0	10	0	0	0	2	no	possible
1 drug from category D according to LiverTox®		3	6	0	0	1	2	no	possible
1 drug from category E according to LiverTox®		8	1	0	0	1	1	no	unlikely
1 drug from category E* according to LiverTox®		7	3	0	0	0	1	no	unlikely
Two drugs rated as possible (=2)		0	5	5	0	0	2.5	yes	possible
Two drugs rated as probable (=3)		0	1	6	3	0	3	no	probable
Torsade de pointes tachycardia									
1 drug with known risk of TdP according to CredibleMeds®		0	4	4	2	0	3	yes	possible

2 drugs taken simultaneously with known risk of TdP according to CredibleMeds®		0	3	4	3	0	3	yes	possible
1 drug with possible risk of TdP according to CredibleMeds®		1	8	1	0	0	2	no	possible
2 drugs taken simultaneously with possible risk of TdP according to CredibleMeds®		0	6	4	0	0	2	yes	possible
2 drugs taken simultaneously with conditional risk of TdP according to CredibleMeds®		1	9	0	0	0	2	no	possible
1 drug with known risk of TdP + 1 drug with possible risk of TdP according to CredibleMeds® (taken simultaneously)		0	4	6	0	0	3	yes	possible
1 drug with known risk of TdP + 1 drug with conditional risk of TdP according to CredibleMeds® (taken simultaneously)		0	6	4	0	0	2	yes	possible
1 drug with possible risk of TdP + 1 drug with conditional risk of TdP according to CredibleMeds® (taken simultaneously)		1	7	2	0	0	2	no	possible

Abbreviations: 5-HT2A: 5-hydroxytryptamine 2A receptor; 5-HT3: 5-hydroxytryptamine 3 receptor; ACB score: Anticholinergic burden score by Kiesel et al.; ACE: Angiotensin-converting enzyme; ARBs: Angiotensin receptor blockers; ASA: Acetylsalicylic acid; CCBs: Calcium channel blockers; COX: Cyclooxygenase; DIRA: Drug-induced rhabdomyolysis atlas; ENaC: Epithelial sodium channel; GIT: Gastrointestinal tract; Excl.: Exclusive; MAO: Monoamine oxidase; MMF: Mycophenolate mofetil; mTOR: Mammalian target of rapamycin; NRTIs: Nucleoside/nucleotide reverse transcriptase inhibitors; NSAIDs: Non-steroidal anti-inflammatory drugs; SSNRI: Selective serotonin and norepinephrine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitors; TdP: Torsade de pointes tachycardia; TKIs: Tyrosine kinase inhibitors

Table S5-2 Expert ratings of the second round

		Number of participants with rating							
Drug-event pairs sorted by event	Certain drugs	1	2	3	4	0	Median	Disagreement	Category
Hyperkalemia									
ACE inhibitors		0	6	3	0	0	2	yes	possible
ARBs		0	7	2	0	0	2	no	possible
Direct renin inhibitors		0	7	2	0	0	2	no	possible
Aldosterone antagonists		0	3	6	0	0	3	yes	possible
ENaC blockers		1	4	4	0	0	2	yes	possible
Beta-blocking agents		7	1	1	0	0	1	no	unlikely
CCBs		8	1	0	0	0	1	no	unlikely
NSAIDs		2	6	1	0	0	2	no	possible
Heparin and derivatives		4	5	0	0	0	2	no	possible
Tacrolimus		0	7	2	0	0	2	no	possible
Other calcineurin inhibitors (excl. Tacrolimus)		2	6	1	0	0	2	no	possible
Pentamidine		2	4	2	0	1	2	no	possible
Cotrimoxazole		1	3	4	0	1	2.5	yes	possible
Agents containing a high amount of potassium		0	1	6	2	0	3	no	probable
Miscellaneous drugs	Digoxin, Mannitol, Propofol, Ketoconazole, Drospirenone, Magnesium sulphate	4	5	0	0	0	2	no	possible
Suxamethonium		0	3	5	1	0	3	yes	possible

Two drugs rated as possible (=2)		0	2	7	0	0	3	no	probable
Two drugs rated as probable (=3)		0	0	7	1	1	3	no	probable
Hyponatremia									
Oncologicals (excl. TKIs)		1	6	1	0	1	2	no	possible
TKIs		3	5	0	0	1	2	no	possible
MAO inhibitors		3	4	1	0	1	2	no	possible
SSNRI / SSRI		0	2	7	0	0	3	no	probable
Tricyclic and tetracyclic antidepressants		0	6	3	0	0	2	yes	possible
Antipsychotics		1	6	2	0	0	2	no	possible
Thiazides		0	1	7	1	0	3	no	probable
Other diuretics		0	2	7	0	0	3	no	probable
ACE inhibitors		4	4	1	0	0	2	no	possible
Carbamazepine and analogues		0	4	3	2	0	3	yes	possible
Other anticonvulsants (excl. Carbamazepine and analogues)		3	4	2	0	0	2	no	possible
Vasopressin and analogues		0	2	5	1	1	3	no	probable
Certain laxatives	Macrogol, Sodium picosulfate	2	7	0	0	0	2	no	possible
NSAIDs		8	0	1	0	0	1	no	unlikely
Opiates		7	1	1	0	0	1	no	unlikely
Proton pump inhibitors		7	2	0	0	0	1	no	unlikely
Certain antibiotics	Ciprofloxacin, Linezolid, Rifabutin, Sulfamethoxazole/Trimethoprim	8	1	0	0	0	1	no	unlikely

Miscellaneous drugs	Amiodarone, Amlodipine, Bromocriptine, Bupropion, Immunoglobulin, Paracetamol, Propafenone, Theophylline, Tolbutamide, Voriconazole	7	2	0	0	0	1	no	unlikely
Two drugs rated as possible (=2)		0	4	5	0	0	3	yes	possible
Two drugs rated as probable (=3)		0	1	6	2	0	3	no	probable
Hypoglycemia									
Incretin therapy		4	4	1	0	0	2	no	possible
Sulfonylureas		0	1	3	5	0	4	no	certain
Glinides		0	4	4	1	0	3	yes	possible
Non-insulinotropic antidiabetics		5	3	1	0	0	1	no	unlikely
Insulin		0	0	3	6	0	4	no	certain
ACE inhibitors		7	1	1	0	0	1	no	unlikely
Beta-blocking agents		4	5	0	0	0	2	no	possible
Certain ARBs	Losartan, Telmisartan, Valsartan	8	1	0	0	0	1	no	unlikely
Certain α2-receptor agonists	Clonidine, Dexmedetomidine	8	1	0	0	0	1	no	unlikely
Certain CCBs (Dihydropyridine type)	Nifedipine, Felodipine	9	0	0	0	0	1	no	unlikely
Certain serotonergic antidepressants	Venlafaxine, Sertraline, Fluoxetine, Imipramine, Maprotiline, Nortriptyline, Doxepin	9	0	0	0	0	1	no	unlikely
Certain anticonvulsants	Gabapentin, Phenytoin, Topiramate, Valproate	7	2	0	0	0	1	no	unlikely
Anti-malaria drugs		3	4	0	0	2	2	no	possible
Quinolones		5	4	0	0	0	1	no	unlikely
Certain other antibiotics	Ceftriaxone, Clarithromycin, Doxycycline, Tetracycline, Oxytetracycline, Isoniazid, Para-aminosalicylic acid, Pentamidine, Piperacillin-	7	2	0	0	0	1	no	unlikely

	tazobactam, Sulfadiazine, Sulfamethoxazole/ Trimethoprim								
Azole antimycotics		8	1	0	0	0	1	no	unlikely
Certain NSAIDs	Ibuprofen, Indomethacin, Phenylbutazone, Salicylates, Piroxicam	5	4	0	0	0	1	no	unlikely
Certain antivirals	Amprenavir, Entecavir, Ganciclovir, Saquinavir, Stavudine, Zidovudine	6	3	0	0	0	1	no	unlikely
Certain growth hormones	IGF-I (Mecasermin), Somatotropin	3	4	1	0	1	2	no	possible
Miscellaneous drugs	Amiodarone, Atorvastatin, Bortezomib, Chlormadinone, Clonazepam Propoxyphene/Dextropropoxyphene, Donepezil, Imatinib, Haloperidol, Etanercept, Ethacrynic acid, Etomidate, Hydralazine, Lidocaine, IL-2, Interferons, Lenalidomide, Lithium, Levothyroxine, 6-Mercaptopurine, Mifepristone, Octreotide, Paracetamol, Ranitidine, Salbutamol, Selegiline, Tramadol	8	0	0	0	1	1	no	unlikely
Two drugs rated as possible (=2)		0	6	3	0	0	2	yes	possible
Two drugs rated as probable (=3)		0	0	7	2	0	3	no	probable
Bleeding of the upper GIT									
NSAIDs (non-selective)		0	0	8	1	0	3	no	probable
Selective COX-2 inhibitors		1	6	2	0	0	2	no	possible
Paracetamol		6	3	0	0	0	1	no	unlikely
Direct oral anticoagulants		0	1	6	2	0	3	no	probable
Vitamin K antagonists		0	1	6	2	0	3	no	probable
Antiplatelet drugs		0	1	6	2	0	3	no	probable
CCBs		9	0	0	0	0	1	no	unlikely

SSRI		1	6	2	0	0	2	no	possible
Glucocorticoids		1	6	2	0	0	2	no	possible
Certain angiogenesis inhibitors	Bevacizumab, Erlotinib, Axitinib, Aflibercept	1	2	5	0	1	3	yes	possible
Two drugs rated as possible (=2)		0	5	3	1	0	2	yes	possible
Two drugs rated as probable (=3)		0	0	7	2	0	3	no	probable
Bleeding outside the GIT									
NSAIDs (non-selective; excl. Diclofenac and ASA)		2	5	2	0	0	2	no	possible
ASA		0	1	8	0	0	3	no	probable
Diclofenac		2	5	2	0	0	2	no	possible
Heparins		0	2	6	1	0	3	no	probable
Vitamin K antagonists		0	1	6	2	0	3	no	probable
Direct oral anticoagulants		0	1	6	2	0	3	no	probable
Certain other anticoagulants	Fondaparinux, Argatroban, Bivalirudin	0	2	4	2	1	3	no	probable
Other antiplatelet drugs (excl. Dipyridamole, Cilostazol, ASA)		0	2	6	1	0	3	no	probable
Certain phosphodiesterase inhibitors	Dipyridamole, Cilostazol	1	4	2	0	2	2	no	possible
SSRI / SSNRI		2	7	0	0	0	2	no	possible
Certain angiogenesis inhibitors	Ranibizumab, Bevacizumab, Sorafenib	1	5	2	0	1	2	no	possible
Certain anticancer drugs	Fludarabine, Cytarabine, Cyclophosphamide, Ifosfamide, Oxaliplatin, Ramucirumab, Ibrutinib, Acalabrutinib, Zanubrutinib, Gefitinib, Azathioprine/Mercaptopurine	0	6	3	0	0	2	yes	possible
Certain beta-lactams	*Penicillin's:* Penicillin, Ampicillin, Piperacillin *Cephalosporins:* Ceftriaxone	6	2	0	0	1	1	no	unlikely

Certain other antibiotics	Trimethoprim/Sulfamethoxazole, Vancomycin, Rifampicin, Mitomycin, Nitrofurantoine	6	2	0	0	1	1	no	unlikely
Certain antiepileptics	Phenytoin, Carbamazepine, Valproic acid	6	2	0	0	1	1	no	unlikely
Fibrinolytics		0	0	7	2	0	3	no	probable
Miscellaneous drugs	Amlodipine, Mirtazapine, Quinine	8	0	0	0	1	1	no	unlikely
Two drugs rated as possible (=2)		0	3	6	0	0	3	yes	possible
Two drugs rated as probable (=3)		0	0	7	2	0	3	no	probable
Stevens-Johnson syndrome and toxic epidermal necrolysis									
Certain antiepileptics	Carbamazepine, Phenytoin, Phenobarbital, Valproate, Lamotrigine, Oxcarbazepine, Levetiracetam	0	3	5	1	0	3	yes	possible
Antibiotics (excl. Sulphonamides and Antituberculotics)		0	6	3	0	0	2	yes	possible
Sulphonamides		0	3	6	0	0	3	yes	possible
Antituberculotics		1	7	1	0	0	2	no	possible
Nevirapine		0	3	5	0	1	3	yes	possible
Antiretroviral therapy		2	4	2	0	1	2	no	possible
Certain antimycotics	Fluconazole, Nystatin, Terbinafine	3	4	2	0	0	2	no	possible
NSAIDs + Paracetamol		0	8	1	0	0	2	no	possible
Certain diuretics	Furosemide, Acetazolamide	3	6	0	0	0	2	no	possible
Glucocorticoids		4	5	0	0	0	2	no	possible
Allopurinol		0	3	6	0	0	3	yes	possible
Certain antidepressants	Sertraline, Mirtazapine, Duloxetine	0	8	1	0	0	2	no	possible
Certain anticancer drugs	*Taxanes:* Docetaxel, Paclitaxel	2	7	0	0	0	2	no	possible

	TKIs: Afatinib, Imatinib, Sunitinib, Vandetanib, *Checkpoint inhibitors:* Ipilimumab, Nivolumab, Pembrolizumab *Other:* Cetuximab, Leflunomide, Lenalidomide, Tamoxifen, Thalidomide, Vemurafenib								
Miscellaneous drugs	Amlodipine, Chloroquine, Famotidine, Isotretinoin, Oseltamivir, Pantoprazole, Ramipril, Tramadol	1	7	0	0	1	2	no	possible
Two drugs rated as possible (=2)		0	7	1	1	0	2	no	possible
Two drugs rated as probable (=3)		0	3	3	2	1	3	yes	possible
Anaphylaxis									
Beta-lactams		0	1	6	2	0	3	no	probable
Fluoroquinolones		1	6	1	1	0	2	no	possible
Sulphonamides		0	6	2	1	0	2	yes	possible
Macrolides		2	6	0	1	0	2	no	possible
Tetracyclines		0	7	0	1	1	2	no	possible
Vancomycin		1	1	5	2	0	3	no	probable
Glycopeptide antibiotics (excl. Vancomycin)		2	5	2	0	0	2	no	possible
Certain other antibiotics	Clindamycin, Metronidazole, Rifampicin, Bacitracin, Gentamicin, Tobramycin	3	5	1	0	0	2	no	possible
Anaesthetic agents		2	6	1	0	0	2	no	possible
Local anaesthetics		1	4	4	0	0	2	yes	possible
Glucocorticoids		7	2	0	0	0	1	no	unlikely
Certain chemotherapy agents (excl. Taxanes)	*Platinum compounds:* Carboplatin, Cisplatin, Oxaliplatin *Topoisomerase II inhibitors:* Podophyllotoxins (Etoposide, Teniposid), Doxorubicin	2	5	2	0	0	2	no	possible

	Other: L-Asparaginase, Procarbazine, Cyclophosphamide, Cytarabine, Methotrexate, Leflunomide								
Taxanes		1	2	5	1	0	3	yes	possible
Iodinated contrast media		0	1	7	1	0	3	no	probable
Other contrast media		0	7	2	0	0	2	no	possible
Neuromuscular blocking agents		0	3	5	0	1	3	yes	possible
NSAIDs		2	5	2	0	0	2	no	possible
Opioids		1	8	0	0	0	2	no	possible
Paracetamol		4	4	1	0	0	2	no	possible
Metamizole (i.v.)		0	4	5	0	0	3	yes	possible
Proton pump inhibitors		6	2	1	0	0	1	no	unlikely
Certain 5-HT3 antagonists	Ondansetron, Palonosetron	5	4	0	0	0	1	no	unlikely
Certain uterotonic drugs	Oxytocin, Dinoprostone	4	4	0	0	1	1.5	no	unlikely
Biologicals with immunological target		0	2	3	2	2	3	no	probable
Biologicals without immunological target		1	2	3	1	2	3	yes	possible
Miscellaneous drugs	Abacavir, Atropine, Cetirizine, Heparin, Hyaluronidase, Mannitol, Neostigmine, Sugammadex, Tranexamic acid	2	6	0	0	1	2	no	possible
Protamine		0	7	1	1	0	2	no	possible
Two drugs rated as possible (=2)		1	5	2	1	0	2	yes	possible
Two drugs rated as probable (=3)		1	0	5	2	1	3	no	probable
Serotonin syndrome									

SSRI		0	0	6	3	0	3	no	probable
SSNRI		0	0	7	2	0	3	no	probable
MAO inhibitors		0	1	7	1	0	3	no	probable
Tricyclic antidepressants (excl. Clomipramine/ Imipramine)		0	5	3	1	0	2	yes	possible
Clomipramine and Imipramine		0	5	3	1	0	2	yes	possible
Tetracyclic antidepressants		2	5	1	1	0	2	no	possible
5-HT2A antagonists		3	4	1	0	1	2	no	possible
Certain atypical antipsychotics	Risperidone, Clozapine, Olanzapine, Quetiapine, Amisulpride, Aripiprazole	4	4	1	0	0	2	no	possible
Triptans		4	4	0	1	0	2	no	possible
Certain antiemetics	Ondansetron, Granisetron, Metoclopramide	3	6	0	0	0	2	no	possible
Certain opioids	Tramadol, Fentanyl, Methadone, Tapentadol, Buprenorphine, Pethidine, Oxycodone, Codeine, Dextromethorphan	0	7	1	1	0	2	no	possible
Certain antibiotics with MAO-inhibiting activity	Linezolid, Tedizolid, Isoniazid	1	3	4	1	0	3	yes	possible
Amphetamines and derivatives		3	4	0	0	2	2	no	possible
Certain antiepileptics	Carbamazepine, Oxcarbazepine, Valproic acid	5	3	0	1	0	1	no	unlikely
Miscellaneous drugs	Bupropion, Buspirone, Chlorphenamine, Lithium, Procarbazine, St John's wort, Thioridazine	2	5	1	0	1	2	no	possible
Two drugs rated as possible (=2)		0	1	8	0	0	3	no	probable
Two drugs rated as probable (=3)		0	0	6	3	0	3	no	probable
Agranulocytosis / Neutropenia									
Cytotoxic anticancer drugs		0	0	7	2	0	3	no	probable

Certain antivirals (excl. Ganciclovir and Valganciclovir)	*Antiretroviral therapy:* Indinavir, Abacavir, Zidovudine *Other:* Acyclovir, Valacyclovir, Oseltamivir	2	6	1	0	0	2	no	possible
Ganciclovir and Valganciclovir		0	3	6	0	0	3	yes	possible
ACE inhibitors		7	2	0	0	0	1	no	unlikely
Antiplatelet drugs (excl. ASA)		7	2	0	0	0	1	no	unlikely
Vitamin K antagonists		9	0	0	0	0	1	no	unlikely
Certain antiarrhythmics (excl. Cardiac glycosides)	Class Ia: Ajmaline Class Ib: Tocainide Class Ic: Flecainide, Propafenone Class III: Amiodarone	7	0	1	0	1	1	no	unlikely
Cardiac glycosides		8	1	0	0	0	1	no	unlikely
Thiazides		5	4	0	0	0	1	no	unlikely
Certain anticonvulsants	Phenobarbital, Carbamazepine, Ethosuximide, Lamotrigine, Levetiracetam, Phenytoin, Valproate	3	4	2	0	0	2	no	possible
Certain H1-receptor blockers (first generation)	Chlorpheniramine, Tripelenamine	4	4	0	0	1	1.5	no	unlikely
H2-receptor blockers		5	4	0	0	0	1	no	unlikely
Phenothiazines		3	6	0	0	0	2	no	possible
Clozapine		0	1	5	3	0	3	no	probable
Certain other neuroleptics (excl. Clozapine and Phenothiazines)	Olanzapine, Quetiapine, Ziprasidone, Haloperidol, Tiapride, Risperidone	3	5	1	0	0	2	no	possible
Retinoids		2	7	0	0	0	2	no	possible
Tricyclic and tetracyclic antidepressants		5	4	0	0	0	1	no	unlikely
NSAIDs (excl. Pyrazolones)		6	3	0	0	0	1	no	unlikely
Pyrazolones		0	2	5	2	0	3	no	probable

Beta-lactams		3	5	1	0	0	2	no	possible
Macrolides		6	3	0	0	0	1	no	unlikely
Tetracyclines		5	3	0	0	1	1	no	unlikely
Sulphonamides		2	4	3	0	0	2	yes	possible
Certain other antibiotics	*Lincosamide:* Clindamycin, Lincomycin *Glycopeptide antibiotics:* Teicoplanin, Vancomycin *Fluoroquinolones:* Norfloxacin, Ciprofloxacin *Aminoglycosides:* Streptomycin, Gentamycin, Tobramycin *Antituberculotics:* Rifampicin, Isoniazid, Ethambutol *Other:* Fusidic acid, Chlorampenicol, Nifuroxazid, Nitrofurantoin, Metonidazole, Linezolid, Dapsone	3	4	1	0	1	2	no	possible
Anti-malaria drugs		4	2	2	0	1	1.5	no	unlikely
Certain antimycotics	Ketoconazole, Fluconazole, Amphotericin B, 5-Flucytosine, Terbinafine	5	3	1	0	0	1	no	unlikely
Sulfonylureas		6	2	1	0	0	1	no	unlikely
Glucocorticoids		8	1	0	0	0	1	no	unlikely
Thionamides		1	6	2	0	0	2	no	possible
Certain immunosuppressants (excl. Biologicals, Azathioprine, MMF)	*mTor inhibitors:* Sirolimus, Everolimus *Other:* Tacrolimus, Lenalidomide, Tofacitinib, Leflunomide	0	8	1	0	0	2	no	possible
MMF and Azathioprine		0	2	7	0	0	3	no	probable
Biologicals		1	6	2	0	0	2	no	possible
Miscellaneous drugs	Acetylcysteine, Allopurinol, Bezafibrate, Chloralhydrat, Chlordiazepoxide, Colchicine, Deferiprone, Diazepam, Diflunisal, Fluoxetine,	4	4	0	0	1	1.5	no	unlikely

	Flutamide, Furosemide, Hydralazine, Imatinib, Levodopa, Mebendazole, Methyldopa, Metoclopramide, Mesalazine, Nifedipine, Omeprazole, Paracetamol, Penicillamine, Propranolol, Riluzole, Spironolactone, Tamoxifen, Venlafaxine								
Two drugs rated as possible (=2)		1	4	4	0	0	2	yes	possible
Two drugs rated as probable (=3)		1	0	6	1	1	3	no	probable
Acute kidney injury									
NSAIDs		0	2	7	0	0	3	no	probable
Anti-angiogenesis drugs		1	7	1	0	0	2	no	possible
Aminoglycosides		0	0	6	3	0	3	no	probable
Beta-lactams		4	4	1	0	0	2	no	possible
Fluoroquinolones/Quinolones		3	5	1	0	0	2	no	possible
Macrolides		6	3	0	0	0	1	no	unlikely
Polymyxins (i.v.)		0	4	4	1	0	3	yes	possible
Sulphonamides		2	7	0	0	0	2	no	possible
Tetracylines		4	5	0	0	0	2	no	possible
Certain other antibiotics (excl. Vancomycin)	Clindamycin, Chloramphenicol, Ethambutol, Nitrofurantoin, Rifampicin	2	4	2	0	1	2	no	possible
Vancomycin		0	1	8	0	0	3	no	probable
Amphotericin B		0	3	4	2	0	3	yes	possible
Certain antiepileptic drugs	Carbamazepine, Phenobarbital, Phenytoin, Topiramate, Valproate, Zonisamide	5	4	0	0	0	1	no	unlikely
ARBs		1	6	2	0	0	2	no	possible

ACE inhibitors		0	6	3	0	0	2	yes	possible
Certain other antineoplastic agents (excl. Methotrexate, Cisplatin, Ifosfamide)	*Platin compounds:* Carboplatin, Oxaliplatin *Checkpoint inhibitors:* Ipilimumab, Nivolumab, Pembrolizumab *Antimetabolites:* Gemcitabine, Pemetrexed *Other:* Mitomycin C, Doxorubicin	1	3	4	0	1	2.5	yes	possible
Methotrexate, Cisplatin, Ifosfamide		0	1	8	0	0	3	no	probable
Bisphosphonates		3	5	1	0	0	2	no	possible
Certain antiplatelet drugs	Clopidogrel, Ticlopidine	9	0	0	0	0	1	no	unlikely
Certain antiretroviral therapy	*Protease inhibitors:* Indinavir, Atazanavir *NRTIs:* Abacavir, Adefovir, Tenofovir	1	8	0	0	0	2	no	possible
Certain other antivirals	*Nucleoside analogues:* Acyclovir, Ganciclovir, Valacyclovir, Valganciclovir *Other:* Cidofovir, Foscarnet	0	2	7	0	0	3	no	probable
Contraceptive agents		8	0	1	0	0	1	no	unlikely
Contrast agents (i.v.)		0	1	8	0	0	3	no	probable
Thiazides		3	6	0	0	0	2	no	possible
Loop diuretics		3	4	2	0	0	2	no	possible
Potassium-sparing diuretics		5	4	0	0	0	1	no	unlikely
Certain H2-receptor blockers	Cimetidine, Ranitidine	8	1	0	0	0	1	no	unlikely
Proton pump inhibitors		5	3	1	0	0	1	no	unlikely
mTor inhibitors		1	5	2	0	1	2	no	possible
Calcineurin inhibitors		0	2	7	0	0	3	no	probable
5-Aminosalicylates		2	6	0	0	1	2	no	possible
Miscellaneous drugs	Allopurinol, Deferasirox, Ephedrine, Guaifenesin, Hydralazine, Infliximab, Interferons, Intravenous	1	7	0	0	1	2	no	possible

	human globulins, Lithium, Paracetamol, Penicillamine, Pentamidine, Propylthiouracil, Quinine, Warfarin								
Two drugs rated as possible (=2)		0	4	5	0	0	3	yes	possible
Two drugs rated as probable (=3)		0	1	5	3	0	3	no	probable
Rhabdomyolysis									
Certain antibiotics	*Fluoroquinolones:* Levofloxacin, Ofloxacin *Macrolides:* Erythromycin, Clarithromycin *Other:* Daptomycin, Cotrimoxazole, Penicillin-Benzathine, Isoniazid, Pyrazinamide	3	5	0	0	1	2	no	possible
Certain antimycotics	Amphotericin B, Fluconazole, Itraconazole (+ Statin), Ketoconazole (+Statin), Voriconazole, Posaconazole, Terbinafine	3	5	1	0	0	2	no	possible
Certain antivirals	Tenofovir, Ritonavir, Ganciclovir, Letermovir, Simeprevir, Etravirin, Didanosine, Darunavir, Atazanavir, Tipranavir, Saquinavir, Raltegravir, Fosamprenavir, Indinavir, Lamivudine, Maraviroc, Nevirapin, Zidovudine	1	7	0	0	1	2	no	possible
Certain antihistamines	Diphenhydramine, Doxylamine, Cimetidine, Famotidine, Hydroxyzine	6	3	0	0	0	1	no	unlikely
Antipsychotics (typical/atypical)		2	6	0	0	1	2	no	possible
Antidepressants		3	5	0	0	1	2	no	possible
Statins		0	0	5	4	0	3	no	probable
Fibrates		0	4	3	2	0	3	yes	possible
Certain cytostatic drugs (excl. Trabectedin)	Cytarabine, Nelarabine, Azacytidine, Oxaliplatin, Cyclophosphamide (+ Mitoxantrone), Ifosfamide	2	6	1	0	0	2	no	possible
Trabectedin		0	0	8	0	1	3	no	probable
Certain hypnotics	*Barbiturates:* Phenobarbital *Benzodiazepines:* Diazepam, Lorazepam, Nitrazepam, Flunitrazepam, Triazolam	3	5	0	0	1	2	no	possible

Certain anticonvulsants	Phenytoin, Felbamate, Lamotrigine, Zonisamide, Pregabalin, Gabapentin	5	4	0	0	0	1	no	unlikely
Thiazides		8	1	0	0	0	1	no	unlikely
Opioids		9	0	0	0	0	1	no	unlikely
NSAIDs		9	0	0	0	0	1	no	unlikely
Corticosteroids		8	1	0	0	0	1	no	unlikely
Retinoids		5	3	0	0	1	1	no	unlikely
Certain iodinated contrast media	Iodixanol, Iohexol, Iopamidol, Iopromid, Ioversol	4	4	0	0	1	1.5	no	unlikely
Miscellaneous drugs with most concern according to DIRA	Certain drugs with most concern according to DIRA: Alteplase, Baclofen, Ciclosporin, Interferon-alfa-2b, Nivolumab, Succinylcholine, Sunitinib, Tolcapone, Ziconotide	2	5	1	0	1	2	no	possible
Miscellaneous drugs with possible concern according to DIRA	Certain drugs with possible concern according to DIRA: Aldesleukin, Diltiazem, Quinine, Cobimetinib, Colchicine, Everolimus, Lithium, Rotigotine, Sirolimus, Vasopressin, Verapamil	3	5	1	0	0	2	no	possible
Miscellaneous drugs with less concern according to DIRA	Certain drugs with less concern according to DIRA: Abirateronacetate, Amiodarone, Dasatinib, Desflurane, Donezepil, Entacapone, Erlotinib, Ezetimibe, Febuxostat, Imatinib, Losartan, Olmesartan, Peginterferon alfa-2b, Propofol, Sonidegib, Sorafenib Sulfasalazine, Tacrolimus, Temsirolimus, Theophyllline, Trametinib	6	3	0	0	0	1	no	unlikely
Miscellaneous drugs not listed in DIRA	Certain drugs not listed in DIRA: Azathioprine, Leflunomide, Paracetamol	7	1	0	0	1	1	no	unlikely
Two drugs rated as possible (=2)		0	7	2	0	0	2	no	possible
Two drugs rated as probable (=3)		0	1	6	2	0	3	no	probable
Delirium									
Total ACB-Score: 1 point		4	5	0	0	0	2	no	possible

Total ACB-Score: 2 points		3	6	0	0	0	2	no	possible
Total ACB-Score: ≥ 3 points		0	2	6	1	0	3	no	probable
SSRI (excl. Paroxetine)		4	5	0	0	0	2	no	possible
Anticonvulsants (excl. Phenobarbitals and Carbamazepine)		0	9	0	0	0	2	no	possible
Dopamine agonists		1	6	1	0	1	2	no	possible
Narcotics		0	2	5	1	1	3	no	probable
GABA-receptor agonists		0	8	1	0	0	2	no	possible
Antiarrhythmics (excl. Digitalis glycosides and Beta-blocking agents)		7	2	0	0	0	1	no	unlikely
Digitalis glycosides		5	3	1	0	0	1	no	unlikely
Beta-blocking agents		7	2	0	0	0	1	no	unlikely
Certain antibiotics	Beta-lactams/Cephalosporins, Quinolone/Fluoroquinolone, Macrolides, Antituberculotics	5	2	1	0	1	1	no	unlikely
Diuretics		5	2	2	0	0	1	no	unlikely
Glucocorticoids (systemic)		5	2	2	0	0	1	no	unlikely
NSAIDs		6	3	0	0	0	1	no	unlikely
Opiates		2	3	4	0	0	2	yes	possible
Miscellaneous drugs	Bupropion, Disulfiram, Interferon Lithium, Methyldopa, Theophylline	2	5	1	0	1	2	no	possible
Two drugs rated as possible (=2)		0	2	7	0	0	3	no	probable
Two drugs rated as probable (=3)		0	0	6	2	1	3	no	probable
Liver damage									

1 drug from category A according to LiverTox®		0	2	5	2	0	3	no	probable
1 drug from category B according to LiverTox®		0	5	4	0	0	2	yes	possible
1 drug from category C according to LiverTox®		0	9	0	0	0	2	no	possible
1 drug from category D according to LiverTox®		2	6	0	0	1	2	no	possible
1 drug from category E according to LiverTox®		7	1	0	0	1	1	no	unlikely
1 drug from category E* according to LiverTox®		6	3	0	0	0	1	no	unlikely
Two drugs rated as possible (=2)		0	5	4	0	0	2	yes	possible
Two drugs rated as probable (=3)		0	1	5	3	0	3	no	probable
Torsade de pointes tachycardia									
1 drug with known risk of TdP according to CredibleMeds®		0	2	5	2	0	3	no	probable
2 drugs taken simultaneously with known risk of TdP according to CredibleMeds®		0	2	5	2	0	3	no	probable
1 drug with possible risk of TdP according to CredibleMeds®		1	7	1	0	0	2	no	possible
2 drugs taken simultaneously with possible risk of TdP according to CredibleMeds®		0	6	3	0	0	2	yes	possible
2 drugs taken simultaneously with conditional risk of TdP according to CredibleMeds®		1	8	0	0	0	2	no	possible
1 drug with known risk of TdP + 1 drug with possible risk of TdP according to CredibleMeds® (taken simultaneously)		0	2	7	0	0	3	no	probable
1 drug with known risk of TdP + 1 drug with conditional risk of TdP according to CredibleMeds® (taken simultaneously)		0	4	5	0	0	3	yes	possible

1 drug with possible risk of TdP + 1 drug with conditional risk of TdP according to CredibleMeds® (taken simultaneously)		1	7	1	0	0	2	no	possible

Abbreviations: 5-HT2A: 5-hydroxytryptamine 2A receptor; 5-HT3: 5-hydroxytryptamine 3 receptor; ACB score: Anticholinergic burden score by Kiesel et al.; ACE: Angiotensin-converting enzyme; ARBs: Angiotensin receptor blockers; ASA: Acetylsalicylic acid; CCBs: Calcium channel blockers; COX: Cyclooxygenase; DIRA: Drug-induced rhabdomyolysis atlas; ENaC: Epithelial sodium channel; GIT: Gastrointestinal tract; Excl.: Exclusive; MAO: Monoamine oxidase; MMF: Mycophenolate mofetil; mTOR: Mammalian target of rapamycin; NRTIs: Nucleoside/nucleotide reverse transcriptase inhibitors; NSAIDs: Non-steroidal anti-inflammatory drugs; SSNRI: Selective serotonin and norepinephrine reuptake inhibitors; SSRI: Selective serotonin reuptake inhibitors; TdP: Torsade de pointes tachycardia; TKIs: Tyrosine kinase inhibitors

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Drug-Event Pairs as Indicators for the Detection of Adverse Drug Reactions during Hospitalization in Routinely Collected Electronic Data Sources

SUPPLEMENT S6: Adjustments after the panel meeting

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Table S6 Adjustments after the panel meeting

Initial drug class (round 1)	Adjusted drug class (round 2)
Hyperkalemia	
Calcineurin inhibitors (whole group)	Tacrolimus
	Other calcineurin inhibitors
Certain anti-infectives (Pentamidine, Cotrimoxazole)	Pentamidine
	Cotrimoxazole
Potassium-containing agents: Penicillin G, Potassium citrate, Potassium supplements (oral or i.v.), Salt substitutes	Agents containing a high amount of potassium: Potassium citrate, Potassium supplements (oral or i.v.; high dose)
Miscellaneous drugs	Miscellaneous drugs (excl. Suxamethonium)
	Suxamethonium
Hyponatremia	
Oncologicals (whole group)	Oncologicals (excl. Tyrosine kinase inhibitors)
	Tyrosine kinase inhibitors
Anticonvulsants (whole group)	Anticonvulsants (excl. Carbamazepine and analogues)
	Carbamazepine and analogues
Hypoglycemia	
Classic insulin secretagogues	Sulfonylureas
	Glinides
Bleeding outside the gastrointestinal tract	
NSAIDs (non-selective; whole group)	NSAIDs (excl. Diclofenac and ASA)
	ASA

Initial drug class (round 1)	Adjusted drug class (round 2)
	Diclofenac
/	Fibrinolytics (whole group)
Anaphylaxis	
Glycopeptide antibiotics (whole group)	Glycopeptide antibiotics (excl. Vancomycin)
	Vancomycin
Certain chemotherapy agents	Certain chemotherapy agents (excl. Taxanes)
	Taxanes
Contrast media (whole group)	Iodinated contrast media
	Other contrast media
Certain other analgesics	Paracetamol
	Metamizole (i.v.)
Biologicals	Biologicals with immunological target
	Biologicals without immunological target
Miscellaneous drugs	Miscellaneous drugs (excl. Protamine)
	Protamine
Serotonin syndrome	
Tricyclic/ tetracyclic antidepressants (whole group)	Tricyclic antidepressants (excl. Clomipramine/ Imipramine)
	Clomipramine and Imipramine
	Tetracyclic antidepressants
Agranulocytosis / Neutropenia	
Certain antivirals	Certain antivirals (excl. Ganciclovir and Valganciclovir)
	Ganciclovir and Valganciclovir
Certain immunosuppressants (excl. Biologicals)	Certain other immunosuppressants (excl. Biologicals, Azathioprine, Mycophenolate mofetil)
	Mycophenolic mofetil and Azathioprine
Acute kidney injury	
Polymyxins	Polymyxins (i.v)
Certain other antibiotics	Certain other antibiotics (excl. Vancomycin)
	Vancomycin
Certain antineoplastic agents	Certain other antineoplastic agents (excl. Methotrexate, Cisplatin, Ifosfamide)
	Methotrexate, Cisplatin, Ifosfamide

Initial drug class (round 1)	Adjusted drug class (round 2)
Certain antiviral agents	Certain antiretroviral therapy
	Certain other antivirals
mTor inhibitors/ Calcineurin inhibitors (whole group)	mTor inhibitors
	Calcineurin inhibitors
Rhabdomyolysis-inducing drugs	Excluded
Rhabdomyolysis	
Certain cytostatic drugs	Certain cytostatic drugs (excl. Trabectedin)
	Trabectedin
Delirium	
SSRI (whole group)	SSRI (excl. Paroxetine)
Anticonvulsants (excl. Phenobarbitals)	Anticonvulsants (excl. Phenobarbitals and Carbamazepine)
Antidiabetics	Excluded

Abbreviations: ASA: Acetylsalicylic acid; Excl.: Exclusive; mTOR: Mammalian target of rapamycin; NSAIDs: Non-steroidal anti-inflammatory drugs; SSRI: Selective serotonin reuptake inhibitors

PLOS Digital Health

RESEARCH ARTICLE

Challenges in detecting and predicting adverse drug events via distributed analysis of electronic health record data from German university hospitals

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Data availability statement: The initial, local data snapshots containing the centres' pseudonymized patient data, i.e. the data from the

Abstract

The Medical Informatics Initiative Germany (MII) aims to facilitate the interoperability and exchange of electronic health record data from all German university hospitals. The MII use case "POLyphamacy, drug interActions and Risks" (POLAR_MI) was designed to retrospectively detect medication-related risks in adult inpatients. As part of POLAR_MI, we aimed to build predictive models for specific adverse events. Here, using the two adverse events gastrointestinal bleeding and drug-related hypoglycaemia as examples, we present our initial investigation to determine whether these adverse events and their associations with potential risk factors can be detected. We applied a two-step distributed analysis approach to electronic health record data from 2018 to 2021. This approach consisted of a local statistical data analysis at ten participating centres, followed by a mixed-effects meta-analysis. For each adverse event, two multivariable logistic regression models were constructed: (1) including only demographics, diagnoses and medications, and (2) extended by laboratory values. As numerically stable estimations of both models were not possible at each centre, we constructed different centre subgroups for meta-analyses. We received prevalence estimates of around 1.2% for GI bleeding and around 3.0% for drug-related hypoglycaemia. Although unavailability of laboratory values was a common reason hindering model estimation, multivariable regression models were obtained for both adverse events from several centres. Regarding our original intention to

patients' electronic medical records from routine inpatient care, cannot be shared, as the General Data Protection Regulation (GDPR) prohibits their transfer to third parties without patient consent. However, researchers can request the data and related analysis via the German Portal for Medical Research Data (Deutsches Forschungsdatenportal für Gesundheit, FDPG; https://forschen-fuer-gesundheit.de; email address: info@forschen-fuer-gesundheit.de). All developed software components, including the R scripts, are available via the 'Health Atlas - Local Data Hub/Leipzig' at https://www.health-atlas.de/lha/8VF7DGV205-4. The authors confirm that the complete meta-analysis results of this study, including the values used to build the graphs, are provided in this article and its supplementary materials.

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build predictive models, the median area under the receiver operating characteristic curve was above 0.70 for all multivariable regression models, indicating feasibility. In conclusion, plausible estimates for prevalence and regression modelling odds ratios were received when using a distributed analysis approach on inpatient treatment data from diverse German university hospitals. Our results suggest that the development of predictive models in a distributed setting is possible if the research question is adapted to the infrastructure and the available data.

Author summary

Undesirable medical occurrences following exposure to a drug are called adverse events. They are a common and often preventable cause of illness in patients. To facilitate their detection and prevention, models can be used to predict the probability of the development or presence of an adverse event. As part of the project "POLypharmacy, drug interActions and Risks" (POLAR_MI) of the Medical Informatics Initiative Germany (MII), we investigated whether two adverse events (gastrointestinal bleeding and drug-related hypoglycaemia) could be detected and their associations with potential risk factors assessed. This was done to test the feasibility of building predictive models within the framework established by the MII using a distributed analysis approach without direct data access for the analyst. We received plausible estimates for the prevalence of the adverse events and risk factors, and observed mainly clinically plausible associations between the adverse events and the related risk factors. One of our major challenges was the unavailability of laboratory values used to define the adverse event drug-related hypoglycaemia and some potential risk factors. Based on our results, we conclude that the development of predictive models is possible if a research question can be defined that fits the IT infrastructure and the available data.

1. Introduction

Germany has 36 university hospitals, of which each runs its independent hospital information system (HIS) [1]. An integral part of such HIS are electronic health records (EHR). The cross-institutional exchange and statistical analyses of EHR data from these hospitals would offer an opportunity to gain insights into health risks and subsequently improve decision making in healthcare at local, national, and global levels [2–5]. The realisation requires improvements in local data quality, processing and analysis, as well as the rapid and standardised cross-institutional exchange of EHR data. However, data protection regulations and the use of diverse clinical systems, resulting in a lack of semantic, syntactic and organisational interoperability, impose a challenge to data sharing between different university hospitals [6,7]. At the local level, the integration of various health IT systems (hospital software, laboratory

systems, imaging systems, etc.) to work seamlessly with the HIS infrastructure remains challenging. At the cross-institutional level, various HIS infrastructures with different documentation standards complicate data exchange.

Against this background, the Medical Informatics Initiative Germany (MII) has been working since 2018 to establish decentralised data infrastructures at German university hospitals to facilitate better interoperability between systems, thus enabling data sharing of EHR data and subsequent multicentre analyses [8]. For this purpose, data integration centres (DIC) were established. At the DIC, data from EHR are available via the MII Core Data Set (CDS), where HL7 FHIR (Health Level Seven; Fast Health Interoperability Resources; http://hl7.org/fhir/ [9]; "FHIR is the registered trademark of HL7 and is used with the permission of HL7; use of the FHIR trademark does not constitute endorsement of this product by HL7") is used as interoperable data format [10–12].

Applying the MII processes and methods to data from routine hospital healthcare, the collaborative use case "POLypharmacy, drug interActions and Risks" (POLAR_MI) was designed to retrospectively detect medication-related risks, e.g., adverse events (AE) and adverse drug events (ADE), in hospitalised adults [13]. This objective was the starting point to demonstrate that it is possible to retrieve and use healthcare data within the MII on a large scale. For this purpose, the "POLAR_MI ETL Pipeline", a tailored distributed analysis approach, was developed to conduct research projects related to the overall aim of POLAR_MI [13].

In our research project within POLAR_MI, we pursued the aim to build models predicting specific inpatient ADE based on information available at hospital admission. Such models can be used to prioritise services such as medication reviews or medication reconciliation for patients at high risk for ADE, thereby facilitating the efficient use of available resources and leading to a greater impact on medication safety [14–17]. Many models predicting ADE have already been developed, often based on prospective studies tailored to this research question, giving the researchers control over the required data and the related documentation quality [17,18]. However, due to the controlled conditions of these studies, they only partly reflect real inpatient care. By contrast, data from EHR, as used in the context of the MII, originate from the documentation of treatment and care. Such data from routine healthcare, of unknown quality and completeness, are increasingly used to complement data from prospective studies for the development of predictive models [19].

Here we present our initial multicentre investigation of whether AE can be detected and their association with potential risk factors assessed (via logistic regression modelling) using a distributed analysis approach. We analysed this feasibility based on two AE (gastrointestinal bleeding, drug-related hypoglycaemia), including an assessment of the impact of integrating laboratory values and considering the chronology of events.

2. Materials and methods

2.1 The POLAR_MI framework

2.1.1 Study design and setting. POLAR_MI was a multicentre, retrospective observational study at German university hospitals. The POLAR_MI-wide inclusion criteria were: (1) admission and discharge within the time interval 2018/01/01 and 2021/12/31, (2) inpatient hospital stay and (3) age ≥ 18 years on admission. Additionally, no technical reasons hindering data processing were permitted to be present.

Trial registration: POLAR_MI was registered on 27/11/2020 in the "HMA-EMA Catalogues of real-world data sources and studies" (EU PAS number: EUPAS36582).

Ethics statement: POLAR_MI received ethics approvals from all participating centres. The primary approval was granted by the Ethics Committee at the Medical Faculty of the University Leipzig (lead ethics committee). The names of the relevant ethics committees and the respective reference numbers are provided in Table 1.

Patient consent: Informed patient consent was not required due to the retrospective, distributed analysis approach in POLAR_MI, where only anonymised data (i.e., summary statistics) not falling under der EU General Data Protection Regulation left the centres.

Table 1. Ethics committees and the reference numbers of the participating centres. Abbreviation: -, not available.

Participating centre	Ethics Committee		Reference number
	Official German name	Official English name	
Bonn	Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn	Ethics Committee at the Medical Faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn	101/21
Erlangen	Ethik-Kommission an der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg	–	368_20 Bc
Freiburg/Breisgau	Ethik-Kommission der Albert-Ludwigs-Universität Freiburg	Ethics Committee of the Albert Ludwig University of Freiburg	20-1267
Gießen	Ethik-Kommission des Fachbereichs Medizin der Justus-Liebig-Universität Gießen	Ethics Committee of the Faculty of Medicine at Justus Liebig University Giessen	adopted the approval granted by the lead ethics committee (Leipzig)
Halle/Saale	Ethik-Kommission der Medizinischen Fakultät der Martin-Luther-Universität Halle-Wittenberg	Ethics Committee at the Medical Faculty of the Martin Luther University Halle-Wittenberg	2021-119
Hamburg	Ethik-Kommission der Ärztekammer Hamburg	–	2020-10251-BO-bet
Heidelberg	Universität Heidelberg Ethikkommission der Me-di-zi-ni-schen Fakultät	Ethics Committee of the Medical Faculty of Heidelberg University	S-240/2021
Jena	Universitätsklinikum Jena Ethik-Kommission	–	2020-1931-Daten
Kiel	Ethik-Kommission der Medizinischen Fakultät der Christian-Albrechts-Universität zu Kiel	Ethics Committee at the Faculty of Medicine of Kiel University	B 280/21
Leipzig (lead)	Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig	Ethics Committee at the Medical Faculty of the University Leipzig	247/20-ek
München	Ethikkommission der Ludwig-Maximilians Universität München	–	20-0961
Tübingen	Ethik-Kommission an der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen	The Ethics Committee at the Medical Faculty of the Eberhard Karls University and at the University Hospital of Tübingen	712/2020BO2

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2.1.2 Data collection and (pre-) processing. We applied the POLAR_MI ETL Pipeline, which is a two-step distributed analysis approach (see Fig 1). In the first step, modules (i.e., a composition of several R scripts) for data retrieval, preparation and statistical analysis on encounter-level were executed locally at each DIC on the CDS-compliant FHIR data. In our analysis, an encounter corresponded to an inpatient hospital stay. After approval of the local aggregated results by the DIC, including a review of data protection issues, we pooled the local results in a second step via random-effects meta-analyses, accounting for heterogeneity of the participating centres. For our research project, we received local results from ten centres (Bonn, Erlangen, Freiburg/Breisgau, Gießen, Halle/Saale, Hamburg, Heidelberg, Jena, Kiel, Leipzig). We used R (version 4.2.2) and the R packages *meta* (version 6.0.0) and *metamedian* (version 0.1.5) for the meta-analyses [20–22].

2.2 Tailoring the POLAR_MI framework to our research project

2.2.1 Inclusion criteria, outcomes and further definitions. Overall inclusion criterion of the research project: For our research project, encounters had to fulfil the POLAR_MI-wide inclusion criteria listed in section 2.1.1. In addition, encounters had to have at least one documented 7-character Anatomical Therapeutic Chemical (ATC) code. Encounters fulfilling these criteria constituted our research project population.

Outcomes and outcome-related inclusion criteria: We considered two clinically relevant outcomes: (1) documented upper gastrointestinal (GI) bleeding and perforations as an AE and (2) documented drug-related hypoglycaemia as an ADE. Subsequently, the outcomes are only called “GI bleeding” and “drug-related hypoglycaemia”. The classification as “clinically relevant” was based on an expert consensus process [23]. The decision in favour for these two outcomes

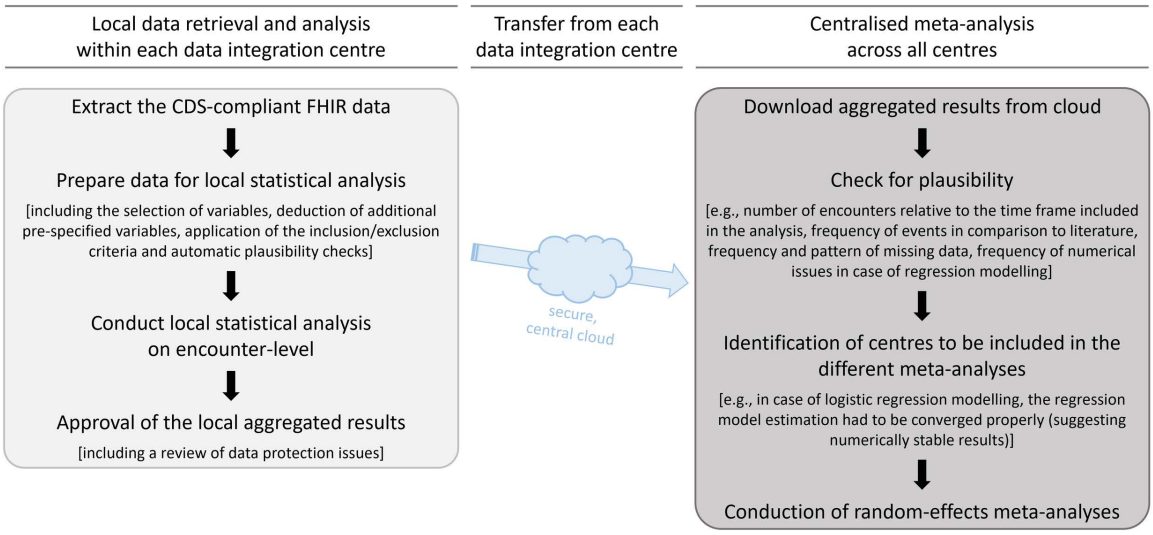

Fig 1. The POLAR_MI ETL Pipeline in a nutshell: A short illustration of the applied two-step distributed analysis approach. For both steps, the sequence of the related tasks (including examples for clarification) is provided. Abbreviations: CDS, core data set; ETL, extract – transform – load.

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was made as they could be defined by different CDS resources, thus enabling the evaluation of the feasibility of regression modelling in general and the impact of including laboratory values in such analyses. In more detail, GI bleeding was defined based on diagnoses according to the German Modification of the International Statistical Classification of Diseases and Related Health Problems (10th Revision; ICD-10-GM). Hypoglycaemia was defined via laboratory values using the Logical Observation Identifiers Names and Codes (LOINC). To assess the impact of considering the AE hypoglycaemia as drug-related, encounters had to have at least one documented antihyperglycaemic drug. Encounters fulfilling this additional inclusion criterion constituted the population considered for analyses related to the outcome drug-related hypoglycaemia. There was no additional inclusion criterion for the outcome GI bleeding, so that the population used for analyses related to this outcome was identical to the overall population of our research project. For convenience, we refer to each of these outcome-related populations as the "study population" for the respective outcome. The exact definitions of the outcomes and the outcome-related inclusion criteria are provided in Table A in S2 File.

Further variable definitions: Besides the variables covered by the inclusion criteria and the outcomes, we required additional variables related to specific medications, diseases, and laboratory values as covariates for the regression models (see section 2.2.2). The definitions and related assumptions for all variables are given in Table A in S2 File. In general, only documented information on the variables could be used.

Additional preparations: We reviewed all applied classification systems for code changes between 2018 and 2021. Due to the heterogeneity in the presentation of laboratory values across centres, it was additionally necessary to provide information on unit conversion, as presented in Table B in S2 File.

2.2.2 Statistical EHR data analysis via meta-analysis. Population description: We provide population descriptions for both study populations. Relevant encounter characteristics are summarised as median and relative frequency, respectively, with 95% confidence interval (95% CI), accompanied by the number of encounters having information on the respective characteristic. The description is provided overall as well as stratified by the respective outcome. Note, that the frequencies of outcomes and distributions of covariates were assessed both as simply documented and considering the chronology of covariate and outcome, i.e., the covariate value had to be documented on admission and the outcome only during the hospital stay (see Table A in S2 File).

Regression modelling: We applied uni- and multivariable logistic regression modelling for each binary outcome to assess its association with selected covariates. The covariates were selected to account for both varying strength of association with the respective outcome and several underlying CDS resources, in order to assess the feasibility of regression modelling in the context of distributed analysis. For each model, encounters were excluded if they had a missing value for at least one variable in the respective model. The meta-analysis was based on the locally derived regression coefficients and the related variance-covariance structure, so that we received the pooled results for the complete regression model. Besides the univariable regression models for each covariate, we built two multivariable models for each outcome: the "base model" and the "extended model". The base model comprised demographics and information derived from medications and diagnoses, while the extended model additionally included laboratory values, which were expected to be more difficult to obtain across centres. The covariates defining the regression models are provided in Table 2. Note that the chronology of covariates and outcomes was not considered for regression modelling (for reasons, see results section 3.3.2) and, thus, the information on the outcome and the covariates only had to be documented. For each meta-analysed model, we provide the number of encounters included in the model, the (adjusted) odds ratios (OR) with 95% CI as well as the Akaike-Information-Criterion (AIC), the Bayesian-Information-Criterion (BIC), and the I^2 statistic to measure heterogeneity. In addition to the number of encounters included in each model, we provide for each variable the number of encounters with missing information for the respective variable and an overview of the patterns of missing information across all variables (including the frequencies of their occurrences). Furthermore, we summarise local model performance indices for each model. Namely, we provide the proportion of centres with likelihood ratio (LR) test p-value below 0.05, the median area under the receiver operating characteristic curve (ROC AUC) and the median variance inflation factor (VIF). The median is accompanied by the first and third quartile (Q1, Q3).

Definition of centre subgroups: For each centre, local results were checked for plausibility. For the population description, the number of encounters as well as median and relative frequencies were compared to expectation and literature. In case of inconsistencies, results were checked and explanations searched. For regression models, results were checked for numerical stability. Stability was assumed if the standard errors (SE) were reasonable, i.e., the magnitude of the SE was not larger than the magnitude of the coefficient. Only numerically stable multivariable regression models were considered for the subsequent analyses. As numerically stable estimations of both models were not possible at each centre, several meta-analyses based on different centre subgroups were performed. The definitions of these analyses are provided in

Table 2. Covariates included in the base and the extended model, respectively, for each outcome.

Covariates in …	Outcome	
	GI bleeding	**Drug-related hypoglycaemia**
… base model	Inclusion of • age, in 10 years • gender • NSAID • ASA • SSRI • bisphosphonate • liver disease	Inclusion of • age, in 10 years • gender • any insulin • long-acting insulin • heart failure • type of DM
… extended model	Base model extended by • AST increased • ALT increased • serum albumin decreased • haemoglobin decreased • creatinine, in mmol/L	Base model extended by • serum albumin decreased • creatinine, in mmol/L

The exact definitions are provided in Tables A and B in S2 File. Abbreviations: ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; DM, diabetes mellitus; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

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Table 3. Based on these analyses, the impact of including different number of centres can be analysed by comparing the analyses (B1.a) and (H1.a) with the analyses (B1.b) and (H1.b), respectively. The influence of including laboratory values in multivariable models can be assessed by comparing the results of the base model and the extended model within (B1.b) and (H1.b). The analyses (B1.c) and (H1.c) were constructed to examine how the results are affected when the chronology of covariate and outcome is considered. Therefore, these analyses were based on the centres that were also included in the analyses (B1.a) and (H1.a), respectively.

3. Results

3.1 Availability of local results for meta-analysis

The number of centres and corresponding encounters constituting the research project populations for the defined analyses (Table 3) are given in Fig 2. Overall, for both outcomes, the requirement of laboratory values was a frequent limiting factor for receiving stable results from regression modelling. As the latter formed the basis for the inclusion of a centre into the respective meta-analysis, this circumstance led to the exclusion of centres.

3.2 Availability of encounters for meta-analysis

For the outcome GI bleeding, there was no outcome-related inclusion criterion, so that the study population for this outcome was identical to the population of our research project (see Fig A in S3 File). The hypoglycaemia-related inclusion criterion of at least one documented antihyperglycaemic drug, required for this AE to be considered as drug-related, induced the exclusion of about 85% of the encounters (see Fig B in S3 File). For example, in the analysis (H1.a), out of the 295,609 encounters that constituted the research project population, 44,101 encounters remained in the study population (see Fig B in S3 File). Besides these encounter exclusions, missing laboratory values were the most common reason for encounter exclusions for both outcomes (see Figs A and B in S3 File). The proportion of encounters with missing laboratory values can be directly assessed by moving from the study population to the population underlying the extended model estimation for the outcome GI bleeding in the analysis (B1.b). There, the number of encounters was reduced by approximately 75% due to missing laboratory values (see Fig A in S3 File). For the outcome drug-related hypoglycaemia, the extent of the impact of a missing blood glucose laboratory value cannot be exactly quantified, as it was one of several reasons for excluding encounters when moving from the study population to the base model population (see Fig B in S3 File). However, requiring laboratory values other than blood glucose in the analysis (H1.b) almost halved the size of the extended model population compared to the size of the base model population (see Fig B in S3 File). Details on the

Table 3. Definitions of the analyses for both outcomes.

Analysis	Inclusion criteria	
	multivariable model(s)	chronology
Outcome: GI bleeding		
(B1.a)	base	none
(B1.b)	base, extended	none
(B1.c)*1		yes
Outcome: Drug-related hypoglycaemia		
(H1.a)	base	none
(H1.b)	base, extended	none
(H1.c)*1		yes

For each analysis, all centres with stable results for the respective models were included, if not stated otherwise. * 1 Same centres as in (B1.a) and (H1.a), respectively. Abbreviation: GI, gastrointestinal.

https://doi.org/10.1371/journal.pdig.0000892.t003

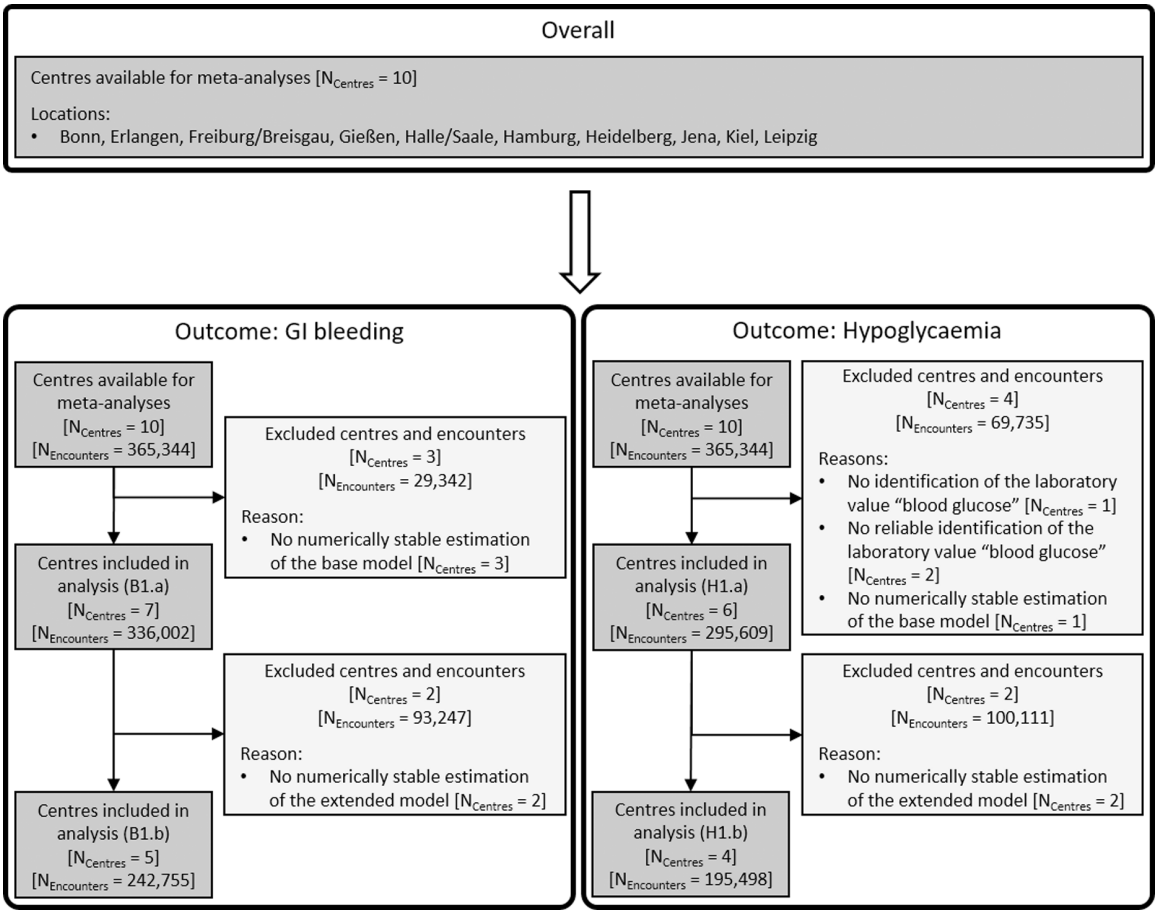

Fig 2. Flowchart visualising the inclusion of centres and encounters within the analyses. Numbers of included and excluded centres ($N_{Centres}$) are provided, with reasons for exclusion. In addition, the numbers of encounters ($N_{Encounters}$) constituting our research project population in the related analyses are provided. The definitions of the analyses are given in Table 3.

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pattern of missing information, i.e., the interplay of different variables (outcomes, independent variables included in the regression models) in inducing a specific constellation of missing information, are provided in Tables C–H in S2 File.

3.3 Frequencies of outcomes and distributions of covariates

In terms of outcome frequencies and covariate distributions, feasibility included two aspects: (1) availability of the respective information and (2) plausible distributions across encounters with the available information. Here we provide the meta-analysed population descriptions, including the impact of considering laboratory values and the chronology of events. The related plausibility of the distributions is examined in the discussion section.

In the analysis (B1.a), we found that 1.2% (95% CI: 0.8% to 1.7%) of encounters had a documented GI bleeding (see Fig 3). A liver disease was documented for 5.8% (4.2%, 8.1%) of all encounters. In terms of medications, the frequency of a documented NSAID was lower in the subgroup of encounters with a documented GI bleeding compared to encounters without a documented GI bleeding. Among laboratory values, decreased haemoglobin was the most common abnormal laboratory value, documented in 55.9% (49.4%, 62.2%) of all encounters. The complete meta-analysed cohort description for the analysis (B1.a) is provided in Table I in S2 File.

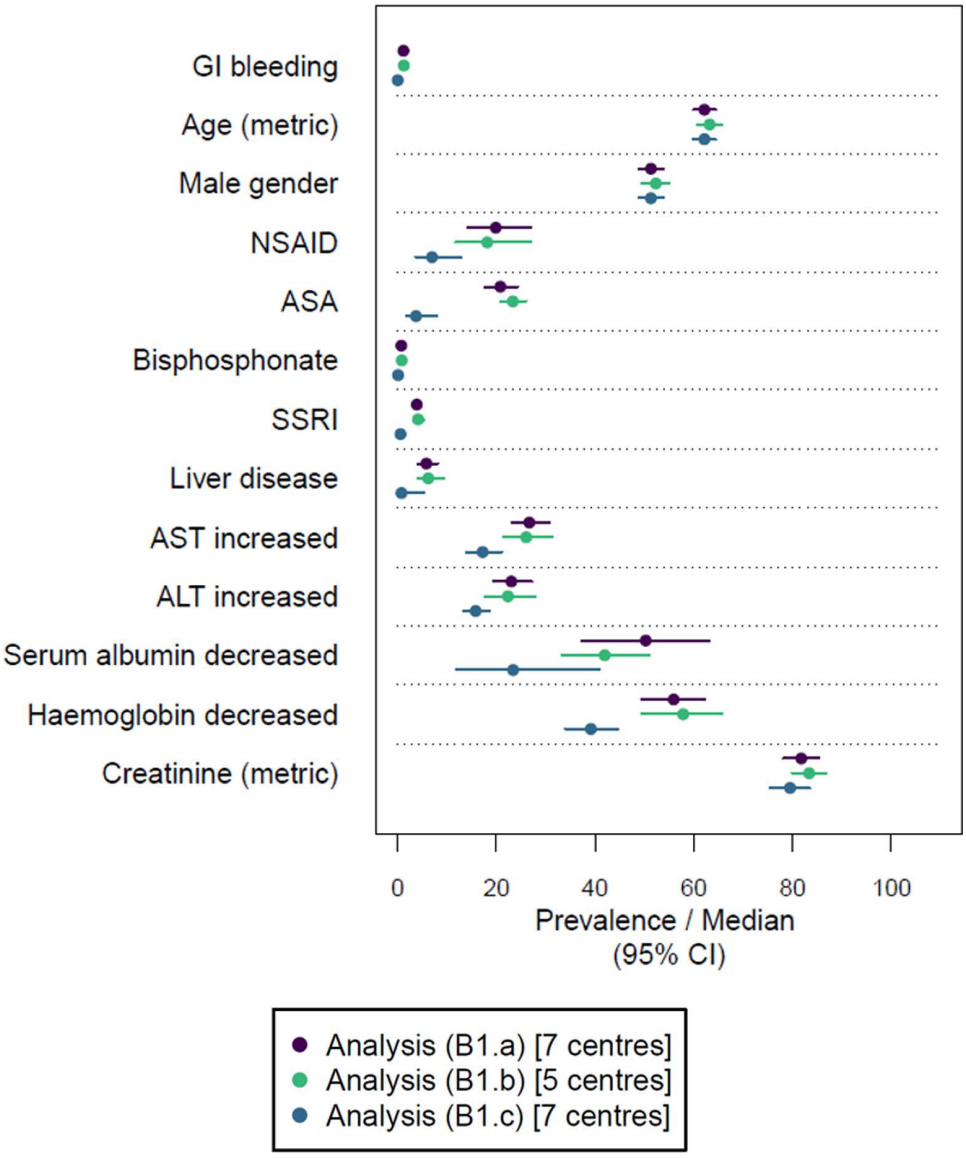

Fig 3. Meta-analysed description of encounter characteristics for the outcome GI bleeding in the study population. Prevalence is provided for categorical variables and median values for metric variables (only age in years and creatinine in μmol/L). Estimates are accompanied by 95% confidence intervals (CI). Descriptions are provided for the analyses (B1.a), (B1.b) and (B1.c). Note that the same centres were included in the analyses (B1.a) and (B1.c). The complete results of the cohort descriptions are provided in Tables I–K in S2 File. The definitions of the analyses are provided in Table 3. Further abbreviations: ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

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In the analysis (H1.a), 2.9% (2.2%, 4.0%) of encounters exhibited the outcome drug-related hypoglycaemia (see Fig 4). Although the inclusion criterion was the documentation of at least one antihyperglycaemic drug, 25.3% (18.8%, 33.3%) of encounters had no documented diabetes mellitus (DM). Type 1, type 2, and other types of DM were documented for 2.4% (1.9%, 3.0%), 68.9% (61.2%, 75.7%) and 2.9% (2.3%, 3.6%) of encounters, respectively. The complete meta-analysed cohort description of the analysis (H1.a) is provided in Table L in S2 File.

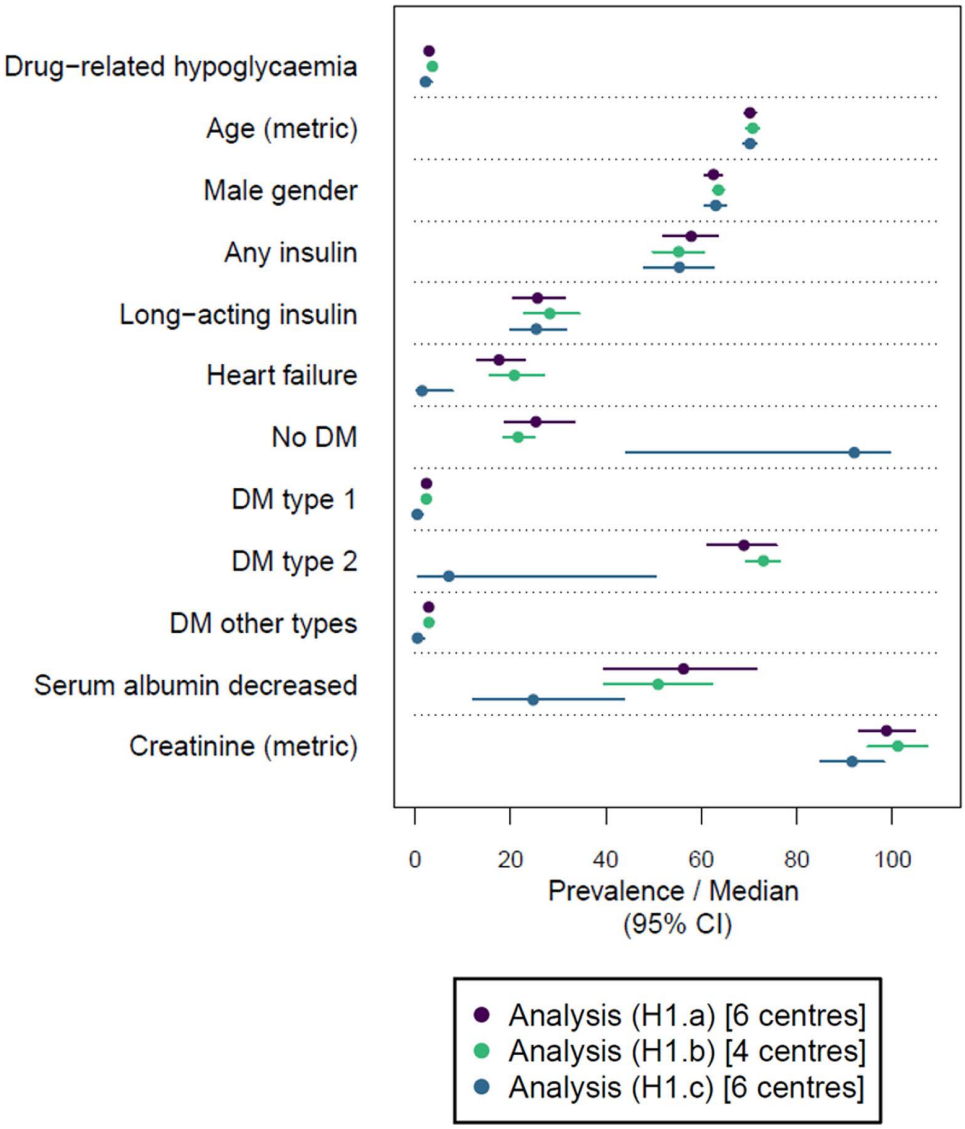

Fig 4. Meta-analysed description of encounter characteristics for the outcome drug-related hypoglycaemia in the study population. Prevalence is provided for categorical variables and median values for metric variables (only age in years and creatinine in μmol/L). Estimates are accompanied by 95% confidence intervals (CI). Descriptions are provided for the analyses (H1.a), (H1.b) and (H1.c). Note that the same centres were included in the analyses (H1.a) and (H1.c). The complete results of the cohort descriptions are provided in Tables L–N in S2 File. The definitions of the analyses are provided in Table 3. Further abbreviation: DM, diabetes mellitus.

https://doi.org/10.1371/journal.pdig.0000892.g004

3.3.1 Influence of considering laboratory values. The point estimates of the prevalences observed in the analyses (B1.a) and (H1.a) were similar to those found in the analyses (B1.b) and (H1.b), respectively, in which less centres were included due to the consideration of laboratory values (see Figs 3 and 4). The complete meta-analysed cohort descriptions for the analyses (B1.b) and (H1.b) are provided in Tables J and M in S2 File, respectively.

3.3.2 Influence of considering the chronology of events. The comparisons between the analyses (B1.a) and (B1.c) as well as the analyses (H1.a) and (H1.c) allow the examination of consequences when considering the chronology of events, i.e., the covariates' timestamp had to be identical to the day of admission (day 1 of hospital stay) and the outcomes' timestamp had to be between day 2 of hospital stay and the day of discharge.

When considering the chronology of events, the prevalence estimates of both outcomes and all covariates decreased (see Figs 3 and 4). For example, a GI bleeding was documented during hospital stay for only 0.02% (0.01%, 0.06%) of encounters according to the analysis (B1.c), corresponding to a reduction of encounters with a documented GI bleeding of approximately 98% compared to the analysis (B1.a), highlighting that most GI bleedings were present on admission, rather than hospital-onset GI bleedings (see Tables I and K in S2 File). For the outcome drug-related hypoglycaemia, the inclusion criterion was less frequently fulfilled. As a result, less than 50% of the encounters that could be included in the analysis (H1.a) could be included in the analysis (H1.c) (see Tables L and N in S2 File). In addition, the proportion of encounters with missing blood glucose information increased in the analysis (H1.c). Due to the substantial sample size reduction observed for both outcomes when considering the chronology of events, regression modelling considering this chronology was not yet performed.

3.4 Regression analyses

In our project, the feasibility of regression modelling included two aspects: (1) stable regression model estimation and (2) regression results consistent with the literature. We will come back to the latter aspect in the discussion section. Here, we present the meta-analysed regression results and the observed impact of including laboratory values. The results of the meta-analysed uni- and multivariable regression analyses for the outcomes GI bleeding and drug-related hypoglycaemia are given and illustrated in Figs 5 and 6, respectively.

In the analyses (B1.a) and (H1.a), all selected diagnoses, laboratory values and medications, except of NSAID, were univariably associated with a higher chance of exhibiting the respective outcome. In the multivariable base model of analysis (B1.a), SSRI and liver disease remained associated with a higher chance of exhibiting a GI bleeding, while for the outcome drug-related hypoglycaemia, any insulin, heart failure and all types of DM remained associated with this outcome in the analysis (H1.a). Encounters with a documented NSAID were less likely to exhibit a documented GI bleeding in all univariable and multivariable models, a seemingly implausible result which will be discussed in section 4.1. The complete meta-analysed regression modelling results of the analyses (B1.a) and (H1.a), including detailed information on the observed substantial heterogeneity ($I^2 > 75\%$), are provided in Tables O and Q in S2 File.

3.4.1 Influence of considering laboratory values. When adjusting for laboratory values in the extended models of the analyses (B1.b) and (H1.b) and compared with the base models of the same analyses (see Figs 5 and 6), evidence for the associations of male gender with GI bleeding as well as of age and heart failure with drug-related hypoglycaemia were no longer observed in the extended models. In contrast, after adjusting for laboratory values, encounters with a documented ASA were less likely to exhibit a documented GI bleeding. Regarding the laboratory values themselves, all included abnormal laboratory values were univariably associated with a larger chance of having the related outcome documented. In the extended model of the outcome GI bleeding, we no longer observed evidence for an association with increased AST and ALT. For both outcomes, the heterogeneity was moderate for the extended models. The complete meta-analysed regression modelling results of the analyses (B1.b) and (H1.b) are provided in Tables P and R in S2 File.

3.4.2 (Local) model performance. We also assessed selected model performance measures (see Tables O–R in S2 File). To answer the question of whether the model including covariates had locally a better fit than the intercept-only model, the likelihood-ratio (LR) test was used. A better fit for the model with covariates was indicated, if the related p-value was below 0.05. For some univariable models, the p-value of the local LR test was not below 0.05 in all centres, even though the covariate was associated globally (in the related meta-analysis) with the respective outcome. For example, when considering the variable bisphosphonates in the analysis (B1.a), this variable was associated with the outcome GI bleeding in the meta-analysis, but the p-value of the local LR tests was only in one centre below 0.05. For the multivariable models, the local LR test results coincided across all centres (all LR test p-values below 0.05). When comparing the multivariable base model and the multivariable extended model within one analysis, AIC and BIC calculated for the meta-analysed regression models indicated a better fit for the base model. Comparing the first quartile

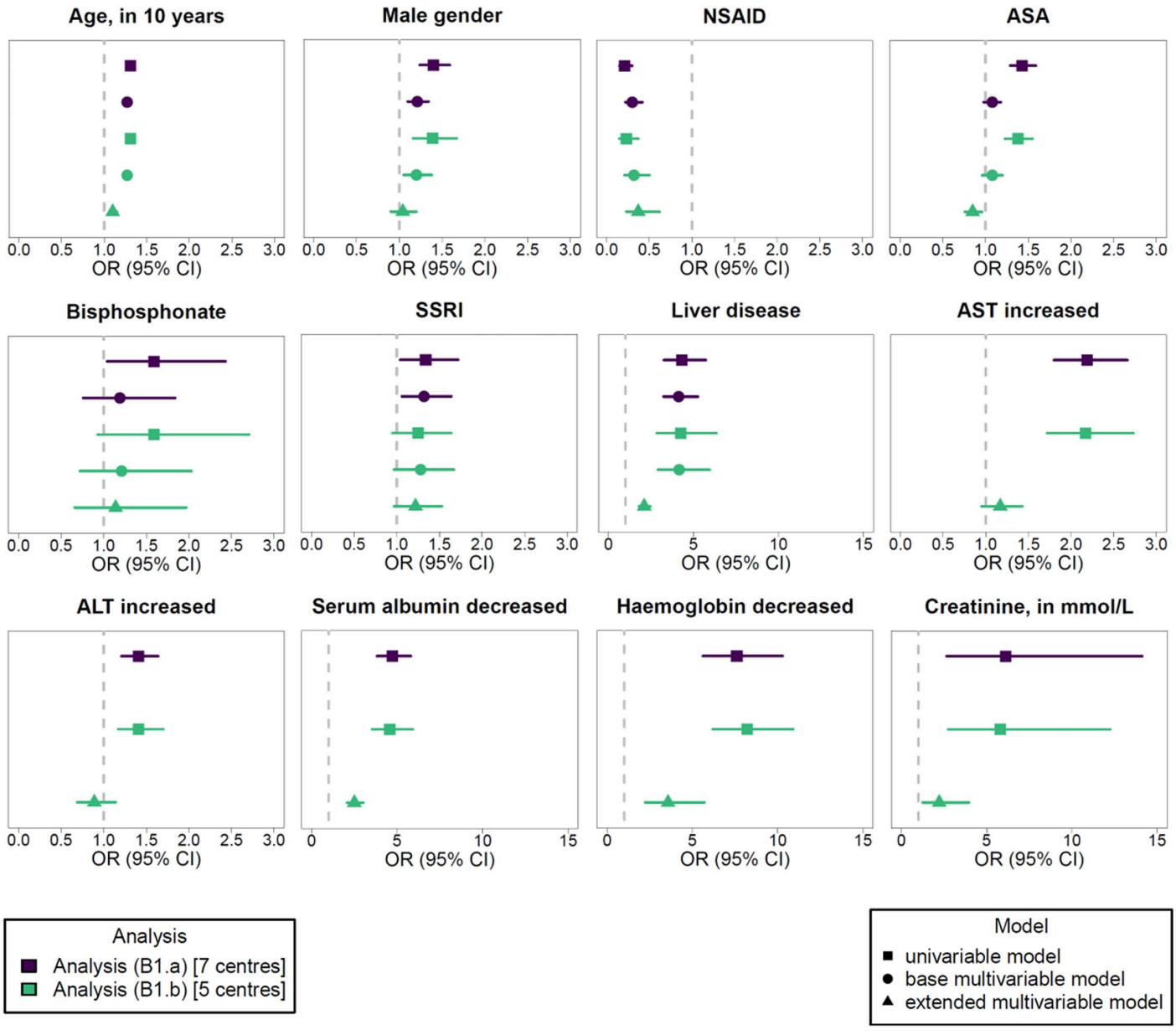

Fig 5. Meta-analysed regression modelling results for the outcome GI bleeding. Odds ratios (OR) with 95% confidence intervals (CI) are given. Results are provided for the analyses (B1.a) and (B1.b). The results of the univariable and multivariable models are provided stratified by the variables included in the extended model. The OR of 1 is indicated by the dashed line. Note that laboratory values were only included in the extended model. The complete results of the regression modelling are provided in Tables O and P in S2 File. The definitions of the analyses are provided in Table 3. Further abbreviations: ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

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of the locally assessed ROC AUC of the extended model to the base model for both outcomes, the extended model exhibited larger values. In general, for the outcome GI bleeding, the extended model of the analysis (B1.b) exhibited a first quartile of the ROC AUC above 0.7. For the outcome drug-related hypoglycaemia, this held for all multivariable models.

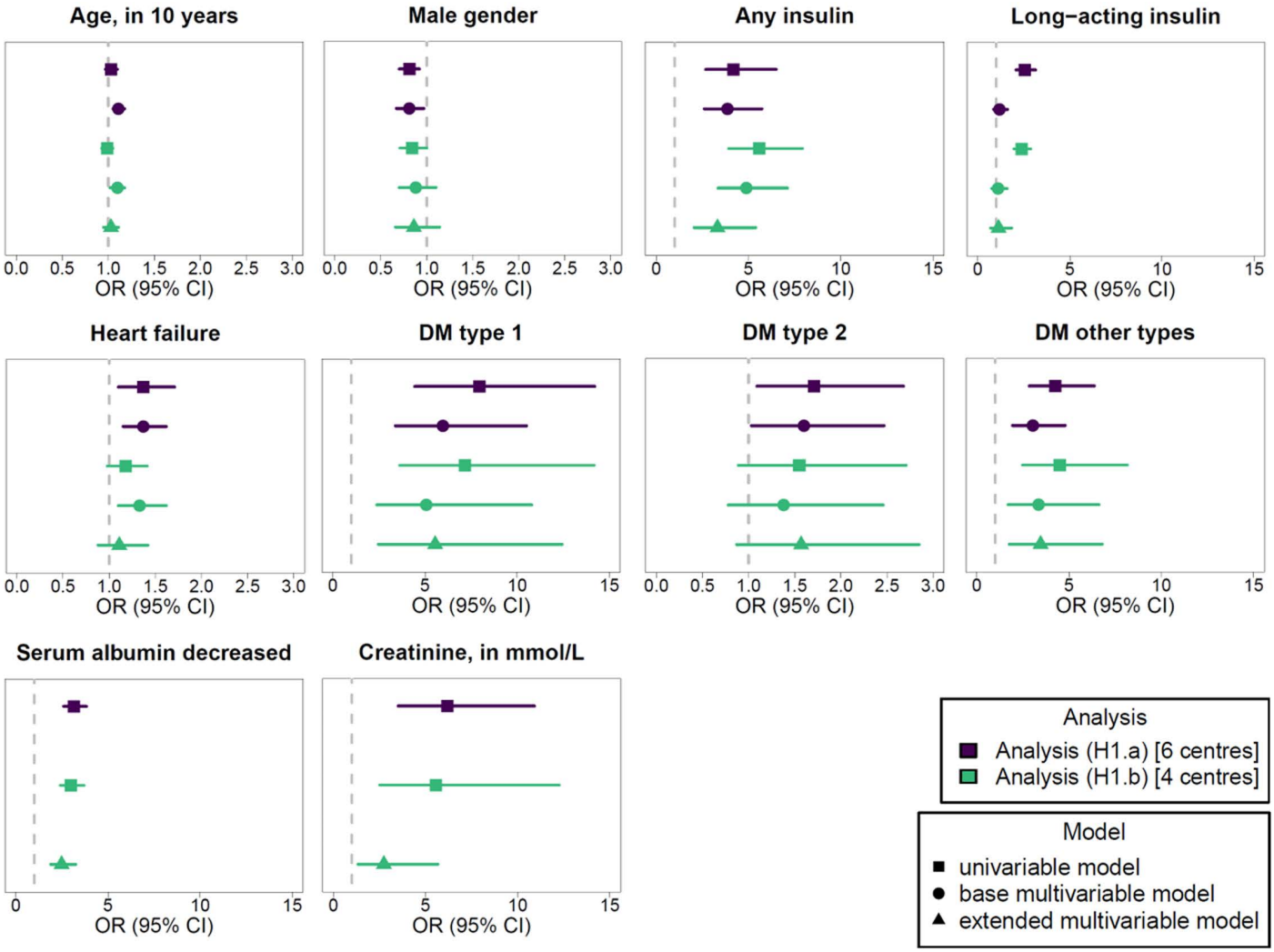

Fig 6. Meta-analysed regression modelling results for the outcome drug-related hypoglycaemia. Odds ratios (OR) with 95% confidence intervals (CI) are given. Results are provided for the analyses (H1.a) and (H1.b). The results of the univariable and multivariable models are provided stratified by the variables included in the extended model. The OR of 1 is indicated by the dashed line. Note that laboratory values were only included in the extended model. The complete results of the regression modelling are provided in Tables Q and R in S2 File. The definitions of the analyses are provided in Table 3. Further abbreviation: DM, diabetes mellitus.

https://doi.org/10.1371/journal.pdig.0000892.g006

4. Discussion

Within our research project, we aimed to investigate the feasibility of distributed regression modelling for detecting and predicting upper GI bleeding and drug-related hypoglycaemia using routine healthcare data from German university hospitals. We applied the POLAR_MI ETL Pipeline at the DIC of the respective hospitals, evaluating patient characteristics and estimating numerically stable regression models in a privacy-compliant manner via the MII core data set (CDS) without direct data access for the analysts. To achieve this, we tailored our research question to the available data by questioning the integration of the chronology of events and by using a step-by-step approach for regression modelling. For the latter, we started with univariable models, moved to a model including demographics, medications and diagnoses, and finally to the desired model adding laboratory values.

4.1 Plausibility of results without considering laboratory values or the chronology of events

The demographics of the study population for the outcome GI bleeding can be compared to the German hospital statistics for the year 2022, showing that the distributions of age and gender were comparable [24]. The prevalences of the documented diagnoses GI bleeding and liver disease were also comparable to those in the literature [25,26]. For the outcome drug-related hypoglycaemia, applying the outcome-specific inclusion criterion of taking at least one antihyperglycaemic drug, which can be seen as a proxy for having DM, resulted in an older study population comprising more men than women. This is consistent with the literature on the demographics of patients with DM in Germany [27].

As all selected covariates are discussed in the literature as risk factors for the respective outcome, the fact that all selected diagnoses, laboratory values and medications, with the exception of NSAID, were at least univariably associated with a higher chance of the respective outcome demonstrates the feasibility of regression modelling (in terms of effect direction, effect size and statistical power) [28–36]. For the outcome GI bleeding, decreased haemoglobin had the strongest association of all covariates, which is in line with expectations and the current literature, as decreased haemoglobin is the physiological consequence of GI bleeding [37,38]. For the outcome drug-related hypoglycaemia, type 1 DM had the strongest association, which is also in line with the current medical knowledge, as hypoglycaemia is more common in patients with type 1 DM than in those with type 2 DM [36,39,40]. Covariates that are more controversial in the literature regarding their association with the outcome, e.g., SSRI and bisphosphonates for GI bleeding or female gender for drug-related hypoglycaemia, only showed an association in analyses with more centres, i.e., analyses with a larger sample size and thus more statistical power [30,32,34,41].

Among the medications evaluated, encounters with a documented NSAID were less likely to exhibit a documented GI bleeding in all analyses (estimated prevalences and regression modelling), being the only seemingly unplausible result [42–44]. A possible explanation for this observation is that most of the observed GI bleedings may have been present on admission. Therefore, NSAID may not have been administered during the hospital stay or may have been discontinued on admission prior to any medication documentation in patients admitted with GI bleeding, as drug labels list previous or acute GI bleedings as contraindications of NSAID, recommending their discontinuation [45,46].

4.2 Consideration of laboratory values

When integrating laboratory values into an analysis, there are several aspects to consider regarding their missing values. First, there are different prerequisites for requesting a specific laboratory value (e.g., ward type, medical specialty, comorbidity), meaning that not every laboratory value is requested for every encounter. Second, the definition of "missing information" differs from that used for diagnoses, for example. For diagnoses, information for a specific disease is missing if the respective FHIR resource is unavailable or empty. For laboratory values, such a general assessment of missing information is not possible. The decision must be made separately for each laboratory value. The individual decision is based on the absence of any of the specified LOINC codes for that specific laboratory value in the CDS data. For example, if no blood glucose value was obtained for an encounter, we categorised the encounter as having missing information on blood glucose. Finally, missing values could be influenced by laboratory systems not connected to the DIC, difficulties in mapping internal coding to LOINC codes, and unexpected LOINC codes or units, despite our attempts in unit conversion and overarching LOINC code specification. These circumstances led to varying amounts of encounters with missing values among the laboratory values considered. However, when comparing the study populations, the exclusion of centres due to missing laboratory values or unstable extended model estimation (including laboratory values) seems to have had no substantial effect on the distribution of outcomes and covariates, which may indicate that the centres were not that different in terms of their cohort characteristics. Overall, the prevalence of decreased haemoglobin stood out, with over 50% of encounters being anaemic, which is in line with the literature as we used the World Health Organisation's high threshold [47].

Despite the missing values, regression modelling with laboratory values was possible and resulted in plausible results. The effect directions in the base models did not differ between analyses requiring laboratory values and those without

(comparisons: base model between the analyses (B1.a) and (B1.b) as well as between (H1.a) and (H1.b)). After the adjustment for laboratory values in the extended models, only the associations of male gender with GI bleeding as well as of age and heart failure with drug-related hypoglycaemia were no longer observed, probably because of reduced statistical power due to the lower number of encounters included. The enzymes AST and ALT, which indicate liver diseases, exhibited an association with GI bleeding in the univariable models, but not in the multivariable model when adjusted for liver disease, which is reasonable [31]. To summarise, the strengths and directions of the associations were mostly maintained when adjusting for laboratory values that caused a reduction in sample size.

4.3 Consideration of the chronology of events

We have made several attempts to incorporate the chronology of covariates and outcomes in the regression models. This kind of analysis requires precise, interpretable timestamps. In our case, the requirement for such timestamps led to a substantial reduction in sample size, so we did not pursue regression modelling considering timestamps in this work, but we plan to return to this issue in the ongoing follow-up project called INTERPOLAR (INTERventional POLypharmacy-drug interActions-Risks) [48].

Possible reasons for our observations are manifold. First, reimbursement of treatments in Germany is based on coded diagnoses. The data for this purpose are coded retrospectively, mostly after discharge, without specifying whether the coded condition was present on admission or occurred during the hospital stay [49,50]. Therefore, although diagnoses may have been present on admission, their timestamps are often delayed. For example, liver disease, heart failure and DM are chronic conditions and their reduction in prevalence when assessed only on day 1 of hospitalisation cannot be explained by diagnoses first identified during the stay. Second, ambiguous filling of mandatory timestamps occurred. For example, in the case of laboratory values, identical timestamps were provided for sampling, ordering the service, sample receipt, analysis and result transmission. Third, the same event was coded more than once at different times, e.g., a GI bleeding was coded on admission and during hospital stay. Finally, timestamps were sometimes set to unknown or were not present.

4.4 Implications for predictive modelling

We estimated multivariable regression models with a median ROC AUC above 0.7. Thus, our original purpose of building models to predict ADE seems possible under certain conditions. However, the decision on which outcomes and independent variables to include in the regression models must always be made weighing medical plausibility, predictive value and sufficient statistical power, as the unavailability of certain variables can induce a considerable loss in sample size and statistical power. Interestingly, when summarising the local ROC AUC values, a better predictive performance was indicated for the extended models considering laboratory values, but the AIC and BIC for the meta-analysed regression models were better for the models without laboratory values, indicating that the penalty term for more variables dominated.

When developing models to predict ADE, a development and a validation dataset are required. Based on the data within the MII, there are generally two approaches to obtain these two datasets. First, a subset of centres (one or more) can be used for model development and the remaining centres for model validation. Second, both model development and model validation can be done in all centres if the dataset is split at a certain point in time. For example, data available at the start of the study can be used for model development and data collected during (and after) model development can be used for model validation. Of course, it is also possible to rely entirely on retrospective data, i.e., data available at study begin. Both approaches (“splitting by centre” and “splitting by time”) have advantages and disadvantages. Splitting by centre – especially if only one centre is used for model development and all others for validation – would facilitate implementation in the context of distributed analysis. Splitting by time would probably lead to more generalisable results, as the development would take place in all centres, taking into account the heterogeneity of the centres.

4.5 Strengths and limitations

For the first time in Germany, the feasibility of evaluating patient characteristics and regression modelling in a privacy-preserving, multicentre, distributed analysis based solely on the data interoperability standards of the MII at the DIC was investigated. We obtained plausible results from a broad dataset reflecting routine healthcare in German university hospitals, which clearly demonstrates the potential of analyses within the MII. Here, one must always bear in mind that we only evaluated two different outcomes. However, these selected outcomes reflected different CDS resources (diagnoses, laboratory values), enabling the assessment of the impact of including laboratory values. In addition, one must keep in mind that we worked with EHR data from 2018 to the end of 2021 and the related MII CDS specifications (version 1.0). In the meantime, the implementation of the CDS version 2.0 is spreading. The extent to which this will improve the potential of such analyses is being investigated in the INTERPOLAR project [48]. Furthermore, the EHR data used were coded for purposes other than research, (documentation) routines varied between centres and wards, and the available data also depended on the way of implementing the MII CDS specifications. This introduced a non-negligible amount of not randomly missing information and heterogeneity (encountered through random-effects meta-analyses) in the received local results, which was related to the reported numbers of patients, encounters, medications, diagnoses, laboratory values and missing values. In particular, missing information on laboratory values affected the statistical power through limiting the number of encounters and centres included in some meta-analyses, and the inability to integrate timestamps in the models affected their predictive value when aiming at predicting ADE based on risk factors present prior to the event. The latter impact on model fit cannot be reflected by any comprehensive evaluation of performance metrics, as missing timestamps affect the contextual value of the models in terms of chronological order. Being aware of these issues and the original purpose of the documented data, we focused in particular on (1) risk factors reflecting both the varying strength of association with the respective outcome and the availability of information based on different CDS resources, and (2) the construction of regression models of varying complexity. This allowed a reliable interpretation of the results despite the issues mentioned above, as in this way results that were not consistent with the literature and issues related to available timestamps could be explained by the data structure and data availability. This led to important insights that will also guide improvements of the MII CDS specifications, thus enhancing interoperability in Germany.

5. Conclusions

German inpatient treatment data from university hospitals with different HIS infrastructures were made accessible in a privacy-preserving manner for AE and ADE evaluation and regression modelling. Using a distributed analysis approach without direct data access for the analysts, we received plausible estimates for prevalence and regression modelling odds ratios. We conclude that the development of predictive models for ADE in a distributed setting is possible across many institutions if the research questions can be tailored meaningful to the infrastructure and data available.

Supporting information

S1 File. Membership list of POLAR_MI.
(PDF)

S2 File. Supplemental tables.
(PDF)

S3 File. Supplemental figures.
(PDF)

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Supporting information file S1: Membership list of POLAR_MI

Challenges in detecting and predicting adverse drug events via distributed analysis of electronic health record data from German university hospitals

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Supporting information file S2: Supplemental tables

Challenges in detecting and predicting adverse drug events via distributed analysis of electronic health record data from German university hospitals

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List of tables

Table A in S2 Supplemental tables. Definitions and assumptions for outcomes and other variables. For the definitions, the German Modification of the International Statistical Classification of Diseases and Related Health Problems (10th Revision, ICD-10-GM) was used for diagnoses, the Anatomical Therapeutic Chemical (ATC) classification system for drugs and the Logical Observation Identifiers Names and Codes (LOINC) for laboratory values. An asterisk (*) indicates that all codes beginning with that prefix have been used. Besides definitions, we provide the scale (nominal, ordinal, metric) as well as the related coding for categorical variables, reasons for missing information on the respective variable, the underlying core data set (CDS) resource and additional comments, if any. For variables related to medications, diagnoses and laboratory values, the time point or period was only applied in those analyses considering the chronology of events. For further details, we refer to Kesselmeier et al. (submitted to *PLoS Digital Health*, PDIG-D-25-00026). Further abbreviations: ∈, element of; ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; DM, diabetes mellitus; GI, gastrointestinal; NA, not available; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Variable	Definition and further information
Outcomes	
Bleeding and perforation of the upper gastrointestinal tract; referred to as "GI bleeding"	• Definition: [ICD-10-GM-Code] ∈ {K22.81, K22.3, K25.0, K25.1, K25.2, K25.4, K25.5, K25.6, K26.0, K26.1, K26.2, K26.4, K26.5, K26.6, K27.0, K27.1, K27.2, K27.4, K27.5, K27.6, K29.0, K92.0, K92.1, K92.2} • Scale: nominal (binary) • Value coding: 0 = no GI bleeding documented; 1 = GI bleeding documented • Time point / period of time (if required): during hospital stay (between day 2 and day of discharge; calendar day, not 24 hours) • Missing value: information on diagnoses not available (not assessed or no ICD-10-GM-Code documented at all or not readable in the data) • CDS resource: Condition • Comment: When considering time points, encounters were excluded if they had a coded GI bleeding on the day of admission, as it can be assumed that if a GI bleeding recured during hospitalisation, it was the same GI bleeding that was present on admission and therefore triggered by outpatient medication.
Hypoglycaemia	• Definition: [LOINC-Code] ∈ {15074-8, 14749-6, 2345-7, 2339-0, 14743-9, 39480-9, 41653-7, 32016-8, 41651-1, 41652-9, 100746-7, 39481-7, 51596-5, 74774-1, 77135-2, 72516-8, 2340-8, 2341-6, 35211-2, 6777-7} • Scale: nominal (binary) • Value coding: 0 = no hypoglycaemia documented; 1 = hypoglycaemia documented • Time point / period of time (if required): during hospital stay (between day 2 and day of discharge; calendar day, not 24 hours)

	• Missing value: LOINC codes not available (laboratory value not obtained or not documented with the appropriate LOINC code during the stay or LOINC code value not provided/readable in the data (including deviation from expected units) • CDS resource: Observation • Comment: We did not exclude encounters with a laboratory value indicating hypoglycaemia on the day of admission, as hypoglycaemia can be treated and resolved more quickly than GI bleeding, and therefore a new episode of hypoglycaemia may occur during hospitalisation. If several laboratory results were available, the most severe value (during the specified period of time) was used. For further details see Table B in S2 Supplemental tables.
Outcome-related inclusion criterion	
Antihyperglycaemic drug	• Definition: [ATC-Code] ∈ {A10*, A08AX02} • Scale: nominal (binary) • Value coding: 0 = no antihyperglycemic drug documented; 1 = antihyperglycemic drug documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: information on medication not available (no medication intake/prescription or no ATC Code documented at all or not readable in the data) • CDS resource: Medication and (MedicationAdministration or MedicationStatement). MedicationAdministration and MedicationStatement contain the administration/prescription with a reference to the medication in the CDS resource Medication. • Comment: none
Covariates for regression models	
Age, in years	• Definition: building ([day of hospitalisation] - [birthday]) and rounding down to year • Scale: metric (integer) • Value coding: none • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: day of hospitalisation or birthday missing • CDS resource: Encounter (day of hospitalization = Encounter.period.start), Patient (birthday = Patient.birthDate) • Comment: If the exact day or month of birth was missing, the first day of the month or January was used (e.g. for August 1999, 1 August 1999 was used and for 1999, 1 January 1999 was used).

Gender	• Definition: not applicable • Scale: nominal • Value coding: 0 = female; 1 = male • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: information missing • CDS resource: Patient • Comment: The local retrieval and analysis scripts were programmed to deal with gender diverse, but this gender was not coded in the analysed data.
NSAID	• Definition: [ATC-Code] ∈ {M01A*, M01BA01, R05XA10, M01BA04, M01BA05, M01BA08, C01EB03, N02AJ05, N02AJ08, N02AJ19, R01BA57, C01EB16, N02AJ14, C08CA51, L01XX33, N02AJ16, M01BA03, N02AJ02, N02AJ07, N02AJ18, N02BA01, N02BA51, N02BA71, R05XA02, R05XA22} • Scale: nominal (binary) • Value coding: 0 = no NSAID documented; 1 = NSAID documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: information on medication not available (no medication intake/prescription or no ATC Code documented at all or not readable in the data) • CDS resource: Medication and (MedicationAdministration or MedicationStatement). MedicationAdministration and MedicationStatement contain the administration/prescription with a reference to the medication in the CDS resource Medication. • Comment: none
ASA	• Definition: [ATC-Code] ∈ {B01AC06, B01AC34, B01AC36, B01AC56, B01AC86, C07FX02, C07FX03, C07FX04, C10BX01, C10BX02, C10BX04, C10BX05, C10BX06, C10BX08, C10BX12, M01BA03, N02AJ02, N02AJ07, N02AJ18, N02BA01, N02BA51, N02BA71, R05XA02, R05XA22} • Scale: nominal (binary) • Value coding: 0 = no ASA documented; 1 = ASA documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: information on medication not available (no medication intake/prescription or no ATC Code documented at all or not readable in the data) • CDS resource: Medication and (MedicationAdministration or MedicationStatement). MedicationAdministration and

	MedicationStatement contain the administration/prescription with a reference to the medication in the CDS resource Medication. • Comment: none
SSRI	• Definition: [ATC-Code] ∈ {N06AB*, N06CA03} • Scale: nominal (binary) • Value coding: 0 = no SSRI documented; 1 = SSRI documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: information on medication not available (no medication intake/prescription or no ATC Code documented at all or not readable in the data) • CDS resource: Medication and (MedicationAdministration or MedicationStatement). MedicationAdministration and MedicationStatement contain the administration/prescription with a reference to the medication in the CDS resource Medication. • Comment: none
Bisphosphonate	• Definition: [ATC-Code] ∈ {M05BA*, M05BB*} • Scale: nominal (binary) • Value coding: 0 = no bisphosphonate documented; 1 = bisphosphonate documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: information on medication not available (no medication intake/prescription or no ATC Code documented at all or not readable in the data) • CDS resource: Medication and (MedicationAdministration or MedicationStatement). MedicationAdministration and MedicationStatement contain the administration/prescription with a reference to the medication in the CDS resource Medication. • Comment: none
Any insulin	• Definition: [ATC-Code] ∈ {A10A*} • Scale: nominal (binary) • Value coding: 0 = no insulin documented; 1 = insulin documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: information on medication not available (no medication intake/prescription or no ATC Code

	documented at all or not readable in the data) • CDS resource: Medication and (MedicationAdministration or MedicationStatement). MedicationAdministration and MedicationStatement contain the administration/prescription with a reference to the medication in the CDS resource Medication. • Comment: none
Long-acting insulin	• Definition: [ATC-Code] ∈ {A10AE*, A10AD06} • Scale: nominal (binary) • Value coding: 0 = no long-acting insulin documented; 1 = long-acting insulin documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: information on medication not available (no medication intake/prescription or no ATC Code documented at all or not readable in the data) • CDS resource: Medication and (MedicationAdministration or MedicationStatement). MedicationAdministration and MedicationStatement contain the administration/prescription with a reference to the medication in the CDS resource Medication. • Comment: none
Liver disease	• Definition: [ICD-10-GM-Code] ∈ {R16.0, R16.2, C22*, Q44.6, Q44.7, C78.7, A06.4*, B67.0, B67.5, B67.8, D13.4, S36.10, S36.11, S36.12, S36.13, S36.14, S36.15, S36.16, T86.4*, Z75.67, Z75.77, B25.1*, B58.1*, B15*, B16*, B17*, B18*, B19*, I82.0, K70*, K71*, K72*, K73*, K74*, K75*, K76*, K77*, Z94.4} • Scale: nominal (binary) • Value coding: 0 = no liver disease documented; 1 = liver disease documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: information on diagnoses not available (not assessed or no ICD-10-GM-Code documented at all or not readable in the data) • CDS resource: Condition • Comment: none
Heart failure	• Definition: [ICD-10-GM-Code] ∈ {I50*, I13.0*, I13.2*, I11.0*} • Scale: nominal (binary) • Value coding: 0 = no heart failure documented; 1 = heart failure documented

	• Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: information on diagnoses not available (not assessed or no ICD-10-GM-Code documented at all or not readable in the data) • CDS resource: Condition • Comment: none

Type of diabetes mellitus (DM)	• Definition:
	  • Diabetes mellitus type 1: [ICD-10-GM-Code] ∈ {E10*}
	  • Diabetes mellitus type 2: [ICD-10-GM-Code] ∈ {E11*}
	  • Diabetes mellitus other or unspecified type: [ICD-10-GM-Code] ∈ {E12*, E13*, E14*}
	• Scale: nominal
	• Value coding: 0 = no DM documented; 1 = type 1 DM documented; 2 = type 2 DM documented; 3 = other or unspecified type of DM documented
	• Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours)
	• Missing value: information on diagnoses not available (not assessed or no ICD-10-GM-Code documented at all or not readable in the data)
	• CDS resource: Condition
	• Comment: We aimed at assessing the impact of DM type 1 and DM type 2 on the outcome. Therefore, we were not primarily interested in whether there was a co-occurrence of DM type 1 or 2 with "other or unspecified" type of DM. Furthermore, we did not initially expect the co-occurrence of DM type 1 and DM type 2, so one variable was created to gather the desired information. However, we observed the co-occurrence of different types of DM, so the following rules applied when encounters were diagnosed with more than one type of DM:
	  • If a type 1 DM and a type 2 DM were documented, the variable was set to unknown (NA). Thus, these encounters were excluded from modelling, but the number of affected encounters (and patients) was assessed.
	  • If a type 1 DM and an "other or unspecified type" of DM were documented, the variable was set to type 1 DM.
	  • If a type 2 DM and an "other or unspecified type" of diabetes mellitus were documented, the variable was set to type 2 DM.

AST increased	• Definition: [LOINC-Code] ∈ {1920-8, 88112-8, 30239-8, 48136-6} • Scale: nominal (binary) • Value coding: 0 = no increased AST documented; 1 = increased AST documented

	• Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: LOINC codes not available (laboratory value not obtained or not documented with the appropriate LOINC code during the stay or LOINC code value not provided/readable in the data (including deviation from expected units) • CDS resource: Observation • Comment: If several laboratory results were available, the most severe value (during the specified period of time) was used. For further details see Table B in S2 Supplemental tables.
ALT increased	• Definition: [LOINC-Code] ∈ {76625-3, 1742-6, 1743-4, 1744-2, 48134-1, 77144-4, 76625-3} • Scale: nominal (binary) • Value coding: 0 = no increased ALT documented; 1 = increased ALT documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: LOINC codes not available (laboratory value not obtained or not documented with the appropriate LOINC code during the stay or LOINC code value not provided/readable in the data (including deviation from expected units) • CDS resource: Observation • Comment: If several laboratory results were available, the most severe value (during the specified period of time) was used. For further details see Table B in S2 Supplemental tables.
Serum albumin categorised	• Definition: [LOINC-Code] ∈ {77148-5, 61151-7, 61152-5, 54347-0, 62234-0, 62235-7, 76631-1, 1751-7, 2862-1, 101198-0} • Scale: ordinal (treated as categorical variable) • Value coding: 0 = normal serum albumin documented; 1 = decreased serum albumin documented; 2 = increased serum albumin documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: LOINC codes not available (laboratory value not obtained or not documented with the appropriate LOINC code during the stay or LOINC code value not provided/readable in the data (including deviation from expected units) • CDS resource: Observation • Comment: If several laboratory results were available, the most severe value (during the specified period of time) was used. This variable was set to unknown (NA) for encounters with conflicting information (one value increased

	and another decreased on the day of interest or over the whole hospital stay). Within risk modelling, increased serum albumin and normal serum albumin were combined into one category (value coding: 0), i.e. the independent variable assessed the impact of decreased serum albumin compared to non-decreased, because increased serum albumin was rarely detected and, thus, hindered (numerically stable) estimation within regression modelling. For further details see Table B in S2 Supplemental tables.
Haemoglobin categorised	• Definition: [LOINC-Code] ∈ {20509-6, 718-7, 30350-3, 59260-0, 14775-1, 30313-1, 97550-8, 97555-7, 93846-4, 76769-9, 75928-2, 55782-7, 97556-5} • Scale: ordinal (treated as categorical variable) • Value coding: 0 = normal haemoglobin documented; 1 = decreased haemoglobin documented; 2 = increased haemoglobin documented • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: LOINC codes not available (laboratory value not obtained or not documented with the appropriate LOINC code during the stay or LOINC code value not provided/readable in the data (including deviation from expected units) • CDS resource: Observation • Comment: If several laboratory results were available, the most severe value (during the specified period of time) was used. This variable was set to unknown (NA) for encounters with conflicting information (one value increased and another decreased on the day of interest or over the whole hospital stay). Within risk modelling, increased haemoglobin and normal haemoglobin were combined into one category (value coding: 0), i.e. the independent variable assessed the impact of decreased haemoglobin compared to non-decreased, because increased haemoglobin was rarely detected and, thus, hindered (numerically stable) estimation within regression modelling. For further details see Table B in S2 Supplemental tables.
Creatinine	• Definition: [LOINC-Code] ∈ {59826-8, 14682-9, 2160-0, 21232-4, 38483-4, 77140-2, 59826-8, 44784-7, 101475-2, 35203-9} • Scale: metric • Value coding: none • Time point / period of time (if required): day of hospital admission (day 1; calendar day, not 24 hours) • Missing value: LOINC codes not available (laboratory value not obtained or not documented with the appropriate LOINC code during the stay or LOINC code value not provided/readable in the data (including deviation from

	expected units) • CDS resource: Observation • Comment: If several laboratory results were available, the most severe value (during the specified period of time) was used. For further details see Table B in S2 Supplemental tables.

Table B in S2 Supplemental tables. Additional information for laboratory value definitions. Due to the heterogeneity in the presentation of laboratory values across centres, it was necessary to identify possible units, including associated cut-off values and plausible value ranges. In some cases, conversion factors were established. Due to the heterogeneity in required decimal places, we did not unify the notation in terms of the number of decimal places provided.

Measure-related unit	Gender	Normal range		Plausibility range		Conversion factor
		Lower limit	Upper limit	Lower limit	Upper limit	
Hypoglycaemia						
mmol/L	male	3	Infinite	0.3	55.5	-
mg/dl	male	55	Infinite	5	1,000	-
mmol/L	female	3	Infinite	0.3	55.5	-
mg/dl	female	55	Infinite	5	1,000	-
AST and ALT						
U/L	male	10	50	0	Infinite	-
IU/L	male	10	50	0	Infinite	-
µmol/(min*L)	male	10	50	0	Infinite	-
µmol/(h*L)	male	600.0002	3,000.0012	0	Infinite	-
µmol/(h*mL)	male	0.5999	2.994	0	Infinite	-
umol/(min*L)	male	10	50	0	Infinite	-
umol/(h*L)	male	600.0002	3,000.0012	0	Infinite	-
umol/(h*mL)	male	0.5999	2.994	0	Infinite	-
µmol/(L*min)	male	10	50	0	Infinite	-
µmol/(L*h)	male	600.0002	3,000.0012	0	Infinite	-
µmol/(mL*h)	male	0.5999	2.994	0	Infinite	-
umol/(L*min)	male	10	50	0	Infinite	-
umol/(L*h)	male	600.0002	3,000.0012	0	Infinite	-
umol/(mL*h)	male	0.5999	2.994	0	Infinite	-
µmol/min/L	male	10	50	0	Infinite	-
µmol/h/L	male	600.0002	3,000.0012	0	Infinite	-
µmol/h/mL	male	0.5999	2.994	0	Infinite	-
umol/min/L	male	10	50	0	Infinite	-

umol/h/L	male	600.0002	3,000.0012	0	Infinite	-
umol/h/mL	male	0.5999	2.994	0	Infinite	-
µmol/L/min	male	10	50	0	Infinite	-
µmol/L/h	male	600.0002	3,000.0012	0	Infinite	-
µmol/mL/h	male	0.5999	2.994	0	Infinite	-
umol/L/min	male	10	50	0	Infinite	-
umol/L/h	male	600.0002	3,000.0012	0	Infinite	-
umol/mL/h	male	0.5999	2.994	0	Infinite	-
nkat/L	male	166.667	833.3333	0	Infinite	-
µkat/L	male	0.1667	0.8333	0	Infinite	-
ukat/L	male	0.1667	0.8333	0	Infinite	-
nmol/(s*L)	male	166.6667	833.3333	0	Infinite	-
µmol/(s*L)	male	0.1667	0.8333	0	Infinite	-
umol/(s*L)	male	0.1667	0.8333	0	Infinite	-
nmol/(L*s)	male	166.6667	833.3333	0	Infinite	-
µmol/(L*s)	male	0.1667	0.8333	0	Infinite	-
umol/(L*s)	male	0.1667	0.8333	0	Infinite	-
nmol/s/L	male	166.6667	833.3333	0	Infinite	-
µmol/s/L	male	0.1667	0.8333	0	Infinite	-
umol/s/L	male	0.1667	0.8333	0	Infinite	-
nmol/L/s	male	166.6667	833.3333	0	Infinite	-
µmol/L/s	male	0.1667	0.8333	0	Infinite	-
umol/L/s	male	0.1667	0.8333	0	Infinite	-
U/L	female	10	35	0	Infinite	-
IU/L	female	10	35	0	Infinite	-
µmol/(min*L)	female	10	35	0	Infinite	-
µmol/(h*L)	female	600.0002	2,100.0008	0	Infinite	-
µmol/(h*mL)	female	0.5999	2.0996	0	Infinite	-
umol/(min*L)	female	10	35	0	Infinite	-
umol/(h*L)	female	600.0002	2,100.0008	0	Infinite	-

umol/(h*mL)	female	0.5999	2.0996	0	Infinite	-
µmol/(L*min)	female	10	35	0	Infinite	-
µmol/(L*h)	female	600.0002	2,100.0008	0	Infinite	-
µmol/(mL*h)	female	0.5999	2.0996	0	Infinite	-
umol/(L*min)	female	10	35	0	Infinite	-
umol/(L*h)	female	600.0002	2,100.0008	0	Infinite	-
umol/(mL*h)	female	0.5999	2.0996	0	Infinite	-
µmol/min/L	female	10	35	0	Infinite	-
µmol/h/L	female	600.0002	2,100.0008	0	Infinite	-
µmol/h/mL	female	0.5999	2.0996	0	Infinite	-
umol/min/L	female	10	35	0	Infinite	-
umol/h/L	female	600.0002	2,100.0008	0	Infinite	-
umol/h/mL	female	0.5999	2.0996	0	Infinite	-
µmol/L/min	female	10	35	0	Infinite	-
µmol/L/h	female	600.0002	2,100.0008	0	Infinite	-
µmol/mL/h	female	0.5999	2.0996	0	Infinite	-
umol/L/min	female	10	35	0	Infinite	-
umol/L/h	female	600.0002	2,100.0008	0	Infinite	-
umol/mL/h	female	0.5999	2.0996	0	Infinite	-
nkat/L	female	166.667	583.3333	0	Infinite	-
µkat/L	female	0.1667	0.5833	0	Infinite	-
ukat/L	female	0.1667	0.5833	0	Infinite	-
nmol/(s*L)	female	166.6667	583.3333	0	Infinite	-
µmol/(s*L)	female	0.1667	0.5833	0	Infinite	-
umol/(s*L)	female	0.1667	0.5833	0	Infinite	-
nmol/(L*s)	female	166.6667	583.3333	0	Infinite	-
µmol/(L*s)	female	0.1667	0.5833	0	Infinite	-
umol/(L*s)	female	0.1667	0.5833	0	Infinite	-
nmol/s/L	female	166.6667	583.3333	0	Infinite	-
µmol/s/L	female	0.1667	0.5833	0	Infinite	-

umol/s/L	female	0.1667	0.5833	0	Infinite	-
nmol/L/s	female	166.6667	583.3333	0	Infinite	-
µmol/L/s	female	0.1667	0.5833	0	Infinite	-
umol/L/s	female	0.1667	0.5833	0	Infinite	-
Serum albumin						
g/L	male	35	54	10	100	-
g/dL	male	3.5	5.4	1	10	-
g/100mL	male	3.5	5.4	1	10	-
g%	male	3.5	5.4	1	10	-
mg/ml	male	35	54	10	100	-
mmol/L	male	0.5073	0.7826	0.14493	1,449.3	-
µmol/L	male	507.255	782.622	144.93	1,449.3	-
umol/L	male	507.255	782.622	144.93	1,449.3	-
g/L	female	35	54	10	100	-
g/dL	female	3.5	5.4	1	10	-
g/100mL	female	3.5	5.4	1	10	-
g%	female	3.5	5.4	1	10	-
mg/ml	female	35	54	10	100	-
mmol/L	female	0.5073	0.7826	0.14493	1,449.3	-
µmol/L	female	507.255	782.622	144.93	1,449.3	-
umol/L	female	507.255	782.622	144.93	1,449.3	-
Creatinine						
mg/dL	male	-	-	0	Infinite	0.011
mg/100mL	male	-	-	0	Infinite	0.011
mg%	male	-	-	0	Infinite	0.011
mg/L	male	-	-	0	Infinite	0.113
µg/mL	male	-	-	0	Infinite	0.113
ug/mL	male	-	-	0	Infinite	0.113
mmol/L	male	-	-	0	Infinite	0.001
µmol/L	male	-	-	0	Infinite	1

umol/L	male	-	-	0	Infinite	1
mg/dL	female	-	-	0	Infinite	0.011
mg/100mL	female	-	-	0	Infinite	0.011
mg%	female	-	-	0	Infinite	0.011
mg/L	female	-	-	0	Infinite	0.113
µg/mL	female	-	-	0	Infinite	0.113
ug/mL	female	-	-	0	Infinite	0.113
mmol/L	female	-	-	0	Infinite	0.001
µmol/L	female	-	-	0	Infinite	1
umol/L	female	-	-	0	Infinite	1
Haemoglobin						
g/dL	male	13	18	1.6	48.3	-
g/100mL	male	13	18	1.6	48.3	-
G%	male	13	18	1.6	48.3	-
mg/mL	male	130	180	16	483	-
g/L	male	130	180	16	483	-
mmol/L	male	8.07	11.17	1	30	-
g/dL	female	12	16	1.6	48.3	-
g/100mL	female	12	16	1.6	48.3	-
G%	female	12	16	1.6	48.3	-
mg/mL	female	120	160	16	483	-
g/L	female	120	160	16	483	-
mmol/L	female	7.44	9.92	1	30	-

Table C in S2 Supplemental tables. Meta-analysed description of the missing data pattern for the analysis (B1.a) of the outcome GI bleeding across seven centres. The patterns are defined by the outcome (dependent variable) and the related independent variables included in the regression models. Each row corresponds to a specific pattern, with green indicating no missing information and red indicating missing information. Abbreviations: ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; GI, gastrointestinal; ID, identifier; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Pattern ID	Outcome	Independent variables												Per pattern: number of …	
	GI bleeding	Age	Gender	NSAID	ASA	SSRI	Bisphosphonate	Liver disease	AST increased	ALT increased	Serum albumin decreased	Haemoglobin decreased	Creatinine	… missing values	… encounters
1														0	66,038
2														1	8,308
3														1	2,502
4														2	85
5														1	58,348
6														2	7,817
7														2	4,290
8														3	228
9														1	4,486
10														2	213
11														2	91
12														3	1
13														2	6,589
14														3	1,307
15														3	175
16														4	24
17														1	4,532
18														2	378
19														2	47
20														3	3
21														2	17,880
22														3	1,193
23														3	720
24														4	25
25														2	2,548
26														3	325
27														3	393
28														4	88
29														3	29,131
30														4	29,965
31														4	4,175
32														5	78,441
33														4	3
34														5	13
35														6	2

36														8	3
37														9	1
38														5	14
39														6	4
40														2	1,127
41														3	9
42														3	236
43														4	1
44														3	119
45														4	14
46														4	5
47														4	1
48														5	1
49														4	3
50														3	26
51														5	1
52														4	94
53														5	1
54														6	1
55														4	6
56														6	7
57														5	235
58														6	134
59														6	46
60														7	3,549

Per variable: number of encounters with missing information

Variable	GI bleeding	Age	Gender	NSAID	ASA	SSRI	Bisphosphonate	Liver disease	AST increased	ALT increased	Serum albumin	Haemoglobin	Creatinine	
Frequency	5,616	0	18	22	22	22	22	5,616	173,966	161,956	244,546	95,156	132,128	

Table D in S2 Supplemental tables. Meta-analysed description of the missing data pattern for the analysis (B1.b) of the outcome GI bleeding across five centres. The patterns are defined by the outcome (dependent variable) and the related independent variables included in the regression models. Each row corresponds to a specific pattern, with green indicating no missing information and red indicating missing information. Abbreviations: ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; GI, gastrointestinal; ID, identifier; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Pattern ID	Outcome	Independent variables												Per pattern: number of …	
	GI bleeding	Age	Gender	NSAID	ASA	SSRI	Bisphosphonate	Liver disease	AST increased	ALT increased	Serum albumin decreased	Haemoglobin decreased	Creatinine	… missing values	… encounters
1														0	61,317
2														1	8
3														1	1,744
4														2	11
5														1	49,678
6														2	235
7														2	1,100
8														3	26
9														1	4,240
10														2	4
11														2	14
12														3	1
13														2	5,927
14														3	14
15														3	29
16														4	5
17														1	4,411
18														2	1
19														2	32
20														3	1
21														2	16,859
22														3	11
23														3	69
24														4	4
25														2	2,265
26														3	33
27														3	295
28														4	82
29														3	21,182
30														4	8,077
31														4	1,536
32														5	57,992
33														5	14
34														6	3
35														2	1,126

36														3	234
37														3	119
38														4	5
39														5	1
40														4	3
41														3	26
42														5	1
43														4	93
44														6	1
45														4	6
46														6	7
47														5	233
48														6	120
49														6	46
50														7	3,514
Per variable: number of encounters with missing information															
Frequency	5,535	0	17	0	0	0	0	5,535	116,914	105,643	166,895	66,767	70,152		
Variable	GI bleeding	Age	Gender	NSAID	ASA	SSRI	Bisphosphonate	Liver disease	AST increased	ALT increased	Serum albumin decreased	Haemoglobin decreased	Creatinine		

Table E in S2 Supplemental tables. Meta-analysed description of the missing data pattern for the analysis (B1.c) of the outcome GI bleeding across seven centres, which were also included in the analysis (B1.a). The patterns are defined by the outcome (dependent variable) and the related independent variables included in the regression models. Each row corresponds to a specific pattern, with green indicating no missing information and red indicating missing information. Abbreviations: ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; GI, gastrointestinal; ID, identifier; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Pattern ID	Outcome	Independent variables												Per pattern: number of …	
	GI bleeding	Age	Gender	NSAID	ASA	SSRI	Bisphosphonate	Liver disease	AST increased	ALT increased	Serum albumin decreased	Haemoglobin decreased	Creatinine	… missing values	… encounters
1														0	31,034
2														1	3,335
3														1	3,896
4														2	63
5														1	37,287
6														2	5,437
7														2	2,983
8														3	154
9														1	3,684
10														2	69
11														2	228
12														3	14
13														2	3,549
14														3	2,793
15														3	113
16														4	73
17														1	1,482
18														2	307
19														2	17
20														3	7
21														2	13,444
22														3	1,842
23														3	681
24														4	48
25														2	1,003
26														3	78
27														3	149
28														4	89
29														3	16,073
30														4	23,920
31														4	2,779
32														5	171,390
33														4	3
34														5	8

35													6	4
36													8	3
37													9	4
38													5	10
39													6	8
40													1	379
41													2	39
42													2	6
43													3	1
44													2	392
45													3	31
46													3	21
47													4	1
48													2	79
49													3	2
50													3	36
51													4	12
52													2	20
53													3	4
54													3	247
55													4	171
56													4	1
57													5	1
58													3	7
59													4	1
60													4	101
61													5	265
62													5	5
63													6	503
64													2	338
65													3	5
66													3	185
67													4	2
68													3	47
69													4	11
70													4	4
71													3	1
72													4	1
73													5	1
74													4	30
75													5	4
76													6	2
77													4	2
78													5	1
79													5	1
80													6	3
81													5	271
82													6	137
83													6	112
84													7	4,458
Per variable: number of encounters with missing information														

Variable	Frequency
GI bleeding	7,941
Age	0
Gender	18
NSAID	22
ASA	22
SSRI	22
Bisphosphonate	22
Liver disease	5,616
AST increased	239,681
ALT increased	232,028
Serum albumin decreased	289,468
Haemoglobin decreased	188,016
Creatinine	215,289

Table F in S2 Supplemental tables. Meta-analysed description of the missing data pattern for the analysis (H1.a) of the outcome drug-related hypoglycaemia across six centres. The patterns are defined by the outcome (dependent variable) and the related independent variables included in the regression models. Each row corresponds to a specific pattern, with green indicating no missing information and red indicating missing information. Abbreviation: ID, identifier.

Pattern ID	Outcome	Independent variables								Per pattern: number of …	
	Drug-related hypoglycaemia	Age	Gender	Any insulin	Long-acting insulin	Heart failure	Diabetes mellitus type	Serum albumin decreased	Creatinine	… missing values	… encounters
1										0	14,108
2										1	25
3										1	16,067
4										2	2,387
5										1	55
6										2	34
7										3	1
8										2	267
9										3	40
10										4	7
11										1	909
12										2	3
13										2	1,696
14										3	7,833
15										2	5
16										3	2
17										4	21
18										4	3
19										4	42
20										5	594
21										3	2
Per variable: number of encounters with missing information											
Frequency	11,110	0	2	0	0	953	1,071	28,726	10,874		
Variable	Drug-related hypoglycaemia	Age	Gender	Any insulin	Long-acting insulin	Heart failure	Diabetes mellitus type	Serum albumin decreased	Creatinine		

Table G in S2 Supplemental tables. Meta-analysed description of the missing data pattern for the analysis (H1.b) of the outcome drug-related hypoglycaemia across four centres. The patterns are defined by the outcome (dependent variable) and the related independent variables included in the regression models. Each row corresponds to a specific pattern, with green indicating no missing information and red indicating missing information. Abbreviation: ID, identifier.

Pattern ID	Outcome	Independent variables								Per pattern: number of …	
	Drug-related hypoglycaemia	Age	Gender	Any insulin	Long-acting insulin	Heart failure	Diabetes mellitus type	Serum albumin decreased	Creatinine	… missing values	… encounters
1										0	11,985
2										1	5
3										1	8,210
4										2	835
5										1	52
6										2	21
7										3	1
8										2	261
9										3	11
10										4	7
11										1	797
12										2	1
13										2	905
14										3	6,394
15										2	5
16										3	1
17										4	20
18										4	3
19										4	41
20										5	563
21										3	2
Per variable: number of encounters with missing information											
Frequency	8,732	0	2	0	0	886	986	17,011	7,829		
Variable	Drug-related hypoglycaemia	Age	Gender	Any insulin	Long-acting insulin	Heart failure	Diabetes mellitus type	Serum albumin decreased	Creatinine		

Table H in S2 Supplemental tables. Meta-analysed description of the missing data pattern for the analysis (H1.c) of the outcome drug-related hypoglycaemia across six centres, which were also included in the analysis (H1.a). The patterns are defined by the outcome (dependent variable) and the related independent variables included in the regression models. Each row corresponds to a specific pattern, with green indicating no missing information and red indicating missing information. Abbreviation: ID, identifier.

Pattern ID	Outcome	Independent variables								Per pattern: number of …	
	Drug-related hypoglycaemia	Age	Gender	Any insulin	Long-acting insulin	Heart failure	Diabetes mellitus type	Serum albumin decreased	Creatinine	… missing values	… encounters
1										0	2,075
2										1	8
3										1	5,206
4										2	6,538
5										1	3
6										2	1
7										3	2
8										3	11
9										4	19
10										1	651
11										2	2
12										2	1,295
13										3	3,619
14										2	3
15										3	1
16										4	1
17										4	3
18										5	28
Per variable: number of encounters with missing information											
Frequency	5,603	0	0	0	0	61	72	16,724	10,217		
Variable	Drug-related hypoglycaemia	Age	Gender	Any insulin	Long-acting insulin	Heart failure	Diabetes mellitus type	Serum albumin decreased	Creatinine		

Table I in S2 Supplemental tables. Meta-analysed description of the study population for the analysis (B1.a) of the outcome GI bleeding across seven centres – overall as well as stratified by the outcome. Proportions for categorical variables and median values for metric variables, respectively, with 95% confidence intervals (CI) are provided. Additionally, the number of encounters (N_{Info}) building the underlying sample for the respective characteristic (in the given strata) is provided, as well as the number of encounters ($N_{Missing}$) with missing information. The analyses definitions are provided in Table 3. Further abbreviations: ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Characteristic	Overall			With GI bleeding			Without GI bleeding		
	$N_{Missing}$	N_{Info}	Distribution (95% CI)	$N_{Missing}$	N_{Info}	Distribution (95% CI)	$N_{Missing}$	N_{Info}	Distribution (95% CI)
GI bleeding (outcome)	5,616	330,386	1.18 (0.84, 1.66)	0	4,283	100.00 (0.00, 100.00)	0	326,103	0.00 (0.00, 100.00)
Age, in years	0	336,002	62.14 (59.90, 64.38)	0	4,283	70.46 (68.96, 71.95)	0	326,103	62.00 (59.66, 64.34)
Gender	18	335,984		0	4,283		18	326,085	
Male			51.31 (48.79, 53.83)			59.30 (57.68, 60.90)			51.17 (48.68, 53.66)
Female			48.69 (46.17, 51.21)			40.70 (39.10, 42.32)			48.83 (46.34, 51.32)
Medications	22	335,980		0	4,283		22	326,081	
NSAID			19.88 (14.23, 27.07)			5.01 (3.39, 7.34)			20.26 (14.69, 27.25)
ASA			20.81 (17.70, 24.31)			27.44 (24.24, 30.89)			20.74 (17.63, 24.24)
Bisphosphonate			0.75 (0.55, 1.02)			1.14 (0.85, 1.54)			0.74 (0.54, 1.01)
SSRI			3.89 (3.20, 4.74)			5.19 (4.37, 6.14)			3.88 (3.17, 4.75)
Diagnoses									
Liver disease	5,616	330,386	5.83 (4.17, 8.09)	0	4,283	20.70 (17.89, 23.83)	0	326,103	5.65 (4.03, 7.87)
Laboratory values									
AST increased	173,966	162,036	26.68 (23.12, 30.57)	1,260	3,023	43.99 (39.64, 48.44)	168,606	157,497	26.56 (22.88, 30.60)
ALT increased	161,956	174,046	23.04 (19.41, 27.12)	1,139	3,144	29.75 (25.55, 34.33)	156,835	169,268	23.06 (19.30, 27.31)
Serum albumin	244,546	91,456		2,037	2,246		238,308	87,795	
Normal			49.64 (36.77, 62.55)			18.32 (12.19, 26.61)			50.15 (37.25, 63.04)
Decreased			50.26 (37.31, 63.18)			81.64 (73.25, 87.83)			49.74 (36.82, 62.70)
Increased			0.06 (0.03, 0.13)			0.03 (0.00, 5.64)			0.07 (0.03, 0.14)
Haemoglobin	95,156	240,846		703	3,580		90,606	235,497	
Normal			42.99 (36.70, 49.52)			8.50 (6.20, 11.56)			43.51 (37.30, 49.94)
Decreased			55.91 (49.43, 62.20)			90.54 (86.95, 93.23)			55.40 (49.02, 61.60)
Increased			0.88 (0.54, 1.42)			0.81 (0.35, 1.86)			0.88 (0.54, 1.42)
Creatinine, in µmol/L	132,128	203,874	81.76 (78.18, 85.33)	1,177	3,106	107.70 (98.63, 116.77)	127,232	19,8871	81.63 (78.02, 85.23)

Table J in S2 Supplemental tables. Meta-analysed description of the study population for the analysis (B1.b) of the outcome GI bleeding across five centres – overall as well as stratified by the outcome. Proportions for categorical variables and median values for metric variables, respectively, with 95% confidence intervals (CI) are provided. Additionally, the number of encounters (N_{Info}) building the underlying sample for the respective characteristic (in the given strata) is provided, as well as the number of encounters ($N_{Missing}$) with missing information. The analyses definitions are provided in Table 3. Further abbreviations: ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Characteristic	Overall			With GI bleeding			Without GI bleeding		
	$N_{Missing}$	N_{Info}	Distribution (95% CI)	$N_{Missing}$	N_{Info}	Distribution (95% CI)	$N_{Missing}$	N_{Info}	Distribution (95% CI)
GI bleeding (outcome)	5,535	237,220	1.26 (0.79, 1.99)	0	3,349	100.00 (0.00, 100.00)	0	233,871	0.00 (0.00, 100.00)
Age, in years	0	242,755	63.20 (60.62, 65.79)	0	3,349	71.15 (69.48, 72.83)	0	233,871	63.20 (60.62, 65.79)
Gender	17	242,738		0	3,349		17	233,854	
Male			52.29 (49.53, 55.03)			59.65 (57.79, 61.49)			52.12 (49.42, 54.82)
Female			47.71 (44.97, 50.47)			40.35 (38.51, 42.21)			47.88 (45.18, 50.58)
Medications	0	242,755		0	3,349		0	233,871	
NSAID			18.15 (11.74, 26.99)			4.94 (2.87, 8.38)			18.57 (12.25, 27.15)
ASA			23.34 (20.92, 25.95)			29.69 (26.88, 32.66)			23.27 (20.85, 25.89)
Bisphosphonate			0.85 (0.67, 1.08)			1.24 (0.87, 1.75)			0.85 (0.67, 1.07)
SSRI			4.15 (3.25, 5.28)			5.20 (4.22, 6.39)			4.15 (3.23, 5.30)
Diagnoses									
Liver disease	5,535	237,220	6.22 (4.05, 9.45)	0	3,349	21.42 (17.74, 25.62)	0	233,871	6.03 (3.92, 9.18)
Laboratory values									
AST increased	116,914	125,841	26.05 (21.35, 31.37)	954	2,395	42.99 (38.05, 48.07)	111,913	121,958	26.00 (21.11, 31.57)
ALT increased	105,643	137,112	22.35 (17.64, 27.90)	891	2,458	29.02 (23.49, 35.23)	100,822	133,049	22.44 (17.53, 28.26)
Serum albumin	166,895	75,860		1,470	1,879		161,291	72,580	
Normal			57.93 (48.88, 66.48)			23.54 (17.65, 30.66)			58.39 (49.27, 66.96)
Decreased			41.94 (33.35, 51.05)			76.37 (69.11, 82.37)			41.49 (32.87, 50.66)
Increased			0.09 (0.04, 0.19)			0.07 (0.00, 3.76)			0.09 (0.04, 0.20)
Haemoglobin	66,767	175,988		648	2,701		62,310	171,561	
Normal			41.23 (33.28, 49.66)			7.46 (5.29, 10.41)			41.76 (33.91, 50.05)
Decreased			57.84 (49.49, 65.76)			91.86 (88.61, 94.24)			57.31 (49.11, 65.13)
Increased			0.75 (0.43, 1.29)			0.51 (0.15, 1.77)			0.75 (0.43, 1.30)
Creatinine, in µmol/L	70,152	172,603	83.36 (79.93, 86.79)	671	2,678	110.45 (99.91, 120.98)	65,837	168,034	83.18 (79.61, 86.75)

Table K in S2 Supplemental tables. Meta-analysed description of the study population for the analysis (B1.c) of the outcome GI bleeding across the seven centres, which were also included in the analysis (B1.a). Proportions for categorical variables and median values for metric variables, respectively, with 95% confidence intervals (CI) are provided. Additionally, the number of encounters (N_{Info}) building the underlying sample for the respective characteristic is provided, as well as the number of encounters ($N_{Missing}$) with missing information. The analyses definitions are provided in Table 3. Within the characteristics derived from diagnoses, the larger number of encounters with missing information for GI bleeding can be attributed to the exclusion of encounters due to coded GI bleeding on the day of admission. Further abbreviations: ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Characteristic	Overall		
	$N_{Missing}$	N_{Info}	Distribution (95% CI)
GI bleeding (outcome)	7,941	328,061	0.02 (0.01, 0.06)
Age, in years	0	336,002	62.14 (59.90, 64.38)
Gender	18	335,984	
Male			51.31 (48.79, 53.83)
Female			48.69 (46.17, 51.21)
Medications	22	335,980	
NSAID			6.97 (3.69, 12.75)
ASA			3.73 (1.72, 7.92)
Bisphosphonate			0.10 (0.03, 0.29)
SSRI			0.58 (0.23, 1.44)
Diagnoses			
Liver disease	5,616	330,386	0.79 (0.11, 5.38)
Laboratory values			
AST increased	239,681	96,321	17.23 (13.94, 21.11)
ALT increased	232,028	103,974	15.80 (13.42, 18.52)
Serum albumin	289,468	46,534	
Normal			76.40 (58.95, 87.95)
Decreased			23.39 (11.86, 40.91)
Increased			0.10 (0.04, 0.21)
Haemoglobin	188,016	147,986	
Normal			59.75 (54.27, 65.00)
Decreased			39.14 (33.99, 44.55)
Increased			0.84 (0.48, 1.45)
Creatinine, in µmol/L	215,289	120,713	79.49 (75.53, 83.46)

Table L in S2 Supplemental tables. Meta-analysed description of the study population for the analysis (H1.a) of the outcome drug-related hypoglycaemia across six centres – overall as well as stratified by the outcome. Proportions for categorical variables and median values for metric variables, respectively, with 95% confidence intervals (CI) are provided. Additionally, the number of encounters (N_{Info}) building the underlying sample for the respective characteristic (in the given strata) is provided, as well as the number of encounters ($N_{Missing}$) with missing information. The analyses definitions are provided in Table 3. Within the characteristics derived from diagnoses, the larger number of encounters with missing information for diabetes mellitus (DM) can be attributed to the exclusion of encounters with documented type 1 DM and type 2 DM (so-called "double diabetes").

Characteristic	Overall			With drug-related hypoglycaemia			Without drug-related hypoglycaemia		
	$N_{Missing}$	N_{Info}	Distribution (95% CI)	$N_{Missing}$	N_{Info}	Distribution (95% CI)	$N_{Missing}$	N_{Info}	Distribution (95% CI)
Drug-related hypoglycaemia (outcome)	11,110	32,991	2.93 (2.15, 3.99)	0	1,027	100.00 (0.00, 100.00)	0	31,964	0.00 (0.00, 100.00)
Age, in years	0	44,101	70.17 (68.99, 71.34)	0	1,027	72.21 (71.05, 73.36)	0	31,964	70.68 (69.86, 71.49)
Gender	2	44,099		0	1,027		0	31,964	
Male			62.51 (60.74, 64.25)			57.49 (53.49, 61.39)			62.50 (60.46, 64.50)
Female			37.49 (35.75, 39.26)			42.51 (38.61, 46.51)			37.50 (35.50, 39.54)
Medications	0	44,101		0	1,027		0	31,964	
Antihyperglycaemic drug			100.00 (0.00, 100.00)			100.00 (0.00, 100.00)			100.00 (0.00, 100.00)
Any insulin			57.86 (52.02, 63.49)			86.77 (82.20, 90.31)			59.36 (52.30, 66.06)
Long-acting insulin			25.66 (20.68, 31.37)			46.30 (40.33, 52.37)			25.48 (20.13, 31.68)
Diagnoses									
Heart failure	953	43,148	17.59 (13.22, 23.02)	6	1,021	23.53 (18.85, 28.97)	308	31,656	18.00 (13.82, 23.10)
Diabetes mellitus (DM)	1,071	43,030		18	1,009		386	31,578	
No DM			25.32 (18.75, 33.25)			13.31 (8.29, 20.67)			23.12 (16.15, 31.94)
DM type 1			2.39 (1.90, 2.99)			9.32 (7.67, 11.27)			2.09 (1.60, 2.73)
DM type 2			68.90 (61.22, 75.66)			69.32 (64.00, 74.17)			71.32 (62.94, 78.46)
DM other type			2.86 (2.28, 3.58)			6.08 (3.87, 9.43)			2.74 (2.08, 3.60)
Laboratory values									
Serum albumin	28,726	15,375		376	651		18,160	13,804	
Normal			43.65 (28.46, 60.13)			21.51 (13.88, 31.78)			44.56 (29.53, 60.64)
Decreased			56.25 (39.72, 71.50)			78.48 (67.99, 86.23)			55.34 (39.21, 70.43)
Increased			0.08 (0.03, 0.26)			0.15 (0.02, 1.08)			0.09 (0.03, 0.26)
Creatinine, in µmol/L	10,874	33,227	98.78 (93.02, 104.53)	23	1,004	133.66 (114.29, 153.04)	2,397	29,567	98.77 (92.99, 104.55)

Table M in S2 Supplemental tables. Meta-analysed description of the study population for the analysis (H1.b) of the outcome drug-related hypoglycaemia across four centres – overall as well as stratified by the outcome. Proportions for categorical variables and median values for metric variables, respectively, with 95% confidence intervals (CI) are provided. Additionally, the number of encounters (N_{Info}) building the underlying sample for the respective characteristic (in the given strata) is provided, as well as the number of encounters ($N_{Missing}$) with missing information. The analyses definitions are provided in Table 3. Within the characteristics derived from diagnoses, the larger number of encounters with missing information for diabetes mellitus (DM) can be attributed to the exclusion of encounters with documented type 1 DM and type 2 DM (so-called "double diabetes").

Characteristic	Overall			With drug-related hypoglycaemia			Without drug-related hypoglycaemia		
	$N_{Missing}$	N_{Info}	Distribution (95% CI)	$N_{Missing}$	N_{Info}	Distribution (95% CI)	$N_{Missing}$	N_{Info}	Distribution (95% CI)
Drug-related hypoglycaemia (outcome)	8,732	21,388	3.64 (2.89, 4.56)	0	785	100.00 (0.00, 100.00)	0	20,603	0.00 (0.00, 100.00)
Age, in years	0	30,120	70.75 (69.51, 71.98)	0	785	71.86 (70.62, 73.10)	0	20,603	71.00 (70.21, 71.80)
Gender	2	30,118		0	785		0	20,603	
Male			63.55 (62.42, 64.67)			59.62 (56.14, 63.00)			63.82 (62.33, 65.28)
Female			36.45 (35.33, 37.58)			40.38 (37.00, 43.86)			36.18 (34.72, 37.67)
Medications	0	30,120		0	785		0	20,603	
Antihyperglycaemic drug			100.00 (0.00, 100.00)			100.00 (0.00, 100.00)			100.00 (0.00, 100.00)
Any insulin			55.24 (49.84, 60.52)			87.58 (81.18, 92.02)			55.50 (50.23, 60.65)
Long-acting insulin			28.24 (22.85, 34.34)			48.40 (40.77, 56.09)			28.31 (22.68, 34.71)
Diagnoses									
Heart failure	886	29,234	20.79 (15.65, 27.08)	2	783	24.00 (17.98, 31.28)	277	20,326	20.76 (15.49, 27.26)
Diabetes mellitus (DM)	986	29,134		13	772		340	20,263	
No DM			21.60 (18.69, 24.82)			11.24 (5.78, 20.73)			18.71 (15.37, 22.57)
DM type 1			2.36 (2.19, 2.54)			9.20 (7.35, 11.45)			2.21 (2.02, 2.42)
DM type 2			72.99 (69.37, 76.34)			70.02 (62.53, 76.58)			76.01 (72.08, 79.54)
DM other type			2.89 (2.13, 3.89)			7.87 (5.86, 10.51)			2.86 (2.07, 3.95)
Laboratory values									
Serum albumin	17,011	13,109		218	567		8,867	11,736	
Normal			48.94 (37.84, 60.14)			24.50 (17.41, 33.30)			49.52 (39.05, 60.03)
Decreased			50.93 (39.63, 62.14)			75.38 (66.34, 82.63)			50.35 (39.75, 60.92)
Increased			0.10 (0.03, 0.33)			0.18 (0.02, 1.24)			0.11 (0.04, 0.33)
Creatinine, in µmol/L	7,829	22,291	101.15 (94.96, 107.34)	8	777	139.70 (117.53, 161.88)	840	19,763	100.93 (94.67, 107.18)

Table N in S2 Supplemental tables. Meta-analysed description of the study population for the analysis (H1.c) of the outcome drug-related hypoglycaemia across the six centres, which were also included in the analysis (H1.a). Proportions for categorical variables and median values for metric variables, respectively, with 95% confidence intervals (CI) are provided. Additionally, the number of encounters (N_{Info}) building the underlying sample for the respective characteristic is provided, as well as the number of encounters ($N_{Missing}$) with missing information. The analyses definitions are provided in Table 3. Within the characteristics derived from diagnoses, the larger number of encounters with missing information for diabetes mellitus (DM) can be attributed to the exclusion of encounters with documented type 1 DM and type 2 DM (so-called "double diabetes").

Characteristic	Overall		
	$N_{Missing}$	N_{Info}	Distribution (95% CI)
Drug-related hypoglycaemia (outcome)	5,603	13,863	2.19 (1.38, 3.45)
Age, in years	0	19,466	70.19 (68.80, 71.57)
Gender	0	19,466	
Male			63.00 (60.83, 65.12)
Female			37.00 (34.88, 39.17)
Medications	0	19,466	
Antihyperglycaemic drug			100.00 (0.00, 100.00)
Any insulin			55.37 (48.09, 62.43)
Long-acting insulin			25.40 (20.05, 31.62)
Diagnoses			
Heart failure	61	19,405	1.46 (0.26, 7.80)
Diabetes mellitus (DM)	72	19,394	
No DM			92.02 (44.31, 99.40)
DM type 1			0.46 (0.13, 1.60)
DM type 2			7.08 (0.57, 50.33)
DM other type			0.51 (0.14, 1.87)
Laboratory values			
Serum albumin	16,724	2,742	
Normal			75.15 (56.08, 87.75)
Decreased			24.75 (12.16, 43.85)
Increased			0.11 (0.04, 0.34)
Creatinine, in µmol/L	10,217	9,249	91.57 (84.99, 98.15)

Table O in S2 Supplemental tables. Meta-analysed results from the regression modelling for the analysis (B1.a) of the outcome GI bleeding across seven centres. For each model, a model summary of the meta-analysed regression models as well as summarised information of the local regression results are provided. The analyses definitions are provided in Table 3. Note that the odds ratio for metric covariates must be read as an increase in odds per 1 unit increase of the covariate. Further abbreviations: AIC, Akaike information criterion; ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; ROC AUC, area under the receiver operating characteristic curve; BIC, Bayes information criterion; CI, confidence interval; GI, gastrointestinal; LR, likelihood-ratio; NSAID, non-steroidal anti-inflammatory drug; N, number of encounters included in the respective model; OR, odds ratio; Q1/Q3, first/third quartile; SSRI, selective serotonin reuptake inhibitor; VIF, variance inflation factor.

Model	Variable	Model summary					Model evaluation: Descriptive summary of local results		
		N	OR (95% CI)	AIC	BIC	I^2	Centres with LR test p-value <0.05 [n (%)]	ROC AUC [median (Q1, Q3)]	VIF [median (Q1, Q3)]
Univariable models									
1	Age, in 10 years	330,386	1.31 (1.28, 1.34)	-38.2	-35.7	97.3%	7 (100.00%)	0.63 (0.62, 0.64)	-
2	Male gender	330,368	1.40 (1.24, 1.59)	4.2	6.6	97.6%	6 (85.71%)	0.54 (0.53, 0.55)	-
3	NSAID	330,364	0.21 (0.15, 0.30)	24.0	26.4	97.1%	7 (100.00%)	0.58 (0.56, 0.60)	-
4	ASA	330,364	1.43 (1.29, 1.59)	4.0	6.5	97.6%	7 (100.00%)	0.53 (0.53, 0.54)	-
5	Bisphosphonate	330,364	1.59 (1.04, 2.43)	27.7	30.1	97.7%	1 (14.29%)	0.50 (0.50, 0.50)	-
6	SSRI	330,364	1.34 (1.04, 1.72)	22.4	24.8	97.7%	3 (42.86%)	0.51 (0.50, 0.51)	-
7	Liver disease	330,386	4.32 (3.26, 5.73)	15.4	17.8	97.3%	7 (100.00%)	0.57 (0.57, 0.58)	-
8	AST increased	160,520	2.19 (1.80, 2.66)	13.1	15.5	95.2%	7 (100.00%)	0.58 (0.56, 0.60)	-
9	ALT increased	172,412	1.41 (1.21, 1.64)	16.1	18.5	96.8%	4 (57.14%)	0.53 (0.52, 0.55)	-
10	Serum albumin decreased	90,041	4.72 (3.83, 5.81)	11.2	13.6	86.9%	7 (100.00%)	0.66 (0.64, 0.68)	-
11	Haemoglobin decreased	239,077	7.61 (5.62, 10.30)	21.5	23.9	96.0%	7 (100.00%)	0.66 (0.65, 0.70)	-
12	Creatinine, in mmol/L	201,977	6.12 (2.65, 14.12)	-46.4	-44.0	97.2%	7 (100.00%)	0.67 (0.63, 0.68)	-
Base model (multivariable)									
13		330,346	-	12.7	95.1	87.3%	7 (100.00%)	0.70 (0.69, 0.73)	-
	Age, in 10 years	-	1.27 (1.24, 1.30)	-	-		-	-	1.07 (1.06, 1.08)
	Male gender	-	1.21 (1.10, 1.34)	-	-		-	-	1.02 (1.02, 1.03)
	NSAID	-	0.30 (0.22, 0.42)	-	-		-	-	1.02 (1.02, 1.04)
	ASA	-	1.08 (0.98, 1.18)	-	-		-	-	1.06 (1.05, 1.06)
	Bisphosphonate	-	1.19 (0.76, 1.84)	-	-		-	-	1.01 (1.00, 1.01)
	SSRI	-	1.32 (1.06, 1.64)	-	-		-	-	1.00 (1.00, 1.01)
	Liver disease	-	4.13 (3.24, 5.26)	-	-		-	-	1.02 (1.02, 1.02)

Table P in S2 Supplemental tables. Meta-analysed results from the regression modelling for the analysis (B1.b) of the outcome GI bleeding across five centres. For each model, a model summary of the meta-analysed regression models as well as summarised information of the local regression results are provided. The analyses definitions are provided in Table 3. Note that the odds ratio for metric covariates must be read as an increase in odds per 1 unit increase of the covariate. Further abbreviations: AIC, Akaike information criterion; ALT, alanine transaminase; ASA, acetylsalicylic acid; AST, aspartate aminotransferase; ROC AUC, area under the receiver operating characteristic curve; BIC, Bayes information criterion; CI, confidence interval; GI, gastrointestinal; LR, likelihood-ratio; NSAID, non-steroidal anti-inflammatory drug; N, number of encounters included in the respective model; OR, odds ratio; Q1/Q3, first/third quartile; SSRI, selective serotonin reuptake inhibitor; VIF, variance inflation factor.

Model ID	Variable	Model summary					Model evaluation: Descriptive summary of local results		
		N	OR (95% CI)	AIC	BIC	I^2	Centres with LR test p-value <0.05 [n (%)]	ROC AUC [median (Q1, Q3)]	VIF [median (Q1, Q3)]
Univariable models									
1	Age, in 10 years	237,220	1.31 (1.26, 1.35)	-21.6	-21.2	97.7%	5 (100.00%)	0.62 (0.61, 0.63)	-
2	Male gender	237,203	1.39 (1.16, 1.67)	7.6	8.0	97.8%	4 (80.00%)	0.53 (0.53, 0.54)	-
3	NSAID	237,220	0.23 (0.15, 0.37)	21.5	21.9	97.3%	5 (100.00%)	0.57 (0.54, 0.58)	-
4	ASA	237,220	1.38 (1.23, 1.55)	6.6	7.0	97.9%	5 (100.00%)	0.53 (0.52, 0.54)	-
5	Bisphosphonate	237,220	1.59 (0.93, 2.71)	22.2	22.6	97.9%	1 (20.00%)	0.50 (0.50, 0.50)	-
6	SSRI	237,220	1.25 (0.95, 1.64)	18.6	19.0	98.0%	2 (40.00%)	0.51 (0.50, 0.51)	-
7	Liver disease	237,220	4.25 (2.84, 6.35)	12.0	12.4	97.5%	5 (100.00%)	0.57 (0.56, 0.59)	-
8	AST increased	124,353	2.17 (1.72, 2.73)	12.1	12.5	96.4%	5 (100.00%)	0.58 (0.57, 0.60)	-
9	ALT increased	135,507	1.41 (1.17, 1.70)	15.7	16.1	97.8%	3 (60.00%)	0.53 (0.52, 0.54)	-
10	Serum albumin decreased	74,459	4.57 (3.53, 5.92)	7.5	7.9	81.1%	5 (100.00%)	0.68 (0.66, 0.69)	-
11	Haemoglobin decreased	174,262	8.22 (6.20, 10.91)	17.0	17.4	96.9%	5 (100.00%)	0.66 (0.65, 0.70)	-
12	Creatinine, in mmol/L	170,712	5.81 (2.75, 12.26)	-28.9	-28.5	97.7%	5 (100.00%)	0.67 (0.65, 0.69)	-
Base model (multivariable)									
13		237,203	-	36.1	100.6	89.2%	5 (100.00%)	0.70 (0.68, 0.70)	-
	Age, in 10 years	-	1.27 (1.24, 1.31)	-	-		-	-	1.06 (1.06, 1.07)
	Male gender	-	1.20 (1.05, 1.38)	-	-		-	-	1.02 (1.02, 1.02)
	NSAID	-	0.32 (0.21, 0.50)	-	-		-	-	1.02 (1.01, 1.03)
	ASA	-	1.08 (0.96, 1.20)	-	-		-	-	1.06 (1.05, 1.06)
	Bisphosphonate	-	1.21 (0.72, 2.03)	-	-		-	-	1.01 (1.00, 1.01)
	SSRI	-	1.28 (0.97, 1.67)	-	-		-	-	1.00 (1.00, 1.00)
	Liver disease	-	4.16 (2.91, 5.94)	-	-		-	-	1.02 (1.02, 1.02)

Extended model (multivariable)								
14	61,317	-	84.3	287.2	41.9%	5 (100.00%)	0.75 (0.72, 0.76)	-
Age, in 10 years	-	1.10 (1.06, 1.15)	-	-		-	-	1.09 (1.08, 1.10)
Male gender	-	1.04 (0.90, 1.20)	-	-		-	-	1.05 (1.05, 1.05)
NSAID	-	0.37 (0.23, 0.62)	-	-		-	-	1.02 (1.02, 1.03)
ASA	-	0.85 (0.76, 0.96)	-	-		-	-	1.06 (1.05, 1.08)
Bisphosphonate	-	1.14 (0.66, 1.97)	-	-		-	-	1.01 (1.00, 1.01)
SSRI	-	1.22 (0.97, 1.53)	-	-		-	-	1.01 (1.01, 1.01)
Liver disease	-	2.10 (1.79, 2.46)	-	-		-	-	1.11 (1.11, 1.13)
AST increased	-	1.17 (0.95, 1.43)	-	-		-	-	1.63 (1.63, 1.77)
ALT increased	-	0.89 (0.69, 1.14)	-	-		-	-	1.56 (1.52, 1.61)
Serum albumin decreased	-	2.50 (2.07, 3.02)	-	-		-	-	1.16 (1.16, 1.17)
Haemoglobin decreased	-	3.57 (2.23, 5.71)	-	-		-	-	1.10 (1.09, 1.12)
Creatinine, in mmol/L	-	2.22 (1.25, 3.97)	-	-		-	-	1.03 (1.03, 1.03)

Table Q in S2 Supplemental tables. Meta-analysed results from the regression modelling for the analysis (H1.a) of the outcome drug-related hypoglycaemia across six centres. For each model, a model summary of the meta-analysed regression models as well as summarised information of the local regression results are provided. The analyses definitions are provided in Table 3. Note that the odds ratio for metric covariates must be read as an increase in odds per 1 unit increase of the covariate. Further abbreviations: AIC, Akaike information criterion; ROC AUC, area under the receiver operating characteristic curve; BIC, Bayes information criterion; CI, confidence interval; DM, diabetes mellitus; LR, likelihood-ratio; N, number of encounters included in the respective model; OR, odds ratio; Q1/Q3, first/third quartile; ref., reference; VIF, variance inflation factor

Model ID	Variable	Model summary					Model evaluation: Descriptive summary of local results		
		N	OR (95% CI)	AIC	BIC	I^2	Centres with LR test p-value <0.05 [n (%)]	ROC AUC [median (Q1, Q3)]	VIF [median (Q1, Q3)]
Univariable models									
1	Age, in 10 years	32,991	1.03 (0.97, 1.10)	-19.1	-17.6	92.2%	1 (16.67%)	0.53 (0.51, 0.54)	-
2	Male gender	32,991	0.81 (0.70, 0.92)	13.2	14.7	92.3%	2 (33.33%)	0.53 (0.51, 0.54)	-
3	Any insulin	32,991	4.17 (2.68, 6.50)	19.7	21.2	93.6%	6 (100.00%)	0.65 (0.64, 0.66)	-
4	Long-acting insulin	32,991	2.55 (2.07, 3.14)	16.8	18.3	93.0%	6 (100.00%)	0.59 (0.58, 0.62)	-
5	Heart failure	32,677	1.37 (1.10, 1.71)	16.0	17.5	91.9%	1 (16.67%)	0.52 (0.51, 0.52)	-
6	Diabetes mellitus (DM) *	32,587	-	47.0	61.0	87.5%	6 (100.00%)	0.58 (0.57, 0.60)	
	DM type 1	-	7.95 (4.45, 14.21)	-	-		-	-	-
	DM type 2	-	1.71 (1.09, 2.68)	-	-		-	-	-
	DM other type	-	4.25 (2.84, 6.38)	-	-		-	-	-
7	Serum albumin decreased	14,455	3.15 (2.59, 3.83)	28.5	30.0	82.0%	6 (100.00%)	0.62 (0.60, 0.64)	-
8	Creatinine, in mmol/L	30,571	6.19 (3.51, 10.91)	-43.9	-42.4	90.4%	5 (83.33%)	0.62 (0.61, 0.64)	-
Base model (multivariable)									
9		32,587	-	77.0	174.5	77.3%	6 (100.00%)	0.72 (0.72, 0.73)	-
	Age, in 10 years	-	1.11 (1.05, 1.18)	-	-		-	-	1.19 (1.17, 1.23)
	Male gender	-	0.81 (0.67, 0.97)	-	-		-	-	1.01 (1.01, 1.01)
	Any insulin	-	3.86 (2.61, 5.72)	-	-		-	-	1.22 (1.20, 1.34)
	Long-acting insulin	-	1.18 (0.86, 1.62)	-	-		-	-	1.36 (1.26, 1.40)
	Heart failure	-	1.37 (1.15, 1.62)	-	-		-	-	1.05 (1.04, 1.07)
	Diabetes mellitus (DM) *	-	-	-	-		-	-	1.31 (1.26, 1.37)
	DM type 1	-	5.97 (3.39, 10.51)	-	-		-	-	-
	DM type 2	-	1.60 (1.03, 2.47)	-	-		-	-	-
	DM other type	-	3.04 (1.93, 4.79)	-	-		-	-	-

*The reference category is “no DM”.

Table R in S2 Supplemental tables. Meta-analysed results from the regression modelling for the analysis (H1.b) of the outcome drug-related hypoglycaemia across four centres. For each model, a model summary of the meta-analysed regression models as well as summarised information of the local regression results are provided. The analyses definitions are provided in Table 3. Note that the odds ratio for metric covariates must be read as an increase in odds per 1 unit increase of the covariate. Further abbreviations: AIC, Akaike information criterion; ROC AUC, area under the receiver operating characteristic curve; BIC, Bayes information criterion; CI, confidence interval; DM, diabetes mellitus; LR, likelihood-ratio; N, number of encounters included in the respective model; OR, odds ratio; Q1/Q3, first/third quartile; ref., reference; VIF, variance inflation factor

Model ID	Variable	Model summary					Model evaluation: Descriptive summary of local results		
		N	OR (95% CI)	AIC	BIC	I^2	Centres with LR test p-value <0.05 [n (%)]	ROC AUC [median (Q1, Q3)]	VIF [median (Q1, Q3)]
Univariable models									
1	Age, in 10 years	21,388	0.99 (0.93, 1.05)	-11.8	-12.8	88.4%	0 (0.00%)	0.51 (0.50, 0.53)	-
2	Male gender	21,388	0.84 (0.71, 1.00)	8.5	7.5	88.9%	2 (50.00%)	0.52 (0.51, 0.54)	-
3	Any insulin	21,388	5.58 (3.93, 7.93)	8.0	7.0	83.6%	4 (100.00%)	0.66 (0.65, 0.66)	-
4	Long-acting insulin	21,388	2.38 (1.97, 2.87)	10.6	9.5	91.9%	4 (100.00%)	0.59 (0.58, 0.61)	-
5	Heart failure	21,109	1.18 (0.98, 1.41)	6.7	5.7	87.4%	0 (0.00%)	0.52 (0.51, 0.52)	-
6	Diabetes mellitus (DM) *	21,035	-	28.4	35.2	81.0%	4 (100.00%)	0.58 (0.56, 0.59)	
	DM type 1	-	7.17 (3.63, 14.18)	-	-	-	-	-	-
	DM type 2	-	1.55 (0.89, 2.71)	-	-	-	-	-	-
	DM other type	-	4.50 (2.49, 8.15)	-	-	-	-	-	-
7	Serum albumin decreased	12,303	2.99 (2.41, 3.70)	9.4	8.3	86.3%	4 (100.00%)	0.62 (0.61, 0.63)	-
8	Creatinine, in mmol/L	20,540	5.56 (2.52, 12.26)	-23.3	-24.3	89.3%	3 (75.00%)	0.63 (0.60, 0.65)	-
Base model (multivariable)									
9		21,035	-	73.0	143.0	62.8%	4 (100.00%)	0.72 (0.72, 0.73)	-
	Age, in 10 years	-	1.10 (1.02, 1.18)	-	-	-	-	-	1.21 (1.19, 1.30)
	Male gender	-	0.88 (0.70, 1.10)	-	-	-	-	-	1.01 (1.01, 1.02)
	Any insulin	-	4.88 (3.35, 7.11)	-	-	-	-	-	1.28 (1.16, 1.39)
	Long-acting insulin	-	1.10 (0.76, 1.59)	-	-	-	-	-	1.31 (1.19, 1.39)
	Heart failure	-	1.33 (1.10, 1.62)	-	-	-	-	-	1.05 (1.05, 1.07)
	Diabetes mellitus (DM) *	-	-	-	-	-	-	-	1.27 (1.24, 1.35)
	DM type 1	-	5.07 (2.38, 10.79)	-	-	-	-	-	-
	DM type 2	-	1.38 (0.78, 2.46)	-	-	-	-	-	-
	DM other type	-	3.35 (1.70, 6.62)	-	-	-	-	-	-

Extended model (multivariable)								
10	11,985	-	87.4	202.6	49.9%	4 (100.00%)	0.76 (0.75, 0.76)	-
Age, in 10 years	-	1.03 (0.95, 1.11)	-	-	-	-	-	1.23 (1.19, 1.32)
Male gender	-	0.86 (0.66, 1.14)	-	-	-	-	-	1.02 (1.02, 1.03)
Any insulin	-	3.32 (2.05, 5.39)	-	-	-	-	-	1.24 (1.13, 1.37)
Long-acting insulin	-	1.13 (0.69, 1.84)	-	-	-	-	-	1.31 (1.21, 1.39)
Heart failure	-	1.11 (0.88, 1.42)	-	-	-	-	-	1.08 (1.08, 1.10)
Diabetes mellitus (DM) *	-	-	-	-	-	-	-	1.43 (1.39, 1.46)
DM type 1	-	5.55 (2.47, 12.45)	-	-	-	-	-	-
DM type 2	-	1.57 (0.87, 2.85)	-	-	-	-	-	-
DM other type	-	3.46 (1.76, 6.80)	-	-	-	-	-	-
Serum albumin decreased	-	2.48 (1.89, 3.25)	-	-	-	-	-	1.07 (1.06, 1.09)
Creatinine, in mmol/L	-	2.74 (1.33, 5.67)	-	-	-	-	-	1.06 (1.05, 1.08)

*The reference category is “no DM”.

Supporting information file S3: Supplemental figures

Challenges in detecting and predicting adverse drug events via distributed analysis of electronic health record data from German university hospitals

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List of supplemental figures

The initial Sankey diagrams in Fig A and Fig B were generated with the *Sankey Diagram Generator* by Dénes Csala, based on the *Sankey plugin for D3* by Mike Bostock (https://sankey.csaladen.es; 2014), and subsequently adapted on 2025/01/16.

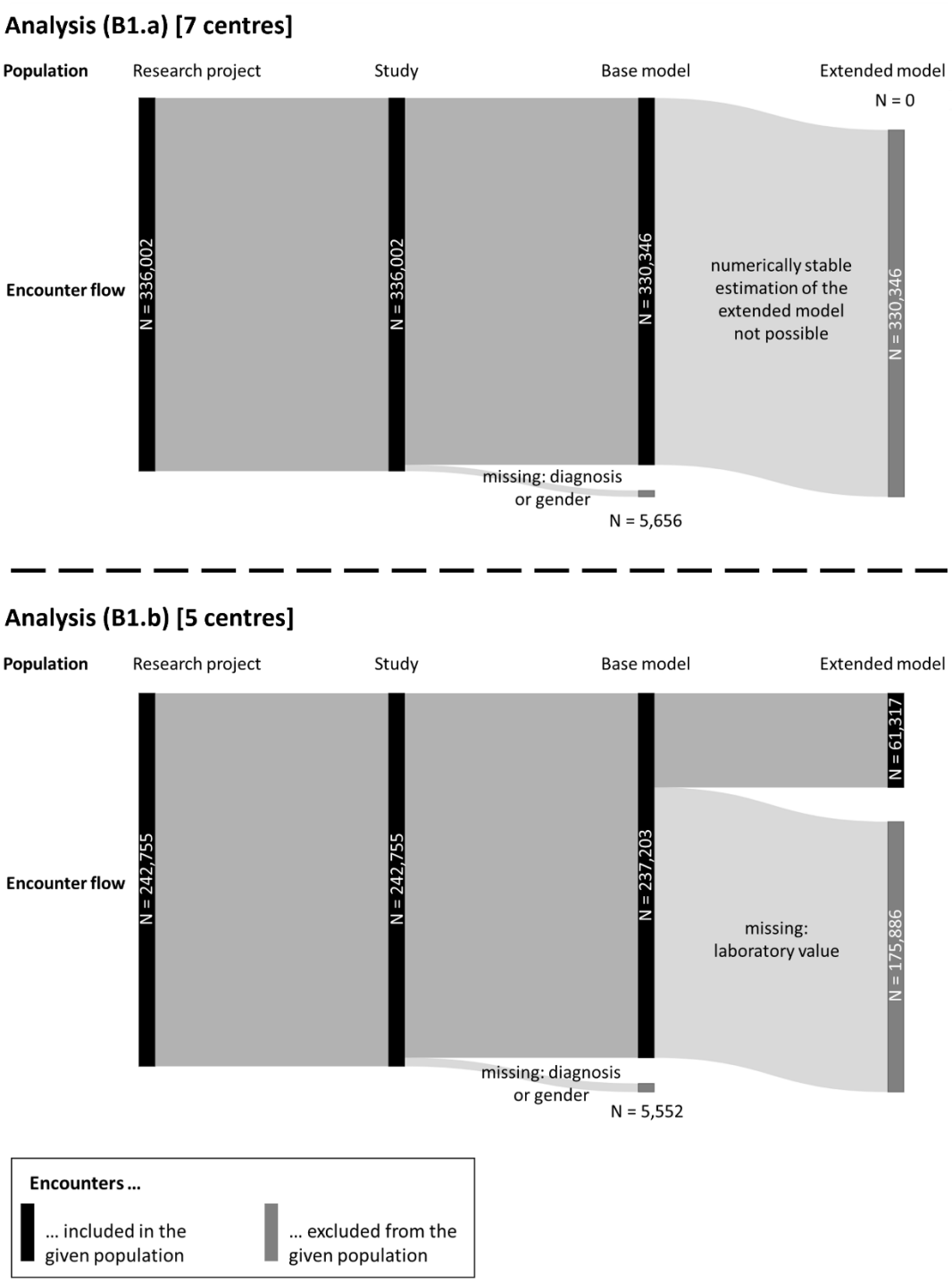

Fig A in S3 Supplemental figures. Number of included and excluded encounters (together with the exclusion reasons) for the outcome GI bleeding for the analyses (B1.a) and (B1.b). These numbers (N) are provided for all populations from the research project population to the extended model population. Please note, that there was no additional inclusion criterion for the outcome GI bleeding, so that the related study population was identical to the overall population of our research project. Furthermore, the extended model population was empty for the analysis (B1.a). The definitions of the analyses are provided in Table 3.

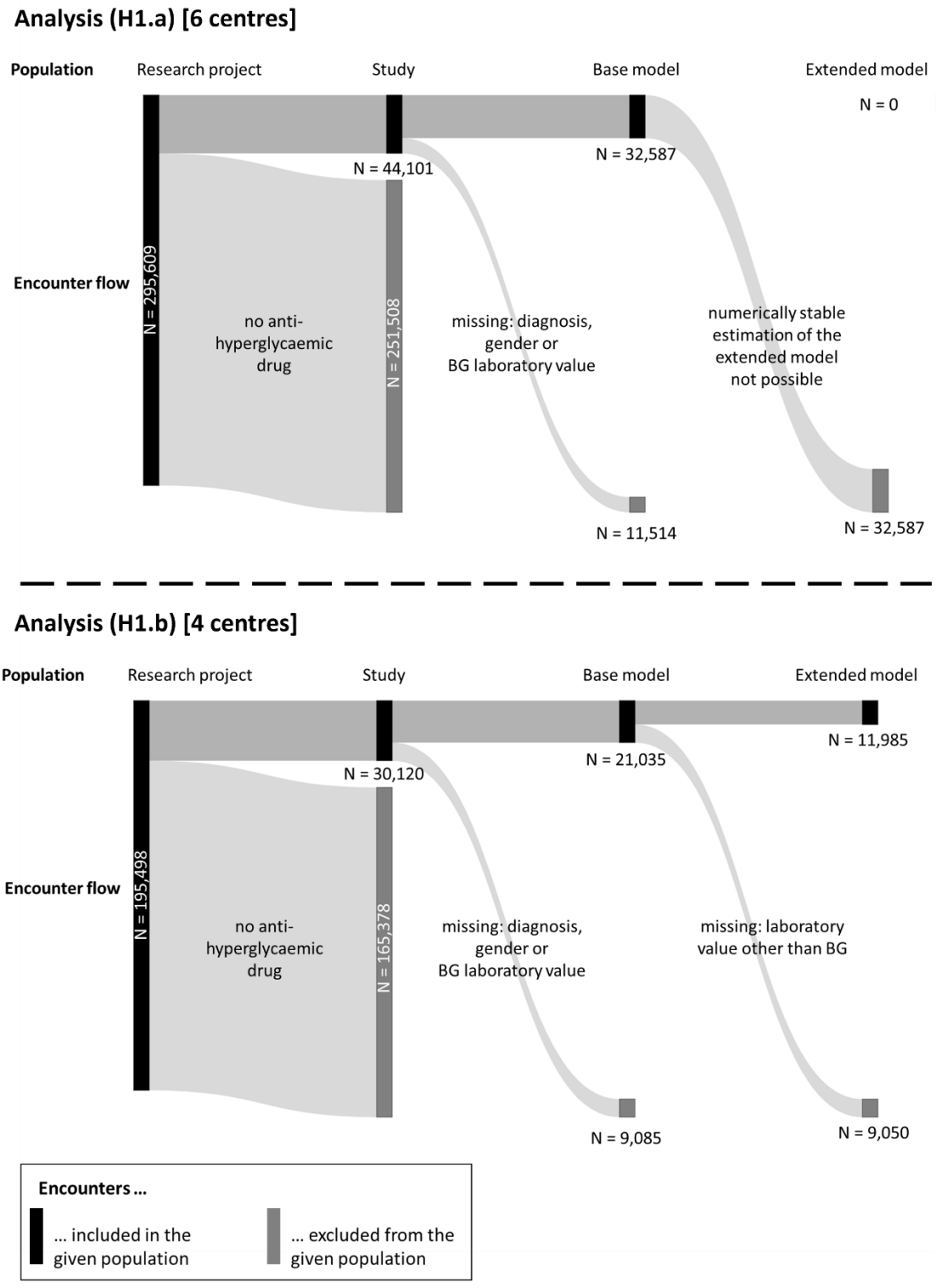

Fig B in S3 Supplemental figures. Number of included and excluded encounters (together with the exclusion reasons) for the outcome drug-related hypoglycaemia for the analyses (H1.a) and (H1.b). These numbers (N) are provided for all populations from the research project population to the extended model population. Please note, that the extended model population was empty for the analysis (H1.a). The definitions of the analyses are provided in Table 3. Further abbreviation: BG, blood glucose.