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Novel methods to support Active Pharmacovigilance in the clinical environment : Active Pharmacovigilance in the context of a Learning Healthcare System

Pantelis Natsiavas

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Pantelis Natsiavas. Novel methods to support Active Pharmacovigilance in the clinical environment : Active Pharmacovigilance in the context of a Learning Healthcare System. Human health and pathology. Sorbonne Université, 2020. English. NNT : 2020SORUS460 . tel-03828456

HAL Id: tel-03828456

<https://theses.hal.science/tel-03828456v1>

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Sorbonne Université

ED 393 - Santé publique : épidémiologie et sciences de l'information
biomédicale

Laboratoire d'Informatique Médicale et d'Ingénierie des Connaissances en e-Santé
UMRS_1142

Novel methods to support Active Pharmacovigilance in the clinical environment

*Active Pharmacovigilance in the context of a Learning
Healthcare System*

Pantelis Natsiavas

Thèse de doctorat de **Informatique médicale**

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Co-encadrée par Dr. Vassilis Koutkias

Présentée et soutenue publiquement le 17 Décembre 2020

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Funding

This research has been partly co-financed by the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneurship and Innovation, under the call RESEARCH – CREATE – INNOVATE (project code: T1EDK-03789) and other institutional funds provided via the Institute of Applied Biosciences at Centre for Research and Technology Hellas (INAB|CERTH).

Dedicated to

my wife and sons, Domniki, Stavros and Thanos,

my mother Areti,

my late mentor Vassilis Koutkias

Acknowledgements

The successful outcome of this dissertation would not be possible without the support by some very special persons, which I should wholeheartedly thank.

First of all, I would like to express my deep gratitude to my PhD supervisor, Dr. Marie-Christine Jaulent, director of Laboratoire d'Informatique Médicale et d'Ingénierie des Connaissances en e-Santé (LIMICS). From my association with her on a scientific and research level I have gained much more than somebody can see at first glance.

I would also like to thank my colleagues at the eHealth Lab of the Institute of Applied Biosciences in the Centre for Research and Technology Hellas (INAB|CERTH). As I was hosted on INAB|CERTH during my PhD period, these people were part of my "research" daily routine. To this end, I should emphatically thank Dr. Kostas Stamatopoulos, director of INAB|CERTH for his support at all levels.

My wife firmly believed in the successful completion of my PhD – some times more than me - and along with my mother they supported it with all their powers from the very beginning. The required endless work, including late nights and weekends, would not be possible without my family's every-day support.

Finally, there are no words to describe my gratitude to my supervisor, collaborator, mentor, and friend Vassilis Koutkias. My PhD will always be marked by his contribution and his painful loss. His integrity, ethos, and selflessness set an example for me, both professionally and personally.

Pantelis Natsiavas

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Acronyms

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AI	Artificial Intelligence
AP	Active Pharmacovigilance
ATC	Anatomical Therapeutic Chemical
BP	Business Process
BPMN	Business Process Management Notation
CDER	FDA Centre for Drug Evaluation and Research
CDM	Common Data Model
CDVC	Care Delivery Value Chain
CDSS	Clinical Decision Support System
CHPS	China Hospital Pharmacovigilance System
CPG	Clinical Practice Guideline
CRO	Contract Research Organization
CST	Control Systems Theory
DDI	Drug-drug interaction
DA	Disproportionality Analysis
D2K	Data to Knowledge
DDM	Discrete Dynamic Modelling
DL	Description Logics
DS	Drug Safety
DSM	Deterministic State Machine
DSMO	Drug Safety Monitoring Organization
DSS	Decision Support Systems
EHR	Electronic Health Record
EMA	European Medicines Agency
EU	European Union
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FSM	Finite State Machine
FuSM	Fuzzy State Machine
HTA	Health Technology Assessment
NDO	Greek National Drugs Organization
NDSM	Non-Deterministic State Machine
HCP	Health Care Professional
HIS	Hospital Information System
ICSR	Individual Case Safety Report
ICD	International Classification of Diseases
ICT	Information and Communication Technologies
IT	Information Technology
IS	Intelligent System
K2P	Knowledge to Performance
KE	Knowledge Engineering
KPI	Key Performance Indicator
LHS	Learning Healthcare System
ML	Machine Learning
MAH	Market Authorization Holder

MM	Markov Model
MoA	Mechanism of Action
NLP	Natural Language Processing
OHDSI	Observational Health Data Sciences and Informatics
ONC	US Office of the National Coordinator for Health Information Technology
OWL	Web Ontology Language
P2D	Performance to Data
PCBRR	Patient-Centric Benefit-Risk Ratio
PD	Pharmacodynamic
PGx	Pharmacogenomics
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	Patient-Reported Outcomes
PRR	Proportional Reporting Ratio
PSM	Probabilistic State Machine
PSURs	Periodic Safety Update Report
PV	Pharmacovigilance
QSP	Quantitative Systems Pharmacology
RDF	Resource Description Framework
RMP	Risk Management Plan
RO	Regulatory Organization
ROR	Reporting Odds Ratio
RWE	Real World Evidence
SBM	State-based model
SM	State Machine
SmPC	Summary of Product Characteristics
SNA	Social Network Analysis
SP	Systems Pharmacology
SPL	Structured Product Label
SRS	Spontaneous Reporting System
TSM	Timed State Machine
UG	User Goal
UMC	Uppsala Monitoring Centre
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

Abstract

Drug safety is a critical issue causing significant public health and financial burden. Pharmacovigilance (PV) is the science related with all aspects of drug safety, focusing on the post-marketing drug safety. Typically, PV activities are not supported by specific tools systematically developed to this purpose. Active Pharmacovigilance (AP) is a new paradigm aiming to increase the PV data space via the active pursue of data which could in principle be produced for another main purpose, but they could also potentially be useful for PV as a secondary use. Technically, the exploitation of these data sources requires the use of Knowledge Engineering (KE) computational approaches, aiming to integrate, mine and semantically align the respective data. The challenges of integrating the use of these KE and potentially other “intelligent” technical paradigms as well as data sources in the clinical environment and beyond that are evident. Revisiting the AP paradigm towards focusing on the exploitation of emerging data sources and technologies is necessary in order to improve medical practice, patient safety and clinical research.

This thesis aims to redefine AP based on the opportunities provided by the potential of integrating emerging data sources and “intelligent” technologies. More specifically, it emphasizes on the legal and organizational aspects, elaborating the related “Business Processes” (BPs) and the respective “User Goals” (UGs) and their value in updating the AP paradigm.

To this end, a systematic review of the research papers focusing on the use of KE for drug safety has been conducted, identifying the technical approaches and the data sources used, while also investigating potential technical and research gaps. Based on these findings a number of activities has been launched, aiming to support the integration of these data sources and technical approaches in the clinical context and beyond. The regulatory context has been analysed, the respective BPs were identified and elaborated and finally a well-defined set of “User-Goals” has been produced and the respective challenges on the integration of “intelligent” technologies were elaborated. Ultimately, based on these findings, the vision of integrating AP as part of a “Learning Healthcare System” is presented.

Finally, a set of technical research lines were also elaborated, providing clear pathways for future research initiatives. More specifically, a Knowledge Graph using PV data is currently under construction, based on PV signal report information published by Uppsala Monitoring Centre, the World Health Organization reference centre for PV. Furthermore, emphasizing on the potential use of Systems Pharmacology oriented data, an ontology enabling the semantic modelling of biochemical pathway information aligned with Systems Theory concepts has also been designed.

Keywords: Active Pharmacovigilance, Drug Safety, Knowledge Engineering, Semantic Web, Ontologies

Résumé détaillé

La sécurité des médicaments (DS) est un problème de santé publique important, car les effets indésirables des médicaments (EIM) entraînent un fardeau de santé publique important. La pharmacovigilance (PV) est définie comme *«la science et les activités liées à la détection, à l'évaluation, à la compréhension et à la prévention des effets indésirables ou de tout autre problème éventuel lié aux médicaments »*. L'une des principales activités de PV est l'investigation de nouveaux effets indésirables potentiels, appelés «signaux», à partir de l'utilisation des données de surveillance post-commercialisation du médicament, mais également des données produites aux stades antérieurs de pré-commercialisation. En règle générale, les signaux PV sont issus des données d'observation individuelle d'effets indésirables (ICSR) soumis par des professionnels de la santé (HCP) ou des patients via des systèmes de déclaration spontanée (SRS). Ces rapports sont analysés statistiquement (par exemple par une analyse de disproportionnalité – AD) pour identifier les signaux PV potentiels. Ces signaux sont ensuite étudiés par des groupes d'experts en combinant d'autres preuves provenant d'autres sources de données (c.-à-d. littérature scientifique, essais cliniques, etc.) pour valider ou invalider le signal. Ce processus est également défini comme «Pharmacovigilance passive» car il est basé sur des rapports soumis volontairement par des patients ou des HCP.

Les progrès des technologies de l'information et de la communication (TIC) permettent l'utilisation de nouvelles sources de données émergentes, généralement construites à d'autres fins principales, élargissant l'espace de preuves du monde réel utilisé pour rechercher de nouveaux signaux PV potentiels. Ces sources de données émergentes pourraient améliorer considérablement l'identification et l'élaboration de signaux PV potentiels, en complément des preuves produites par l'analyse des ICSR. Ainsi, la pharmacovigilance active (PA) va au-delà de l'utilisation des bases de données ICSR et peut être définie comme *«un processus systématique qui cherche à identifier les problèmes de sécurité grâce à des analyses épidémiologiques des bases de données de soins de santé»*, faisant généralement référence à l'exploitation des dossiers patients (DP) dans les systèmes d'information hospitaliers ou des bases de données d'observation, s'étendant parfois également à d'autres types de sources de données.

L'exploitation de ce déluge de données à des fins de DS comporte ses défis et nécessite d'introduire des méthodes de calcul puissantes pour permettre de prendre en compte l'hétérogénéité et la complexité des données sous-jacentes et en extraire de façon efficace des connaissances. Ce besoin exigeant dont l'objectif est de renforcer les preuves peut être abordé du point de vue de l'ingénierie des connaissances.

L'ingénierie des connaissances (KE) est une discipline de l'intelligence artificielle qui fait référence à l'[ingénierie](#) de systèmes intelligents incorporant beaucoup de connaissances tels les [systèmes experts](#). KE se concentre sur l'identification, la création, le stockage et la mise à disposition des connaissances afin de rester neutre face aux outils de partage et d'utilisation.

Les sous-disciplines associées sont : (a) l'extraction des connaissances (par exemple basée sur le traitement du langage naturel), (b) la représentation des connaissances (par exemple des représentations formelles telles que des ontologies), (c) l'intégration des connaissances (c'est-à-dire l'alignement syntaxique et sémantique et la normalisation de différents types de connaissances du domaine), (d) la diffusion des connaissances (c.-à-d. modélisation des informations à des fins de communication, se concentrant par exemple sur l'interopérabilité entre des systèmes TIC hétérogènes), et (e) la génération de connaissances par exemple en utilisant des techniques de fouille de données).

Nous soutenons que les technologies émergentes collectivement appelées « Intelligence Artificielle » (IA), et en particulier KE pourraient jouer un rôle crucial dans le contexte de la sécurité des médicaments. Cependant, les paradigmes technologiques « intelligents » sont difficiles à intégrer dans l'environnement clinique ou le contexte du soin en général. En se concentrant sur le domaine de la PV, le contexte réglementaire et les particularités des processus métiers (*Business processes* - BP) respectifs, crée un environnement complexe où l'intégration d'outils informatiques innovants est aujourd'hui difficile. Étant donné que l'intégration d'applications « intelligentes » dépend fortement des interactions spécifiques de l'utilisateur final, la détection précoce et la répartition appropriée de ces interactions ou conflits entre les BP sont cruciales, car elles affectent considérablement les « objectifs de l'utilisateur » (UG) et affectent aussi la conception des processus de soins de santé appliqués et l'intégration de nouveaux outils informatiques.

Par conséquent, l'hypothèse principale de cette thèse est que *l'intégration des technologies KE émergentes pourrait être utile pour définir la « pharmacovigilance active » en tant que nouveau paradigme de fonctionnement de la PV clinique basé sur l'identification et l'analyse des processus métiers et des objectifs des utilisateurs.*

L'objectif principal de cette thèse est de définir clairement le concept de pharmacovigilance active et de le réviser, en mettant l'accent sur l'impact potentiel des approches d'ingénierie des connaissances et en identifiant les étapes nécessaires en termes de «feuille de route». Pour atteindre cet objectif, un certain nombre d'objectifs intermédiaires ont été définis comme suit :

- Fournir un aperçu détaillé des travaux de recherche menés concernant l'application de l'ingénierie des connaissances à des fins de sécurité des médicaments et mettre en évidence les lacunes potentielles des recherches dans ce domaine
- Identifier les processus métiers liés à la pharmacovigilance
- Définir un ensemble d'objectifs utilisateur en fonction des commentaires des utilisateurs finaux

- Élaborer sur les développements techniques nécessaires afin d'identifier les défis à venir de l'utilisation des approches KE, sur la base d'une expérience pratique

Methodology

Cette thèse a été menée dans le cadre du projet PVClinical¹, qui vise à construire une plate-forme Web basée sur KE pour faciliter l'investigation des signaux d'effets indésirables potentiels dans le contexte clinique et au-delà. La méthodologie appliquée au cours de cette thèse peut se résumer aux étapes suivantes :

1. Revue systématique des approches KE utilisées pour DS
2. Vue d'ensemble du cadre réglementaire de la PV en Europe
3. Analyse des processus métiers (BP) actuellement appliqués et liés à la PV
4. Définition des objectifs de l'utilisateur sur la base 1) des BP élaborés, 2) des commentaires des utilisateurs finaux et 3) d'une analyse de l'état de l'art (SotA)
5. Sur la base de ce qui précède, fournir un nouveau paradigme permettant l'intégration de l'AP dans la pratique clinique.

L'état de l'art

Un article présentant un aperçu de l'état de l'art concernant l'utilisation des approches KE dans le contexte du DS a été publié comme l'un des principaux résultats de la thèse présentée. Une recherche systématique a été effectuée en interrogeant deux référentiels bibliographiques : PubMed² et Web of Science³. L'étude comprenait l'étape de recherche d'articles et deux étapes de révision consécutives, la première visait à filtrer les articles non pertinents avec les domaines KE et DS à partir de leur titre et de leur résumé, et la seconde était consacrée à l'évaluation détaillée du texte intégral des articles restants. Ces derniers ont été cartographier wen fonction de critères d'analyse spécifiques.

Sur la base des résultats de l'article, si un large intérêt pour l'exploitation de sources de données diverses et émergentes est évident, cela soulève de nombreux défis et de la place pour des recherches supplémentaires. Par exemple, les connaissances biologiques sous-jacentes au métabolisme des médicaments et aux mécanismes pharmacologiques n'ont pas été suffisamment élaborées pour déduire de nouvelles relations de cause à effet entre les médicaments et les effets indésirables. Outre les sites polymorphes et les altérations de l'expression génique, d'autres mécanismes moléculaires, tels que les éléments régulateurs et les modifications épigénétiques, peuvent avoir une relation directe ou indirecte avec les

¹ <https://pvclinical-project.eu>

² <https://www.ncbi.nlm.nih.gov/pubmed/>

³ <https://webofknowledge.com/>

médicaments et par conséquent les EIM. En outre, la standardisation des données d'observation des soins de santé est un problème. Les modèles de données communs reposant sur des terminologies de référence, telles que le MDP OMOP, peuvent accroître l'applicabilité et la reproductibilité des méthodes d'analyse computationnelle dans le domaine. Malgré le bruit et la complexité inhérents à l'analyse du contenu des médias sociaux, cette source de données ne peut être négligée en raison de sa large pénétration dans la vie quotidienne et de sa capacité à fournir des informations en particulier sur les événements de santé arrivant rarement.

En termes d'activités KE, l'extraction et la représentation des connaissances ont été largement élaborées, tandis que l'accent mis sur la diffusion des connaissances était assez limité. De même, la détection des événements indésirables, la collecte d'informations et l'évaluation ont attiré la plupart des efforts de recherche parmi les activités de base du DS, tandis que la détection du signal, l'analyse MoA (*Mechanism of Action*) et l'identification des interactions médicamenteuses sont les trois sujets les plus ciblés du DS. Inversement, l'accent mis sur la déclaration des événements indésirables est limité et peut être identifié comme une lacune pour des recherches ultérieures.

Il est intéressant de noter que certaines études ont exploité conjointement plusieurs sources de données, illustrant, par exemple, la valeur ajoutée des méthodes KE en matière d'intégration des données, ainsi que l'intérêt pour une liaison/modélisation systématique entre le phénotype et les éléments du génome/protéome qui interagissent avec le médicament. Ce besoin d'une approche systématique facilitant l'intégration d'informations biochimiques et génotypiques de bas niveau avec des modèles phénotypiques appliquant le paradigme de la pharmacologie des systèmes (*Systems Pharmacology – SP*) a déjà été identifié comme une opportunité de recherche. Si ces modèles illustrent des résultats remarquables, ils n'exploitent pas pleinement la puissance de certaines approches KE telles que des ontologies, étant généralement basés sur des règles (au moins partiellement) afin de modéliser des processus physiologiques, biologiques ou pharmacodynamiques / pharmacocinétiques. En particulier, ils n'utilisent pas de modèles ontologiques de référence décrivant la biologie des systèmes ou les concepts de SP de manière systématique. Par conséquent, la modélisation holistique des effets indésirables, combinant la puissance des ontologies et du raisonnement en logique de description (DL) avec les modèles mathématiques ou empiriques de pharmacocinétique et de pharmacodynamique est un sujet de recherche ouverte. Une telle approche pourrait permettre l'intégration de sources de big data (via des ontologies) avec des modèles multi-échelles SP, pour faciliter la médecine de précision. Des résultats très prometteurs ont été obtenus en combinant l'inférence statistique sur les données des déclarations spontanées et la modélisation basée sur l'ontologie et l'inférence sur les caractéristiques et les catégories de l'EIM. Ainsi, cette approche enrichie avec des modèles SP sera également considérée comme une opportunité de recherche et élaborée plus avant par des études futures.

En ce qui concerne les défis techniques, la performance du raisonnement constitue un enjeu important, en particulier lorsque l'on considère des modèles de connaissances à grande échelle. Par exemple, afin d'éviter l'héritage multiple, OAE (une ontologie de référence assez

grande dans le domaine des effets indésirables) n'accepte qu'un seul terme parent dans la hiérarchie et permet aux autres termes parents d'être obtenus automatiquement par raisonnement. Un autre exemple de compromis à la modélisation des connaissances dans un souci de performance est le cas de DINTO (ontologie des interactions médicamenteuses), où l'ontologie a dû être simplifiée pour être traitée par des raisonneurs existants. Ainsi, les problèmes de performances dans les logiciels de raisonnement DL peuvent être considérés comme un goulot d'étranglement pour l'adoption dans le monde réel de modèles d'ontologies complexes / volumineux.

En conclusion, malgré le nombre croissant d'études exploitant KE pour DS, l'absence d'une «success-story» majeure - au-delà de la preuve de concept - est évidente. Cela constitue un défi important pour les chercheurs du domaine, qui doivent répondre s'ils souhaitent valoriser les approches KE dans le contexte du DS et, par conséquent, faciliter leur adoption plus large par les parties prenantes du DS. Bien que peu d'études aient atteint ou se soient explicitement concentrées sur la pratique de routine du DS, nous soutenons que l'implication des méthodes KE dans les processus DS établis peut considérablement contribuer au développement d'un système de santé avancé et d'apprentissage continu, ce qui est nécessaire pour une surveillance efficace du DS. Enfin, nous suggérons que l'utilisation d'approches KE, par ex. les ontologies, en combinaison avec des modèles *pharmacocinétiques* et *pharmacodynamiques*, pourraient faciliter la construction d'un cadre SP capable de fournir une voie vers la *médecine de précision* en exploitant des preuves du monde réel.

Contexte réglementaire et aspects de gestion

Dans le cadre de la thèse présentée, une analyse a été menée dans le but de consolider diverses informations, y compris provenant des utilisateurs finaux, pour identifier les «objectifs utilisateurs» (UG) à propos de l'adoption de paradigmes techniques «intelligents» pour la sécurité des médicaments dans le contexte clinique. Les UG sont des « exigences abstraites des utilisateurs, ne faisant pas directement référence à des approches techniques spécifiques », directement attribuées aux utilisateurs comme « rôles » ou « acteurs ». La définition des UG vise à mettre en évidence les «lacunes» dans les processus métiers (BP) actuellement appliqués et la résolution des conflits potentiels entre les acteurs et les BP, en fournissant ainsi une contribution à la conception globale du système.

À cette fin, l'accent a été mis sur les résultats de deux parties du processus global: (a) un « aperçu du cadre réglementaire » basé sur un examen approfondi de la législation européenne relative à la PV et la contribution d'experts PV, et (b) « Identification et élaboration de BP ».

Cadre réglementaire

Les organisations de surveillance des médicaments (DSMO) jouent un rôle crucial dans les étapes pré et post-commercialisation du cycle de vie d'un médicament, c'est-à-dire des essais

cliniques et de l'autorisation de mise sur le marché à la surveillance post-commercialisation, et généralement, elles maintiennent également le SRS. Par exemple, la Food & Drug Administration (FDA) aux États-Unis maintient le système de déclaration d'événements indésirables et en Europe, l'Association européenne des médicaments (EMA) maintient EudraVigilance. Par ailleurs, le Centre de surveillance d'Uppsala (WHO-UMC) est le centre de référence de l'OMS (Organisation Mondiale de la Santé) sur la PV et gère la plus grande base de données de ICSR à l'échelle mondiale, VigiBase.

Insistant sur le contexte européen, la directive 2010/84 (appliquée en juillet 2012 via le règlement n ° 520/2012 et les bonnes pratiques de pharmacovigilance - GVP - modules I à XVI), a marqué une mise à jour politique majeure concernant les exigences de sécurité pour les médicaments à usage humain. En ce qui concerne la surveillance post-commercialisation, elle a ordonné le déploiement de SRS nationaux permettant également des déclarations par les citoyens. En outre, les sociétés pharmaceutiques étaient tenues de maintenir et de mettre à jour régulièrement des plans de gestion des risques (PGR) et de fournir des rapports périodiques de mise à jour de sécurité (PSUR). Toutes les parties prenantes ont été chargées d'échanger activement des données et enfin, toutes les informations collectées sont évaluées par le comité d'évaluation des risques de pharmacovigilance (PRAC) de l'EMA, chargé d'évaluer les risques médicamenteux dans l'UE.

Processus métiers

Le tableau 1 et le tableau 2 décrivent les BP pertinents tels qu'ils ont résulté des ateliers et des entretiens avec des cliniciens et des experts en PV. Pour chacun de ces BP, les avantages potentiels de l'utilisation d'outils informatiques pour soutenir ont été élaborés pour identifier et hiérarchiser les objectifs de l'utilisateur pertinents.

Tableau 1. Les processus métiers en relation avec PV dans l'environnement clinique

<i>Nom</i>	<i>Description</i>	<i>Acteurs</i>	<i>Données</i>
BP1: Consultations externes	BP1 pourrait inclure l'enregistrement du patient et ses antécédents médicaux dans le DP de l'hôpital, l'examen clinique, la prescription électronique, etc.	<ul style="list-style-type: none"> • Médecin • Infirmière 	Démographie, antécédents médicaux, résultat de laboratoire, diagnostic, ePrescription
BP2: Hospitalisation	BP2 comprend les étapes BP1 ainsi que les procédures cliniques (par exemple une opération), les entrées informatisées des prescriptions du médecin (CPOE), la maintenance des notes cliniques et la sortie du patient.	<ul style="list-style-type: none"> • Médecin • Pharmacologue • Infirmière 	Données BP1 et aussi notes cliniques, données CPOE, notes de sortie

BP3: évaluation de service	Le BP3 ne fait pas référence à la pratique clinique mais est régulièrement appliqué dans les hôpitaux pour évaluer des paramètres cliniquement pertinents (effets indésirables, infections hospitalières, erreurs, etc.).	<ul style="list-style-type: none"> • Médecin • Pharmacologue • Infirmière • Scientifique informatique • Gestionnaire 	Statistiques sur les DP, liste priorisée d'effets indésirables d'intérêt, comparaison avec d'autres sources de données
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Tableau 2. Les processus métiers en relation avec PV en dehors de l'environnement clinique

<i>Nom</i>	<i>Description</i>	<i>Acteurs</i>	<i>Données</i>
BP4: Essais cliniques	BP4 comprend la conception d'une étude / intervention, la définition des cohortes de patients, la collecte et la conservation des données, la comparaison avec d'autres essais cliniques et également la communication des résultats	<ul style="list-style-type: none"> • Médecin • Expert PV 	Données démographiques, antécédents médicaux, profilage génétique, résultats de laboratoire, notes cliniques, rapports de sécurité et d'efficacité
BP5: mise à jour des rapports périodiques de sécurité	BP5: mise à jour des rapports périodiques de sécurité	<ul style="list-style-type: none"> • Médecin • Expert PV 	Données sur l'innocuité des médicaments, statistiques, documentation / rapports, listes hiérarchisées d'événements indésirables d'intérêt
BP6: revue de la littérature hebdomadaire	BP6 fait référence à des revues de littérature, y compris la mise en forme de requêtes basées sur des mots-clés et des synonymes par rapport à diverses sources de littérature	<ul style="list-style-type: none"> • Médecin • Expert PV 	Documentation / rapports
BP7: Gestion des risques	BP7 comprend une revue de la littérature, une revue des données d'essais cliniques pertinentes, ainsi que le calcul des facteurs de risque	<ul style="list-style-type: none"> • Expert PV 	Données, statistiques, documentation / rapports sur la sécurité des médicaments

Objectifs et défis des utilisateurs concernant l'intégration de systèmes informatiques «intelligents» dans l'environnement clinique

L'identification des objectifs de l'utilisateur en ce qui concerne l'intégration de systèmes informatiques «intelligents» dans l'environnement Clinique a été identifié comme une étape clé pour l'adoption du paradigme de PA en vie réelle.

Objectifs de l'utilisateur

La liste finale des UG identifiés est résumée dans le tableau 3.

Tableau 3. Liste finalisée des objectifs des utilisateurs

<i>ID</i>	<i>Titre</i>	<i>Description</i>	<i>Référence aux BP</i>
<i>UG1</i>	<i>L'utilisation de synonymes de nom de médicaments doit être encouragée</i>	La recherche d'informations sur le médicament en utilisant la substance active, le nom empirique ou commercial doit être soutenue	Tous les BP sont pertinents, mais cette fonctionnalité serait particulièrement utile pour BP5, BP6 où des requêtes complexes sont formées
<i>UG2</i>	<i>Une approche graphique avec une visualisation hiérarchique des concepts (pour le codage) doit être possible</i>	Les niveaux / hiérarchies conceptuels et les regroupements de concepts fournis par des codages bien définis (par exemple, les niveaux MedDRA et WHO-ATC) pourraient faciliter la formulation des requêtes de recherche par les utilisateurs de manière plus succincte, en exploitant la sémantique fournie par les codages respectifs dans le cadre du Interface utilisateur.	Tous
<i>UG3</i>	<i>Des concepts non ambigus bien définis devraient être utilisés sur la base de thésaurus, dictionnaires et ontologies médicales largement acceptés</i>	L'utilisation de termes bien définis devrait améliorer la formulation des requêtes en réduisant l'ambiguïté sémantique et en améliorant l'accès à des sources de données pertinentes et bien normalisées.	Tous les BP sont pertinents, mais cette fonctionnalité serait particulièrement utile pour BP5, BP6 où des requêtes complexes sont formées
<i>UG4</i>	<i>Une multitude de sources de données doivent être utilisées, y compris, mais sans s'y limiter, les ICSR</i>	Il convient d'utiliser à la fois des sources bien établies (c'est-à-dire des sources largement utilisées dans la pratique quotidienne), ainsi que des sources émergentes qui font l'objet de recherches approfondies pour leur intérêt potentiel dans les études sur l'innocuité des médicaments.	BP2, BP3, BP4, BP5, BP6, BP7
<i>UG5</i>	<i>Évaluation statistique des signaux possibles et évaluation computationnelle de la causalité</i>	Des métriques statistiques basées sur des techniques d'analyse de la disproportionnalité est la principale approche pour la détection et la hiérarchisation des signaux de sécurité potentiels qui en résulte et celles-ci devraient être largement utilisés.	BP3, BP4, BP5, BP7

UG6	<i>Exploiter les caractéristiques spéciales fournies par chaque source de données</i>	Chaque source de données fournit des données de différents types avec des caractéristiques différentes, exploitables en termes d'investigation des signaux de sécurité des médicaments. Par exemple, si les statistiques DA (par exemple, PRR, ROR, etc.) peuvent être extrêmement utiles dans les bases de données ICSR, ces mesures peuvent ne pas être pertinentes pour les médias sociaux et par conséquent, les caractéristiques spéciales de chaque source de données doivent être prises en compte.	BP2, BP3, BP4, BP5, BP7
UG7	<i>Des fonctionnalités avancées d'analyse visuelle doivent être intégrées</i>	En plus des données statistiques-numériques, des aides visuelles pourraient faciliter une enquête approfondie sur les signaux de sécurité potentiels	BP2, BP3, BP4
UG8	<i>Des processus à long terme / «en pause» pour enquêter sur un signal d'innocuité des médicaments doivent être disponibles</i>	Une fonction «enregistrer pour l'instant et reprendre plus tard» est essentielle, car de tels processus prennent du temps et sont laborieux. Surtout dans l'environnement clinique où la PV n'est pas la priorité absolue des HCP, une telle caractéristique serait de la plus haute importance.	BP2, BP3, BP4, BP5, BP6, BP7
UG9	<i>La capacité de surveillance à long terme d'un signal doit être fournie</i>	De nombreux signaux de sécurité peuvent impliquer la recherche d'études longitudinales ou la surveillance à long terme d'un médicament et peuvent donc s'étendre sur de longues périodes. De même, l'analyse des essais cliniques ou la fourniture de services cliniques sont également considérées comme des processus longs.	BP3, BP4, BP5, BP6
UG10	<i>Les «scénarios» d'enquête doivent être identifiés comme le principal paradigme d'utilisation</i>	Malgré la valeur avérée des recherches directes pour la détection de signaux, la formulation de scénarios d'investigation pourrait être encore plus bénéfique en raison de l'analyse plus approfondie avec des capacités améliorées qu'ils offrent. Néanmoins, une certaine fonction de «recherche / enquête rapide» peut également être incluse.	BP2, BP3, BP4, BP5, BP6, BP7
UG11	<i>Contrôle d'accès basé sur les rôles pour les utilisateurs</i>	Ce contrôle peut permettre l'analyse simultanée de plusieurs signaux PV. Les utilisateurs peuvent créer, modifier ou supprimer des scénarios, en fonction des autorisations spécifiques accordées à chacun d'entre eux. De plus, la collaboration et le travail d'équipe peuvent être encouragés et ainsi éviter les erreurs	Tous
UG12	<i>Génération complète de rapports à partir de chaque scénario d'enquête</i>	Un rapport de scénario d'enquête serait très utile pour diffuser les résultats de l'enquête à d'autres experts cliniques ou à d'autres parties prenantes (par exemple, les agences de réglementation, etc.).	BP2, BP3, BP4, BP5, BP6, BP7

<i>UG13</i>	<i>Accès aux informations pour chaque cas de patient individuel</i>	En raison de la variabilité inter-patient, l'enquête sur les effets indésirables suspectés exige l'accès à autant d'informations détaillées disponibles. Cela pourrait concerner, par exemple, le profil génétique d'un patient affecté par un EIM lors d'essais cliniques ou la forme originale des ICSR qui documentent un signal.	BP2, BP4, BP5, BP7
<i>UG14</i>	<i>Possibilité de remonter à la source de données brute d'origine</i>	La fiabilité ne peut être évaluée ou prouvée que si l'origine exacte des données peut être retracée, une caractéristique qui peut également être importante pour le partage de données médicales.	BP4, BP5
<i>UG15</i>	<i>Convivialité</i>	Relever les défis cruciaux du milieu clinique, tels que le calendrier serré des cliniciens ou la sous-estimation de la PV en raison de la priorité plus élevée des autres procédures cliniques	Tous
<i>UG16</i>	<i>Protection des données et confidentialité</i>	Conformité au cadre réglementaire et aux légalités strictes (par exemple le règlement général sur la protection des données RGPD)	Tous
<i>UG17</i>	<i>Extensibilité et adaptabilité</i>	Être polyvalent avec de nouvelles sources de données potentielles de pharmacovigilance et opérationnel dans des environnements distincts (différents hôpitaux, CRO, etc.), quelle que soit l'infrastructure informatique utilisée (par exemple, le dossier médical électronique) ou les procédures appliquées	Tous
<i>UG18</i>	<i>Interopérabilité</i>	Les données générées (par exemple les rapports consolidés) doivent également être exploitables de manière informatique par d'autres systèmes d'information.	BP2, BP5, BP7

Défis

Les obstacles à l'adoption de systèmes intelligents (SI) dans les activités PV axées sur le contexte clinique sont élucidés (au moins en partie) par les UG identifiés, cependant, ils peuvent être généralisés en faisant référence à l'adoption des SI dans le domaine de la santé dans son ensemble, au-delà de la pharmacovigilance.

- *Ensembles de données médicales fragmentées*
- *Pièges techniques inhérents aux SI (c.-à-d. Polyvalence, validité et interprétabilité)*
- *Convivialité*
- *Problème juridique*
- *Sécurité des informations*

Pharmacovigilance active dans le contexte d'un système de santé auto-apprenant

Sur la base des BP et des UG identifiés dans les chapitres précédents, il est apparu clairement qu'un changement de paradigme des processus de sécurité des médicaments actuellement appliqués devait être appliqué, allant vers l'intégration d'approches informatiques «intelligentes» et de sources de données «réelles».

Plus précisément, renforcer les hôpitaux avec de meilleures infrastructures informatiques pour les soutenir dans la collecte et l'analyse des données, et les interconnecter via des réseaux d'échange d'informations avec d'autres domaines qui ne sont pas strictement cliniques (par exemple, les services sociaux ou les soins primaires, la recherche, le développement de médicaments, les sources de données sur le mode de vie, etc. .) pourrait offrir des avantages bidirectionnels et également soutenir la prise de décision politique. Ces avantages concernent les processus de santé dans leur ensemble, y compris la sécurité des médicaments et la PV.

Dans cette nouvelle ère de développement de médicaments et de gestion de la sécurité où les technologies joueront inévitablement un rôle de premier plan, nous soutenons que le passage aux paradigmes de «Learning Healthcare System» (LHS) et de «Active Pharmacovigilance» (AP) pourrait apporter des avantages importants, principalement pour la sécurité et la santé mais aussi en terme de gestion des coûts. Bien que les défis administratifs, financiers et réglementaires ne doivent pas être sous-estimés, nous soutenons qu'une telle approche pourrait considérablement améliorer le temps et le coût global du développement de médicaments menant à de nouveaux médicaments plus sûrs plus rapidement.

Un concept clé pour LHS est l'idée de «médecine centrée sur le patient» où les citoyens sont identifiés comme (a) producteurs de données, (b) cocréateurs de services et (c) consommateurs de services. Les principaux axes politiques généralement définis dans le contexte de la vision LHS sont: (a) l'adoption rapide des résultats de la recherche dans la pratique clinique de routine; (b) le changement de culture parmi les différentes parties prenantes; et (c) la collaboration des patients et des médecins pour produire des preuves. Il est à noter que la vision LHS met l'accent sur la participation du patient à la prise de décision

globale afin de personnaliser les plans de soins au lieu de délivrer un traitement standard conçu pour la «personne moyenne» évoluant vers la vision de la médecine de précision.

À cette fin, le paradigme LHS se concentre également sur l'utilisation de preuves «du monde réel» basées sur des données collectées dans la pratique clinique quotidienne via les DP. Les données du DP sont constamment mises à jour et constituent une source d'information évolutive qui peut être utilisée comme base pour des conclusions et des connaissances spécifiques à la population, plus faciles à utiliser car elles sont déjà produites dans le cadre de la pratique clinique quotidienne et plus simples à utiliser que les connaissances produites via un essai contrôlé randomisé. Bien que le paradigme LHS ne soit pas nouveau et que certaines initiatives orientées LHS dans le monde entier puissent être identifiées, les réformes visant à appliquer la LHS dans des contextes réels restent largement théoriques.

Le flux de l'information dans un système de soins de santé typique aujourd'hui est illustré dans la figure 1, mettant en évidence le manque de traduction de la recherche en pratique clinique. En alignant les activités PV typiques dans le contexte de ce flux d'information, les preuves utilisent généralement des approches «passives» produites via une analyse de disproportionnalité basée sur les ICSR. Il convient de noter que la principale contribution des patients concernant les effets indésirables potentiels provient de la soumission des ICSR et qu'il s'agit clairement d'un canal de communication très faible, car les ICSR sont fortement sous-déclarés. Par conséquent, bien que beaucoup d'efforts soient déployés pour réduire le temps entre l'apparition des premières preuves et les mesures réglementaires pour la sécurité des médicaments, l'écart de traduction est toujours là principalement en raison du manque de données, ce qui affecte fortement le processus global.

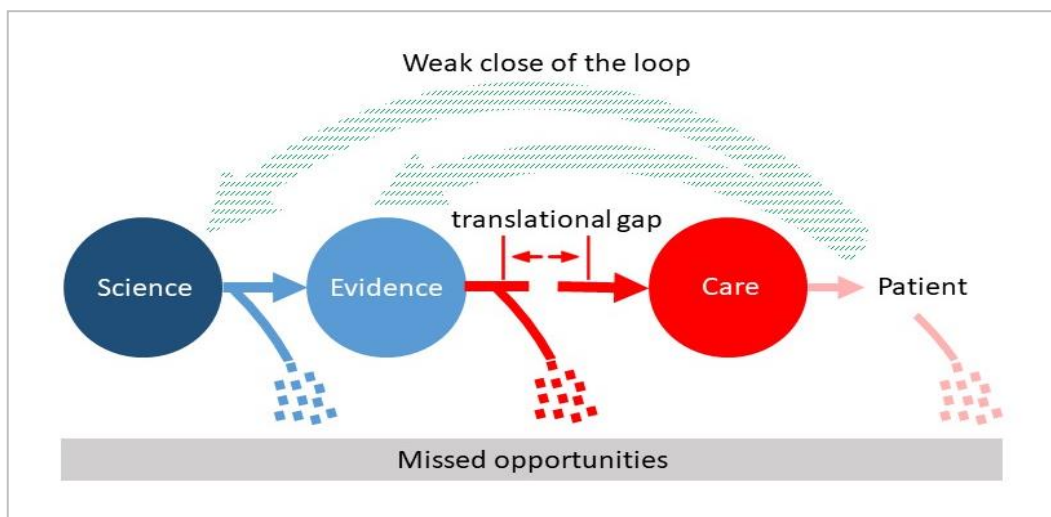


Figure 1: Flux informationnel d'un système de santé typique

En combinant les deux paradigmes de LHS et AP, nous proposons une mise à jour du cycle de vie principal de l'information LHS, en mettant l'accent sur deux concepts: (a) le besoin de diffuser les connaissances produites à la communauté, et (b) le besoin de transparence. Bien

que ces deux concepts aient été élaborés dans une certaine mesure dans le contexte de LHS, nous les soulignons car ils sont particulièrement importants pour AP.

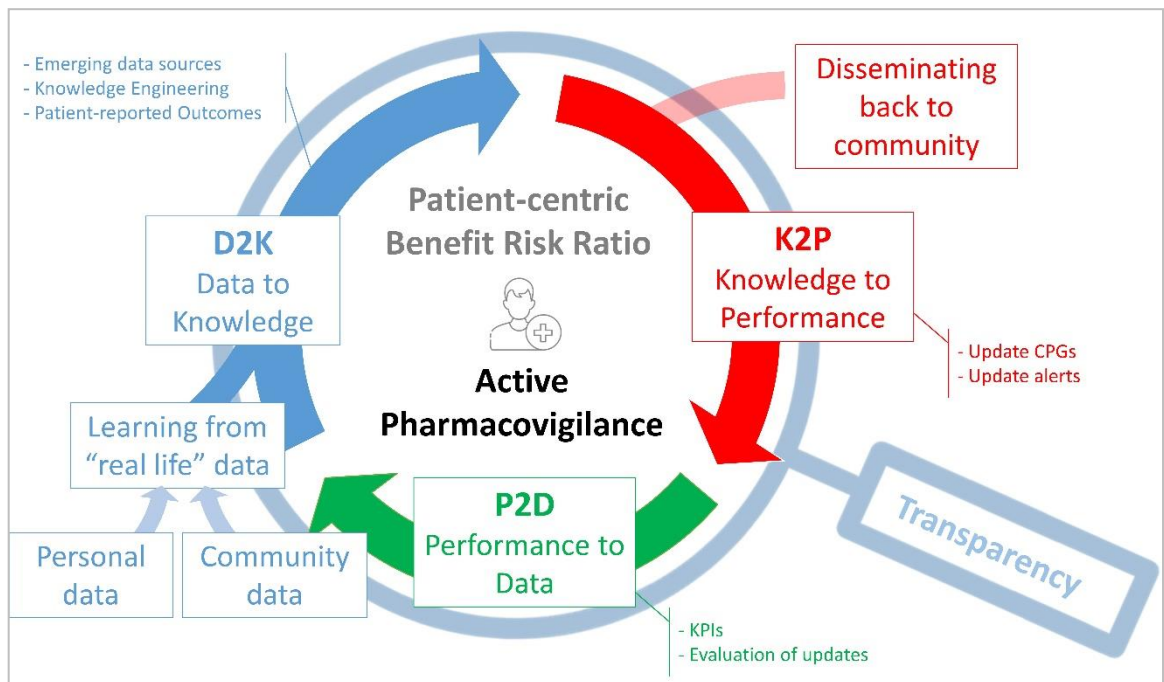


Figure 2: Le cycle AP-LHS: le cycle de vie des informations du système de santé d'apprentissage adapté à la pharmacovigilance active

À cette fin, la définition et le calcul itératif d'un rapport bénéfice-risque centré sur le patient (PCBRR) joue un rôle important car il est utilisé dans toutes les parties du cycle AP-LHS respectif visant à soutenir un traitement personnalisé. PCBRR pourrait être décrit via les fonctionnalités suivantes:

1. Doit prendre en compte les approches AD sur les données communautaires
2. Devrait prendre en compte les données personnelles liées à la clinique
3. Devrait prendre en compte les données de style de vie personnelles
4. Doit prendre en compte les préférences personnelles du patient
5. Doit être spécialisé pour des effets indésirables spécifiques
6. Le résultat global doit être lié aux sources d'information / données brutes d'origine

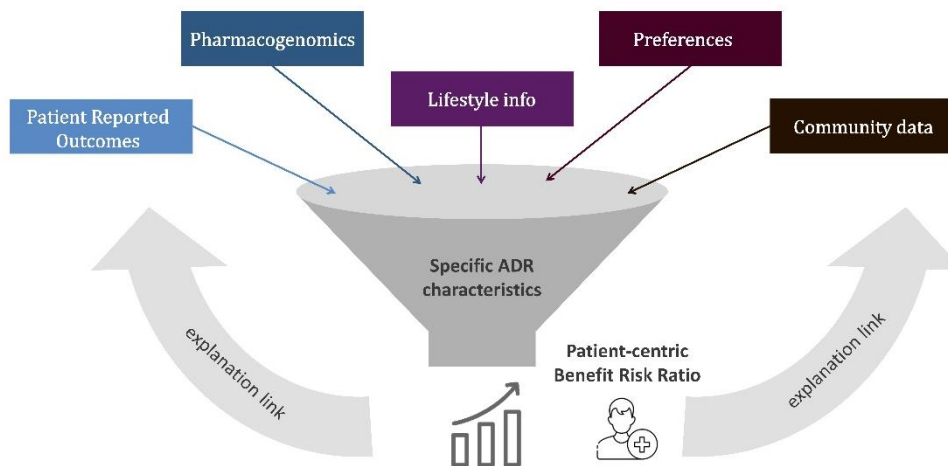


Figure 3: Le rapport bénéfice-risque axé sur le patient - principales sources d'information

Sur la base de ce qui précède, l'AP pourrait être définie comme la «poursuite systématique» de RWE (real world evidences – preuves basées sur es données de vie réelles) dans toutes les sources de données possibles visant à « apprendre » afin de soutenir une prise de décision clinique personnalisée basée également sur des informations individuelles, y compris le patient en tant qu'acteur du processus de décision proprement dit ».

Même si le paradigme AP-LHS semble être aligné sur les UG identifiés dans cette thèse, les défis du changement de paradigme proposé ne doivent pas être sous-estimés. À cette fin, nous considérons que les UG et les BP identifiés pourraient apporter des éclairages utiles et faciliter les prochaines étapes de la vision d'intégration des AP dans le cadre d'un LHS. Techniquement, nous soutenons que l'adoption d'approches de calcul KE et d'outils basés sur KE pourrait être cruciale pour cette vision car ils pourraient fournir l'infrastructure technique pour soutenir cette vision. À cette fin, plusieurs défis peuvent être identifiés (par exemple, changement de *mentalité*, *engagement de la direction*, *financement*, *biais de diverses natures*, *interopérabilité*, *utilisabilité*, *sécurité de l'information*).

Nous soutenons que les approches informatiques liées à la KE pourraient fournir des solutions et faciliter la résolution (au moins en partie) des défis techniques identifiés. Par exemple, les paradigmes des données liées (*link data*) et du Web sémantique, c'est-à-dire l'utilisation d'ontologies OWL / RDF, pourraient améliorer l'interopérabilité sémantique. En outre, de nouveaux modèles de données permettant l'expansion de l'espace de données de manière pratique pourraient être déployés, en utilisant des ontologies (par exemple, OpenPVSIGNAL est un modèle ontologique construit afin de permettre l'intégration d'informations de signal PV en texte libre). De même, les modèles ontologiques pourraient faciliter l'intégration de la pharmacogénomique, des informations sur les voies, des informations sur le mode de vie, etc.

Plus spécifiquement, les avantages de se concentrer sur les approches KE pour chacune des trois branches du cercle AP-LHS peuvent être résumés comme suit:

- *D2K: Data to Knowledge*

Les approches KE peuvent considérablement faciliter l'intégration des données provenant de diverses sources de données dans un format unifié exploitable par ordinateur. En outre, les méthodes d'extraction de connaissances (par exemple, le traitement automatique des langues sur des données réelles ou une autre source) pourraient (semi) automatiquement alimenter le cercle AP-LHS avec les connaissances requises.

- *K2P: Knowledge to Performance*

La diffusion des connaissances de manière opportune et interopérable est cruciale pour améliorer les performances. À cette fin, représenter les connaissances en utilisant des normes bien définies, garantissant à la fois l'interopérabilité syntaxique et sémantique, pourrait avoir un impact significatif sur la manière dont ces connaissances sont intégrées dans les outils informatiques pour augmenter les performances et également sur la façon dont elles sont diffusées aux parties prenantes (par exemple, les professionnels de la santé).

- *P2D: Performance to Data*

Intégrer des données via plusieurs sources de données afin de mesurer l'impact potentiel et d'intégrer cet impact quantifié dans les données utilisées pour alimenter le prochain cycle du paradigme AP-LHS. De plus, les connaissances produites dans le cadre de la branche K2P pourraient être intégrées dans l'ensemble du processus via des modèles de connaissances spécifiques (par exemple, des signaux PV non confirmés pourraient alimenter la branche D2K via le modèle OpenPVSignal)

Enfin, il convient de souligner que les approches techniques KE pourraient également améliorer la *transparence*, qui est un aspect transversal de la vision proposée. Par exemple, l'application des principes de données FAIR (Findable, Accessible, Interoperable, Reusable) pourrait être cruciale pour accroître la confiance dans les diverses composantes du cycle AP-LHS.

Il convient de souligner que les technologies KE respectives référencées ici sont relativement matures. Par exemple, les principes FAIR peuvent être très bien soutenus par les normes techniques liées aux données liées et au Web sémantique qui sont activement soutenues depuis 20 ans. En outre, les techniques d'extraction des connaissances sont activement étudiées et ont déjà été (au moins en partie) réussies, également à des fins de sécurité des médicaments. Par conséquent, au moins en principe, les technologies clés de KE sont là, prêtes à soutenir la vision d'AP-LHS.

Perspectives de travaux futurs

Au fur et à mesure que cette thèse évoluait, un certain nombre de futurs cheminements de travail ont été identifiés et activement étudiés. Ceux-ci se réfèrent principalement à des travaux techniques non encore validés qui demandent plus de temps et dépassent le cadre de cette thèse. Plus précisément, deux chemins de travail techniques ont été élaborés car nous soutenons qu'ils pourraient apporter une valeur significative dans l'intégration de la vision AP dans l'environnement clinique. En tant que tels, nous les soulignons comme deux perspectives de travaux futurs clairs en termes d'utilisation d'approches KE pour intégrer l'AP dans des applications du monde réel.

Graphe de connaissances OpenPVSignal

Les informations sur les signaux PV sont généralement publiées par les DSMO après avoir été minutieusement étudiées par des groupes d'experts en les combinant de surcroît avec des informations provenant d'autres sources de données pertinentes (par exemple, la littérature scientifique, les essais cliniques, les informations sur la sécurité des médicaments similaires, etc.) afin de fournir des informations sur la « force » du signal et quelle pourrait être la relation causale entre le médicament et les effets indésirables respectifs. De toute évidence, ces informations sont inestimables pour les activités de sécurité des médicaments à toutes les étapes du cycle de vie d'un médicament.

Étant donné que le format textuel actuel des rapports sur les signaux PV ne peut pas être traité automatiquement, les experts en sécurité des médicaments doivent examiner manuellement les sources PV pertinentes, un processus laborieux et potentiellement sujet aux erreurs. Étant donné que ces informations / données pourraient jouer un rôle important dans les activités de sécurité des médicaments, nous soutenons que leur publication dans un format conforme aux principes FAIR pourrait permettre leur réutilisation systématique, y compris le traitement (semi) automatique et le raisonnement. Pour résoudre ce problème, nous avons récemment développé et publié OpenPVSignal, pour faciliter la normalisation, la diffusion, l'interconnexion et la vérification des informations de signal ADR d'une manière conforme à FAIR, basée sur les paradigmes du Web sémantique et des données liées permettant également un raisonnement automatique sur le modèle OpenPVSignal et Sémantique du langage d'ontologie Web (OWL). À cette fin, nous avons commencé le développement d'un graphe de connaissances (KG), basé sur OpenPVSignal, modélisant les rapports sur les signaux PV, tels que produit par l'OMS-UMC dans le cadre de leur lettre bimensuelle pour les dix dernières années (entre 2011-2019)⁴.

Pharmacologie des systèmes

La PV dans l'environnement clinique pourrait être considérablement améliorée grâce à l'engagement de sources de données émergentes, en engageant des informations sur le mécanisme d'action pharmacologique (MoA). Les sources de données biochimiques,

⁴ <https://www.who.int/medicines/publications/newsletter/en/>

génétiques, sur les voies et la pharmacogénomique font partie de cet écosystème de sources de données émergentes. Comme l'analyse des profils biochimiques et génétiques personnels devient moins onéreuse et fait partie d'une vision globale de la « médecine personnalisée », l'exploitation de ces sources de données dans le contexte de la PV, combinée à d'autres données cliniquement pertinentes (par exemple les résultats des tests de laboratoire) soutiendrait le paradigme de « pharmacovigilance personnalisée ». À cette fin, la *pharmacologie des systèmes (SP)* pourrait être le lien vers des connaissances, fournissant les moyens d'intégrer des données hétérogènes de granularité variable.

L'une des approches de modélisation formelle les plus négligées dans le contexte de SP est l'utilisation de modèles basés sur les états (issus de la théorie des systèmes de contrôle (CST), comme les *machines à états (SM)* ou les *automates*. Les modèles SM sont souvent considérés comme un sous-domaine de CST mais au lieu d'utiliser le concept de *fonctions de transfert*, les SM sont définis sur des *états* et des *transitions*. Dans un système modélisé à l'aide de SM, chaque nouvelle entrée conduit potentiellement le système à un autre état via une transition.

Nous soutenons que les modèles basés sur les états (SBM) permettent la représentation des transitions basées sur des approches probabilistes et l'utilisation du temps comme dimension de modélisation principale, et s'inscrivent donc dans le contexte d'applications du monde réel concernant la PV ou la pharmacologie en général, comme les concepts *d'état*, *d'entrée* et de *transition* correspondent au paradigme général d'une administration de médicament agissant comme un événement déclencheur (*entrée*) provoquant une turbulence biochimique (*transition*) conduisant à un nouvel *état* biochimique (ou physiologique). En règle générale, ces séquences de divers «états» en pharmacologie et en biologie sont appelées «informations sur les voies» et ont été utilisées pour élucider le MoA des médicaments parmi d'autres cas d'utilisation. Les SBM ont un énorme avantage par rapport aux modèles de calcul QSP typiques, car ils ne dépendent pas nécessairement de modèles quantitatifs (par exemple, des équations différentielles) qui sont très difficiles à produire et à valider, alors qu'ils pourraient encore les inclure dans le modèle global de transition d'états. Les SBM pourraient utiliser ces modèles mathématiques bien définis (lorsqu'ils sont disponibles), mais ils pourraient également être utilisés pour exploiter des connaissances d'experts non quantitatives ou empiriques concernant le comportement des systèmes biologiques. Étant donné que la plupart des connaissances de domaine bien validées en pharmacologie et en biologie (c'est-à-dire le comportement PK / PD d'un médicament) ne peuvent pas être quantifiées en détail et validées (ou du moins, il est très difficile de le faire car cela dépend fortement des approches en biologie humide) , l'utilisation de tels modèles dans le contexte de la SP est inestimable.

En outre, nous soutenons que l'utilisation des technologies du Web sémantique et des ontologies utilisées comme infrastructure technologique pour exploiter ces modèles pourrait également fournir des avantages informatiques significatifs, en particulier en ce qui concerne l'intégration de données et les capacités de raisonnement automatique. Pour consolider ce qui précède, un tel modèle pourrait probablement être utile dans le contexte de diverses

applications, également non liées à la sécurité des médicaments ou à la PV. Cependant, la PV est un bon choix pour une application exemplaire d'un tel modèle de données en raison de sa grande importance clinique et de l'existence de données probantes provenant de sources de données multiples (et potentiellement hétérogènes).

À cette fin, nous avons commencé à travailler sur une *ontologie de pharmacologie des États (SPO)* comme moyen pratique d'intégrer les sources de données respectives dans un KG et d'étudier les avantages informatiques respectifs. SPO permet de représenter les principaux concepts et modèles SBM de manière systématique, facilitant ainsi la combinaison des logiques de description (DL) et des SBM dans un seul cadre de calcul. Le but ultime serait de construire un KG, basé (au moins en partie) sur SPO pour combiner la puissance du raisonnement DL avec la modélisation SM pour identifier les effets indésirables potentiels sur une base personnalisée, basée sur des données personnelles (par exemple des tests de laboratoire, un profil génétique, etc. .) et aussi le mécanisme ADR d'information sur l'action.

Conclusion

Une méthodologie basée sur le «design thinking» a été appliquée dans le cadre du projet PVClinical afin d'étudier l'impact potentiel que les méthodes de calcul KE pourraient avoir dans la révision des processus PV dans l'environnement clinique. Plus spécifiquement, dans le projet PVClinical, une plate-forme Web est développée afin de faciliter l'étude des signaux PV potentiels, en utilisant KE comme son principal paradigme technique. Alors que les développements techniques du développement de la plate-forme sont considérés comme hors de portée de la thèse actuelle, un certain nombre d'objectifs ont été identifiés concernant la révision et la définition claire de l'AP et l'impact que les approches de calcul KE pourraient avoir à cet égard. Enfin, deux voies de travail techniques ont été activement étudiées, décrivant deux voies de recherche futures en termes d'utilisation d'ontologies pour construire des KG qui pourraient soutenir les objectifs DS et AP.

Résumant la contribution de la thèse présentée, les points clés suivants pourraient être soulignés:

- Une analyse qualitative et quantitative détaillée des tendances de la recherche de la dernière décennie concernant l'utilisation de la KE à des fins de DS a été présentée via une revue systématique et cartographique approfondie de la littérature scientifique respective.
- Sur la base de cet examen systématique, les lacunes de la recherche ont été mises en évidence
- Un ensemble de BP liés au PV a été défini et élaboré, en tenant compte du contexte légal et réglementaire
- Un ensemble d'UG a été identifié sur la base des BP respectifs et de la contribution des HCP et des experts PV
- AP a été redéfini dans le cadre d'un paradigme LHS plus large, basé sur les derniers développements techniques

En conclusion, nous soutenons que ce nouveau paradigme (et potentiellement l'élaboration des résultats intermédiaires de cette thèse, c'est-à-dire les BP et UG identifiés) pourrait avoir des avantages significatifs dans les aspects suivants et qu'il devrait donc être activement étudié en termes d'élaboration des politiques car il pourrait avoir un impact significatif sur (a) *la qualité des soins de santé*, (b) *le développement de médicaments* et (c) *les coûts de santé*.

1. Introduction

Drug Safety (DS) is an important issue of public health interest, as Adverse Drug Reactions (ADRs)⁵ cause a significant public health burden with a very big financial impact. A recent review of European studies estimated that the cost of ADRs between €2,851 and € 9,015 for the inpatient setting and €174 to €8,515 for the outpatient setting. Furthermore, the impact of ADRs on the length of stay is estimated at 9.2 ± 0.2 days (outpatient setting) and 6.1 ± 2.3 days (inpatient setting) (Formica et al., 2018). According to the US Office of Disease Prevention and Health Promotion Adverse Drug Events (ADEs) account for 1 in 3 of all hospital adverse events, concern about 2 million hospital stays each year, and prolong hospital stays by 1.7 to 4.6 days. Regarding outpatient settings, each year ADEs account for over 3.5 million physician office visits, about 1 million emergency department visits and, approximately, 125,000 hospital admissions (Adverse Drug Events | health.gov).

Due to the importance of DS and its major impact, numerous concepts around this domain have been developed and elaborated as part of various research initiatives. This introductory section provides the definitions of the main concepts as well as an overview of the domain, also identifying the problem addressed by this thesis.

Pharmacovigilance (PV) is defined as “*the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems*” (World Health Organization, 2002). Obviously, the domain of PV intersects with all aspects of DS, but the use of term “vigilance” highlights the focus on the investigation of data/information coming in the realm of drug development from the outer “real-world”. To this end, one of the main PV activities concerns the discovery and investigation of clues for potential new or partially documented ADRs, also known as “*signals*”. Signals are typically identified based on Drug-Event Combinations (DEC) which are “suspiciously” frequently identified in the respective data sources, disproportionally compared to what expected. Signal identification processes are based on the use of post-marketing surveillance data but it could also exploit data produced in pre-marketing stages of drug development and testing, i.e. clinical trials. Typically,

⁵ Throughout the thesis, the term “Adverse Drug Reaction” is used. As this term is sometimes used interchangeably with the term “Adverse Drug Event” (ADE), we clarify that ADEs refer to side-effects that may or may not have causal relationship with the drug, including the events caused by drug misuse (e.g. overdose). Respectively, ADR refer to side-effects that occur after a legitimate drug use (i.e. there is no overdose) and therefore “characterised by the suspicion of a causal relationship between the drug and the occurrence”. For a comprehensive definition of terms used in DS we refer the reader to (Lindquist, 2007)

PV signals are identified based on the frequency of Individual Case Safety Reports (ICSRs) manually submitted by Health Care Professionals (HCPs) or patients via Spontaneous Reporting Systems (SRSs). These reports are analysed using “Disproportionality Analysis” (DA) approaches (Montastruc et al., 2011) to identify potential PV signals. The latter are further elaborated by expert groups who combine evidence from other data sources (i.e. scientific literature, clinical trials etc.) and then communicated via public communication channels (websites, newsletters, etc.). This process is also defined as “Passive Pharmacovigilance” as it is based on voluntarily submitted reports by patients or HCPs (World Health Organization, 2018).

Advances in Information and Communication Technologies (ICT) and vast data collection capabilities enable the use of new, emerging data sources, typically built for other primary purposes, expanding the real-world evidence (RWE) space used to explore potential PV signals. The information produced from these emerging data sources, could significantly improve the identification and the elaboration of potential PV signals, acting complementary to the evidence produced via the analysis of ICSRs.

Active Pharmacovigilance (AP) goes beyond the use of ICSR databases and can be defined as “*a systematic process that seeks to identify safety issues through epidemiologic analyses of healthcare databases*” (Wiktorowicz et al., 2012), usually referring to the exploitation of Electronic Health Record (EHR) systems or observational databases (Wiktorowicz et al., 2012)(Li et al., 2018)(Coloma et al., 2011), sometimes also extending to other kinds of web based data sources too (Hrmark and Van Grootheest, 2012) (e.g. mining data from forums, social media, search logs etc.).

The term “real-world” evidence (RWE) refers to information mined primarily from EHRs but can also include other data sources, e.g. social media, behavioural information mined from electronic device usage patterns like internet browsing, use of mobile phones etc. (Real-World Evidence | FDA)(Sherman et al., 2016). It should be noted that some regulatory and drug safety monitoring organizations have already opened the discussion regarding the usage of these emerging information data sources (Guidance for Industry Internet/Social Media Platforms with Character Space Limitations-Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices, 2014) (Brosch et al., 2019). The ultimate goal of these approaches would be the “*hypothesis free signal detection*” where potential signals would be

automatically identified using evidence derived from or produced by data mining approaches upon multimodal data repositories.

However, the vision of exploiting the current data deluge for DS purposes comes with its challenges and clearly dictates the need to introduce high-throughput computational methods to enable efficient knowledge extraction and management, compensating for the underlying data heterogeneity and complexity. This need becomes more demanding, especially considering the concurrent investigation of diverse types of data, in order to strengthen the evidence of the outcomes provided by the respective computational methods (Koutkias and Jaulent, 2015) and then produce the needed “knowledge”, i.e. the respective signal.

In Computer Science, knowledge is represented “by facts, rules and other symbolic structures, rather than the traditional representation as abstract numbers or algorithms” (Fox, 1984). *Knowledge Engineering* (KE) is the discipline that elaborates on the theories, methods, and tools for developing knowledge-intensive applications (Schreiber, 2008). KE is generally considered part of the wider Artificial Intelligence (AI) technologies and typically entails: (a) knowledge extraction (e.g. based on Natural Language Processing (NLP)), (b) knowledge integration (i.e. syntactic and semantic alignment and normalization of different kinds of knowledge), (c) knowledge representation (i.e. modelling of domain/application knowledge in computationally exploitable formats like ontologies), (d) knowledge dissemination (i.e. modelling information for communication purposes focusing for example on interoperability among heterogeneous ICT systems), and (e) knowledge elicitation (i.e. generating or discovering new knowledge via AI and/or advanced KE techniques like semantic mining).

1.1. Definition of the problem

Despite the fact that DS is a crucial aspect of the overall provided healthcare, it lacks IT tools and processes which could systematically support DS and integrate it as a part of everyday clinical practice. Furthermore, given the overwhelming development of IT based technologies and paradigms (e.g. big data, machine learning - ML) and their wide adoption in various domains, the lack of their adoption in the DS domain (and healthcare as a whole) marks a clear gap.

To this end, we argue that the emerging technologies collectively referred as “Artificial Intelligence” (AI), and especially KE could play a crucial role towards the improvement of IT

tools aiming to support DS and their integration in the every-day clinical practice. However, “intelligent” technological paradigms are challenging to integrate in the context of the clinical environment or in wider healthcare settings. Recently, a high profile paper identified the need to develop a “delivery science” for this intelligent technical paradigms, moving beyond the process of building machine learning algorithms but also emphasizing on the overall operational/business processes and the new systems for care delivery enabled by these technical approaches (Li et al., 2020). Focusing on the domain of PV, the regulatory context and the peculiarities of the respective Business Processes (BPs) applied in healthcare, create a complex environment where the integration of innovative IT tools is even more challenging. For example, the assessment of potential ADRs by HCPs could be considered a BP (let’s call it BP1) which might interfere with other BPs e.g. patient’s treatment (let’s call it BP2). In the clinical setting, BP2 is of the utmost importance but it cannot be standardized due to variations in patients’ treatments and the distinct structure of medical facilities, as even clinics in the same hospital might apply different BPs for various reasons. The early detection and proper chartering of interactions or conflicts among the applied BPs is crucial, as they significantly affect the so-called “*User Goals*” (UGs), and therefore such a process can significantly facilitate the integration of “intelligent” applications.

Therefore, the main hypothesis of this thesis is that *the integration of emerging Knowledge Engineering technologies could be used to revision of “Active Pharmacovigilance” as a new clinical functioning paradigm, based on the analysis of the respective Business Processes and User Goals.*

1.2. Background

1.1.1. Drug Safety

DS processes can be roughly organized in two main parts along a drug’s lifetime: (a) the *pre-marketing* DS procedures and, (b) the *post-marketing* DS procedures.

The pre-marketing DS processes are heavily affected by the drug licensing procedure and are typically based on a set of long clinical trials organized in order to ensure safety and efficacy of the drug under development. While there is no clear and universally accepted definition of the clinical trial phases as they are designed in an ad-hoc manner, they can be roughly described as following (Friedman et al., 2010b)(Friedman et al., 2015b):

Table 1: Clinical trial phases

Phase	Goal	Typical number of participants
Preclinical	Non-human (lab and/or animal testing) to collect information regarding toxicity, efficacy, pharmacokinetics and pharmacodynamics	N/A
Phase 0	Pharmacokinetics evaluation (e.g. oral bioavailability and active substance half-life)	10 people
Phase I	Healthy volunteers/may be patients who have failed to improve via standard therapies. Testing mostly emphasizing on tolerability and safety (various dosage schemes). Also aiming to characterize pharmacokinetics and pharmacodynamics.	20–100 healthy volunteers
Phase II	Testing on patients to assess efficacy and side effects, aiming to decide if the drug development should be further pursued. Participants selected with narrow inclusion/exclusion criteria.	100–300 patients
Phase III	Testing of drug on patients to assess efficacy, effectiveness and safety. Typically, they aim to support regulatory purposes (e.g. drug approval). Participants selected with wider inclusion criteria.	300–3,000 patients
Phase IV	Post-marketing surveillance	Depending on the target patient group

In all clinical trial phases, the patient “cohorts” are carefully selected in order to confirm or reject a specific hypothesis. The design of pre-marketing clinical trials is far from trivial and a number of systematic design challenges have already been identified (Singh and Loke, 2012). In order to overcome such challenges, innovative design approaches like “adaptive” clinical trial designs are also actively pursued (Bhatt and Mehta, 2016).

Despite the application of the clinical trials processes and the respective regulations, medical history is full of drug safety tragedies (Paine, 2017) including drugs which were successfully tested in the pre-marketing clinical trials and withdrawn afterwards (Onakpoya et al., 2016). The post-marketing DS procedures are very different as the drug is used by the general population. Compared to the pre-marketing phase, regardless of the cohort size of the respective clinical trial, in the post-marketing phase the drug is “tested” in real-world conditions, by a vastly wider and heterogeneous population. Post-marketing DS includes

surveillance of potential ADRs in real-world circumstances, including interactions with other drugs, conditions etc. As post-marketing DS is a data intensive process, it needs to use all potential means to support public health including the integration of novel IT technologies aiming to exploit the currently available data deluge.

1.1.2. Clinical practice and Drug Safety

Typically, prescribing HCPs do not have systematic support in terms of DS, and mostly depend on the information provided by the package leaflet, a.k.a. Patient Information Leaflet (PIL), the Summary of Product Characteristics (SmPC) document or an online search in order to avoid ADRs or drug-to-drug interactions (DDIs) or provide guidance to the patient. In some hospitals/clinics, there is also support from specialized PV departments, engaging clinical pharmacologists to support clinicians in their decision making when there are doubts or contradicting evidence, however this cannot be considered a standard practice. It should also be noted that some healthcare organizations retrospectively analyse ADR prevalence in order to define specific guidelines as part of their quality assurance processes.

There are also some approaches which can be marginally positioned between research and clinical practice. For example, the Clinical Decision Support Systems (CDSSs) raising “alerts” during the prescription process have been extensively investigated in terms for research purposes and have also been deployed in many hospitals. However, still, CDSSs are far from being considered as a standard approach. Furthermore, pharmacogenomics (PGx), i.e. the prediction of potential ADRs/DDIs based on the patient’s genetic profile, is a relatively new approach which is still in its infancy as Clinical Practice Guidelines (CPGs) based on pharmacogenomics are currently being developed (Relling and Klein, 2011) and have only recently been adopted by regulatory organizations. Finally, as part of research projects, various aspects of KE were also investigated to elaborate on potential PV signals, based on EHR systems (Bernonville et al., 2013; Yuksel et al., 2016; Natsiavas et al., 2019b).

Regardless of the clinical treatment setting specifics (e.g. if the patient is hospitalized or not, or he/she is treated by a private doctor), both HCPs and patients are urged to submit ICSRs if an ADR occurs, but it has been identified that these are heavily underreported (Hazell and Shakir, 2006). To this end, initiatives like the Sentinel project in the United States⁶ and the

⁶ <https://www.fda.gov/safety/fdas-sentinel-initiative>

China Hospital Pharmacovigilance System (CHPS) (Li et al., 2018) could be a step forward as they aim to collect data from EHR system hospitals in a wide scale. Indicatively, during the COVID-19 pandemic, significant findings were published based on analysis conducted using data provided by CHPS (Sun et al., 2020). That said, it is clear that the currently applied practices are significantly lacking as they solely depend on EHR systems and therefore do not fully exploit the potentials of modern technologies.

1.1.3. Knowledge Engineering and Drug Safety

Recent research has illustrated that KE can contribute in addressing DS challenges. In particular, KE applications for DS can facilitate the integration and analysis of heterogeneous data sources (Koutkias and Jaulent, 2015), and represent the respective knowledge in a manner which facilitates advanced processing capabilities like automatic inference (Natsiavas et al., 2018a).

KE emphasizes on the definition of explicit semantics via well-defined knowledge structures, i.e. common reference terminologies, thesauri, or ontologies. The use of such reference knowledge structures is a key aspect in KE, as it facilitates “machine-understandable” interlinking, comparison, reuse and further processing of data in two ways: (a) it enhances semantic interoperability through common reference concepts, and (b) it provides the underlying semantic infrastructure for automatic inference, as these concepts are typically part of well-defined structures (e.g. concept hierarchies/graphs) defining each concept’s semantics. Thus, the use of reference knowledge structures is crucial in order to characterize a computational method/system as “knowledge-based”.

1.3.Objectives

This thesis has been conducted in the context of PVClinical project⁷, which aims to build a KE-based web platform facilitating the investigation of potential ADR signals in the clinical context and beyond. More specifically, the PVClinical project aims to provide a web application/tool to integrate various data sources, using KE as its main technical paradigm. Ultimately, PVClinical aims to support PV experts, regulators and clinicians in potential ADRs

⁷ <https://pvclinical-project.eu>

investigation and therefore their decision-making process, both in the clinical setting and beyond.

As this thesis focuses on AP and the potential impact of KE approaches on it, the technical development of the PVClinical web application is considered out of this thesis scope. However, since PVClinical engages various KE-oriented technical activities and aims at the same end-user categories, the overall project design and most importantly the process of communicating with end-users and partners in the context of the PVClinical project design provided a valuable input for the successful completion of this PhD thesis.

The main goal of this thesis is to clearly define the concept of Active Pharmacovigilance and revision it, emphasizing on the potential impact of Knowledge Engineering approaches and, moreover, propose further steps towards its practical application in real-world conditions. To reach this goal, a number of intermediate objectives were defined and can be summarized as follows:

- Provide a detailed overview of the research work conducted regarding the application of KE for Drug Safety purposes and highlight potential research gaps
- Identify the Business Processes related with Pharmacovigilance
- Define a set of User Goals based on the end-users' input
- Provide pilot developments of technical artefacts supporting the vision of AP in the clinical context, ultimately aiming to identify the practical challenges of using KE approaches, based on hands-on experience

1.4.Methodology

The presented PhD thesis significantly overlaps with the “user requirements analysis” and design phase of the PVClinical project. The detailed methodological steps applied are based on the process described in (Natsiavas et al., 2018c) and can be summarized in the following steps, also shown in Figure 1:

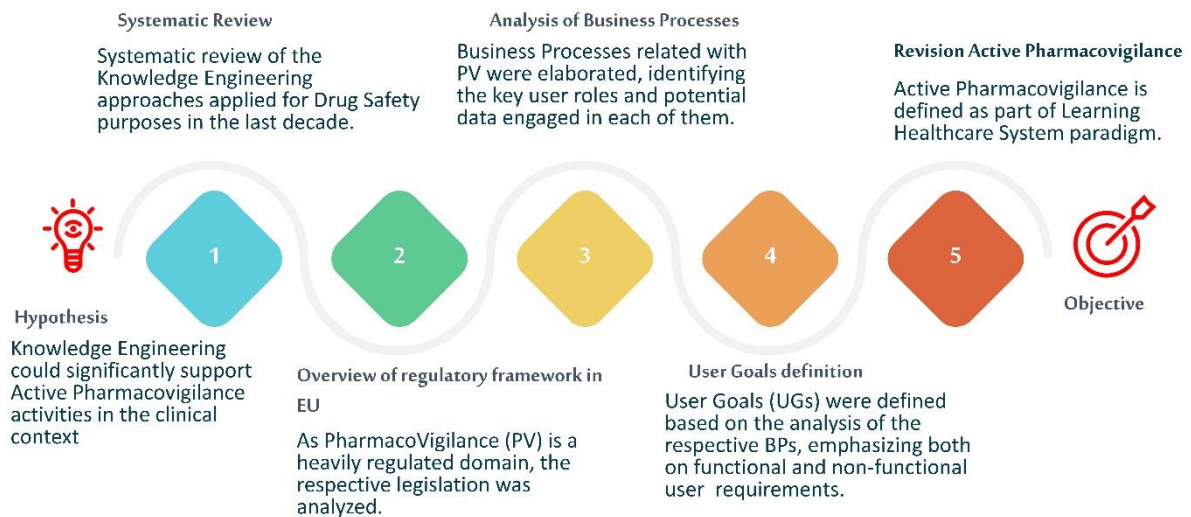


Figure 1: Methodology overview

Initially, a thorough assessment of the Regulatory Framework for all PV processes in the European Union (EU) was conducted based on the pertinent literature and was further refined by the input as well as the empirical knowledge provided by the PVClinical project partners.

A crucial, early identified point of interest concerned the need to elaborate on the respective BPs engaged with the various PV activities. BPs are defined as a collection of relevant and ordered structured activities/tasks aiming to produce a specific outcome (Weske, 2012). For example, ADR evaluation can be considered as a BP conducted in the context of a hospital, in tandem with other BPs (e.g. patient treatment, administrative processes, etc.). Novel IT tools, like the one designed by PVClinical could reshape the current practices of ADR assessment, which today are typically performed manually with no systematic support of specialized IT tools. Realizing this, workshops and interviews with various stakeholders were conducted in order to identify, classify and analyse the BPs in arbitrary categories. Based on this input, it was early identified that integrating “intelligent technologies” aiming to support PV activities in the context of real-world healthcare activities is far from trivial.

These challenges were clearly depicted in the so-called *User Goals (UGs)* which outline the priorities raised by the end-users. UGs are defined as “*abstract user requirements, not directly referring to specific technical solutions or components*” (Natsiavas et al., 2018c),

directly attributed to specific user actors or “roles”. The definition of UGs facilitates the early identification and resolution of potential conflicts between actors. The presented UGs have been analysed based on feedback provided by clinicians and PV experts in the context of the PVClinical project.

It should be highlighted that the above steps were not conducted sequentially. On the contrary, the outcomes presented were iteratively refined. More specifically, a “Design Thinking” based approach was used in order to integrate the user feedback in the overall process (Roberts et al., 2016). Design Thinking emphasizes on the need for empathy for end-users and urges designers to “get in the user’s shoes”, and use “action-oriented rapid prototyping” in an iterative fashion. While Design Thinking is fully compatible with “agile” software development practices⁸ and has been used with some success in healthcare (Altman et al., 2018), it is still not widely adopted. However, it has been recently identified as one of the methodological tools which could potentially enable the successful integration of intelligent technical paradigms in the healthcare settings (Li et al., 2020).

Figure 2 depicts the rationale of the process applied in this thesis in order to integrate end-user feedback, so as to elaborate on the respective UGs and the challenges regarding the integration of Intelligent Systems (ISs) in real-world healthcare realms. A noteworthy point concerns the adoption of “Design Thinking” oriented approaches in the overall process, e.g. the so-called “Think-aloud” testing sessions, where end users are encouraged to test a prototype, in this case, a prototype of the PVClinical project platform, while thinking aloud. At the same time, the “development team” keeps notes, or even records the session in order to mine potential useful features, in this case UGs. The main benefit of applying a “Design Thinking” based approach is that the “development team” can extract end-users’ opinions in high detail via the interaction with an existing prototype without the need to reach a big number of end-users (e.g. via surveys or questionnaires).

⁸ Agile software development is a term typically used to characterize approaches emphasizing on pragmatic software code production instead of applying rigor methodologies focusing on formal procedures (strict design procedures, laborious documentation management etc.). The term « agile » has been widely adopted after the so-called « agile manifesto » produced by some high profile software engineering experts in 2001 – <http://agilemanifesto.org>

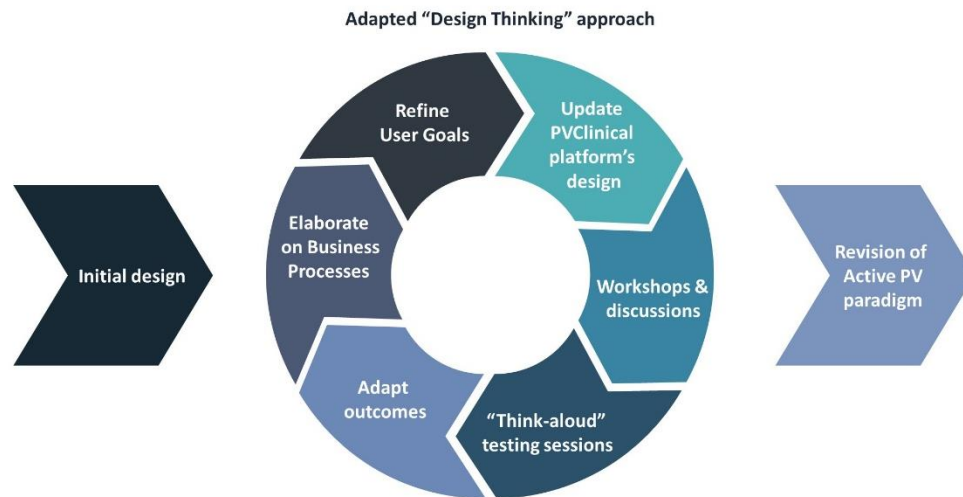


Figure 2: Process applied to integrate user feedback

1.5. Thesis structure

This PhD thesis is organized in 7 chapters, following the rationale presented in Figure 1. Along this line, the manuscript format is based on the papers published in the context of this PhD presented as “free standing” papers in respective chapters⁹. Furthermore, in each of these chapters, a subsection named “Beyond the paper” describes progress made after the paper was published and comments on how the presented work contributes to the overall goal of the thesis.

More specifically, in Chapter 1, we define the main concepts and the problem targeted in the thesis via the definition of a formal “hypothesis”. Moreover, a background regarding the clinical practice and DS is provided. The value of KE in the context of DS is highlighted and the methodology applied is described. Finally, the contribution of the thesis is summarized.

In Chapter 2, a Systematic and Mapping Review is presented regarding the KE computational approaches and the respective data sources used in the last decade for research on DS (the paper was originally published on May 2019 (Natsiavas et al., 2019b). To this end, a complete map of the used data categories is provided referring to both established and emerging data sources. Furthermore, the respective computational methods are analysed and

⁹ As the manuscript is based on the presentation of already published papers, inevitably there are things which are repeated/overlap (e.g. concept definitions). While the author recognizes that this might be tiring or even confusing for this thesis end-reader, it was the selected way to outline this PhD’s work in terms of its main outcomes, and therefore present the respective work in a more cohesive manner.

prominent research works are highlighted. Conclusively, several research gaps and new trends are highlighted based on the provided quantitative and qualitative analysis.

Chapter 3 presents the paper providing an overview of the EU legal context and identifies the BPs related with PV activities, (originally published in April 2020(Natsiavas et al., 2020)). These are elaborated both regarding the clinical environment and beyond, i.e. processes conducted by PV activities run by pharma industry companies or regulatory organizations.

Similarly, Chapter 4 presents the paper regarding the *UGs* and the main information workflow identified as part of the PVClinical project platform design. The original UGs are further elaborated in the same chapter, beyond the paper, which was originally published in August 2019(Natsiavas et al., 2019a).

Chapter 5 redefines AP in the context of a Learning Healthcare System (LHS) paradigm. More specifically, LHS paradigm is explained and the vision of integrating multi-modal AP in every-day clinical practice is depicted, also emphasizing the need to provide personalized treatment and therefore, personalized DS clinical decision too.

Chapter 6 summarizes a set of research paths which have been actively investigated during this PhD and can be used as future research work tracks. These research paths include the building of a big Knowledge Graph of PV information and the use of ontologies to model Systems Pharmacology information along the gaps identified by the systematic review presented in Chapter 2.

Finally, Chapter 7 concludes the thesis, summarizing the work done and providing its final conclusions.

2. State of the Art

This chapter provides an overview of the State of the Art regarding the use of KE approaches in the context of DS. To this end, the first paper published in the context of this PhD is presented (Natsiavas et al., 2019b), titled “Computational Advances in Drug Safety: Systematic and Mapping Review of Knowledge Engineering Based Approaches”. Furthermore, an extra subsection describes on how this thesis conducted in the context of the PVClinical project stands against the findings of the presented systematic review.

2.1. Computational Advances in Drug Safety: Systematic and Mapping Review of Knowledge Engineering Based Approaches

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Keywords: Drug Safety, Pharmacovigilance, Knowledge Engineering, Knowledge Discovery, Knowledge Representation, Ontologies, Terminologies, Semantic Technologies

2.1.1. Abstract

Drug Safety (DS) is a domain with significant public health and social impact. Knowledge Engineering (KE) is the Computer Science discipline elaborating on methods and tools for developing “knowledge-intensive” systems, depending on a conceptual “knowledge” schema and some kind of “reasoning” process. The present systematic and mapping review aims to investigate KE-based approaches employed for DS and highlight the introduced added value as well as trends and possible gaps in the domain.

Journal articles published between 2006 and 2017 were retrieved from PubMed/MEDLINE and Web of Science® (873 in total) and filtered based on a comprehensive set of inclusion/exclusion criteria. The 80 finally selected articles were reviewed on full-text, while the mapping process relied on a set of concrete criteria (concerning specific KE and DS

core activities, special DS topics, employed data sources, reference ontologies/terminologies and computational methods, etc.). The analysis results are publicly available as online interactive analytics graphs.

The review clearly depicted increased use of KE approaches for DS. The collected data illustrate the use of KE for various DS aspects, such as Adverse Drug Event (ADE) information collection, detection and assessment. Moreover, the quantified relation of using KE for the respective DS core activities highlighted room for intensifying research on KE for ADE monitoring, prevention and reporting. Finally, the assessed use of the various data sources for DS special topics demonstrated extensive use of dominant data sources for DS surveillance, i.e. Spontaneous Reporting Systems, but also increasing interest in the use of emerging data sources, e.g. observational healthcare databases, biochemical/genetic databases and social media.

Various exemplar applications were identified with promising results, e.g. improvement in ADR prediction, detection of drug interactions and novel ADE profiles related with specific mechanisms of action, etc. Nevertheless, since the reviewed studies mostly concerned proof-of-concept implementations, more intense research is required to increase the maturity level that is necessary for KE approaches to reach routine DS practice.

In conclusion, we argue that efficiently addressing DS data analytics and management challenges, requires the introduction of high-throughput KE-based methods for effective knowledge discovery and management and, ultimately, the establishment of a learning DS system.

2.1.2. Introduction

Pharmacovigilance (PV)¹⁰, also known as Drug Safety (DS), is “*the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems*” (World Health Organization, 2002). DS is an important issue of public health interest, given that adverse drug reactions (ADRs¹¹) and

¹⁰ Due to the numerous abbreviations used in the article, Appendix provides an abbreviation index to facilitate reading.

¹¹ ADEs: Side-effects that may or may not have causal relationship with the drug, including the events caused by drug misuse (e.g. overdose). ADRs: Side-effects that occur after a legitimate drug use (i.e. there is no overdose) and therefore “characterised by the suspicion of a causal relationship between the drug and the occurrence”. For a comprehensive definition of terms used in DS we refer the reader to (Lindquist, 2007).

adverse drug events (ADEs¹) cause a significant social and financial burden¹². An important part of DS concerns the identification of the so-called “signals”¹³, performed by national and international drug monitoring/regulatory organizations (e.g. the Uppsala Monitoring Centre (UMC), the European Medicines Agency (EMA), the Food and Drug Administration (FDA) in the United States, etc.). Signal detection is typically based on the analysis of individual case safety reports gathered in Spontaneous Reporting Systems (SRSs), e.g. using disproportionality-based statistical methods (Montastruc et al., 2011).

The current era of “data explosion” affects the entire spectrum of health, including DS. While traditionally post-marketing DS surveillance relied on SRSs as well as clinical studies and the scientific literature, advances in Information and Communication Technologies (ICT) recently enabled the exploitation of new/emerging data sources, such as observational healthcare databases, biochemical and genetic databases, social media, internet search logs, etc. To this end, various computational analysis methods have been proposed for post-marketing DS surveillance (Harpaz et al., 2012), illustrating both strengths and weaknesses (Hauben and Norén, 2010). For the development and safety monitoring of new drugs (i.e., prior to market authorization), computational approaches attract lately a major interest as well, especially in the scope of *in silico clinical trials* (Pappalardo et al., 2018) and *Precision Medicine* (Collins and Varmus, 2015). Multi-scale modelling approaches (exploiting low-level biochemical information regarding the behaviour of molecular structures as well as more abstract information regarding the phenotypic action of a drug via mathematic models, systems, or network-based structures) are being used in *Systems Pharmacology (SP)* (Mager and Kimko, 2016). In particular, SP-based approaches have been used for DS (Trame et al., 2016) (Bai et al., 2014) (Schotland et al., 2016) (Boland et al., 2016) and regulatory actions (Lorberbaum et al., 2015), as they facilitate *in silico clinical trials* (Ramanujan et al., 2016)(Rieger et al., 2018), including the simulation of individual patient characteristics towards the overall vision of *Precision Medicine* (Birtwistle et al., 2016).

¹² By reviewing European studies (Formica et al., 2018) estimated: a) the cost of ADRs between €2,851 and € 9,015 for the inpatient setting and €174 to €8,515 for the outpatient setting; (b) the impact of ADRs on the length of stay to be 9.2 ± 0.2 days (outpatient setting) and 6.1 ± 2.3 days (inpatient setting). Furthermore, the US Office of Disease Prevention and Health Promotion estimated that ADEs account for 1 in 3 of all hospital adverse events, concern about 2 million hospital stays each year, and prolong hospital stays by 1.7 to 4.6 days. Regarding outpatient settings, each year ADEs account for over 3.5 million physician office visits, about 1 million emergency department visits and, approximately, 125,000 hospital admissions (<https://health.gov/hcq/ade.asp>).

¹³ “Information that arises from one or multiple sources (including observations and experiments) which suggests a new, potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action” (Council for International Organizations of Medical Sciences (CIOMS), 2010).

To this end, the recent data deluge dictates the need to introduce high-throughput computational methods in DS, that will enable efficient knowledge extraction and management, compensating the underlying data heterogeneity and complexity. This need becomes more demanding, especially considering the concurrent investigation of diverse types of data, in order to strengthen the evidence of the outcomes provided by the respective computational methods (Koutkias and Jaulent, 2015).

In Computer Science, *knowledge* is represented “by facts, rules and other symbolic structures, rather than the traditional representation as abstract numbers or algorithms” (Fox, 1984). *Knowledge Engineering* (KE) is the discipline that elaborates on the theories, methods, and tools for developing knowledge-intensive applications (Schreiber, 2008). KE typically entails: (a) *knowledge extraction* (e.g. based on Natural Language Processing (NLP)¹⁴), (b) *knowledge integration* (i.e. syntactic and semantic alignment and normalization of different kinds of knowledge), (c) *knowledge representation* (i.e. modelling of domain/application knowledge in computationally exploitable formats like ontologies¹⁵), (d) *knowledge dissemination* (i.e. modelling information for communication purposes focusing for example on interoperability among heterogeneous ICT systems), and (e) *knowledge elicitation* (i.e. generating or discovering new knowledge via advanced KE techniques like semantic mining).

Recent research has illustrated that KE can contribute in addressing DS challenges. In particular, KE applications for DS can facilitate the integration and analysis of heterogeneous data sources (Koutkias and Jaulent, 2015), and represent the respective knowledge in a manner which facilitates advanced processing capabilities like automatic inference (Natsiavas et al., 2018a). The latter requires the definition of explicit semantics via well-defined knowledge structures, i.e. common reference terminologies, thesauri, or ontologies. The use of such reference knowledge structures is a key aspect in KE, as it facilitates “machine-understandable” interlinking, comparison, reuse and further processing of data in two ways: (a) it enhances semantic interoperability through common reference concepts, and (b) it provides the underlying semantic infrastructure for automatic inference. Thus, the use of reference

¹⁴ An interesting review on text mining for ADEs has been presented by Harpaz et al. (Harpaz et al., 2014).

¹⁵ “In Computer and Information sciences, an ontology defines a set of representational primitives for modelling a domain of knowledge or discourse. The representational primitives are typically classes (or sets), attributes (or properties), and relationships (or relations among class members). The definitions of the representational primitives include information about their meaning and constraints on their logically consistent application.” (Gruber, 2009).

knowledge structures is crucial in order to characterize a computational method/system as “knowledge-based”.

In KE, semantics are expressed via relationships among the referred concepts (e.g. “Myocardial Infarction” *occurs_in* ‘Myocardium’), or via a hierarchy of concepts and their properties using “*sub-concepts*” (e.g. the term “Myocardial Infarction” *is_a* “Cardiac Disorder”) and “*sub-properties*”, respectively. A knowledge structure could describe how ADEs such as ‘myocardial infarction’ may be associated to the corresponding pathological process and anatomical location, e.g. ‘Myocardial Infarction’ *is_a* ‘Cardiac Disorder’ *and occurs_in* ‘Myocardium’. An ICT system would represent this knowledge and the respective concepts using a reference terminology, e.g. MedDRA¹⁶. Such an explicit and computationally exploitable representation of knowledge enables “reasoning”. As an example of how a computer may perform automatic reasoning, explicit linking of an ADE to its corresponding biological process (e.g., ‘Cardiac Failure’ is associated to ‘Heart Contraction’) allowed the identification of 190 genes that are associated with heart contraction and could potentially have a role in cardiac failure (Sarntivijai et al., 2016).

This study constitutes a “systematic and mapping review”¹⁷, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). It aims to present KE-based approaches for DS and their potential application in current DS practice, illustrating the added value through exemplar research efforts spanning diverse dimensions of DS research. Thus, the main research question of the current study is: “*What are the main KE methods applied in the DS domain, upon which knowledge models and data sources are they applied, what is their contribution/added value for DS, and what are the potential gaps, challenges and opportunities for further research?*”.

2.1.3. Methods

A systematic search was performed by querying two reference bibliographic repositories: PubMed¹⁸ and Web of Science¹⁹. The study comprised of the article retrieval step

¹⁶ MedDRA® (the Medical Dictionary for Regulatory Activities) is a reference, international terminology in the domain of DS, developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The MedDRA® trademark is owned by IFPMA on behalf of ICH.

¹⁷ A mapping review aims “*to map out and categorize existing literature on a particular topic, identifying gaps in research literature from which to commission further reviews and/or primary research*” (Grant and Booth, 2009).

¹⁸ <https://www.ncbi.nlm.nih.gov/pubmed/>

¹⁹ <https://webofknowledge.com/>

and two consecutive review stages (Figure 3); the first aimed to filter irrelevant articles with the domains of KE and DS based on their title and abstract, and the second was devoted to evaluating the remaining papers' full-text in detail, and map them based on specific analysis criteria.

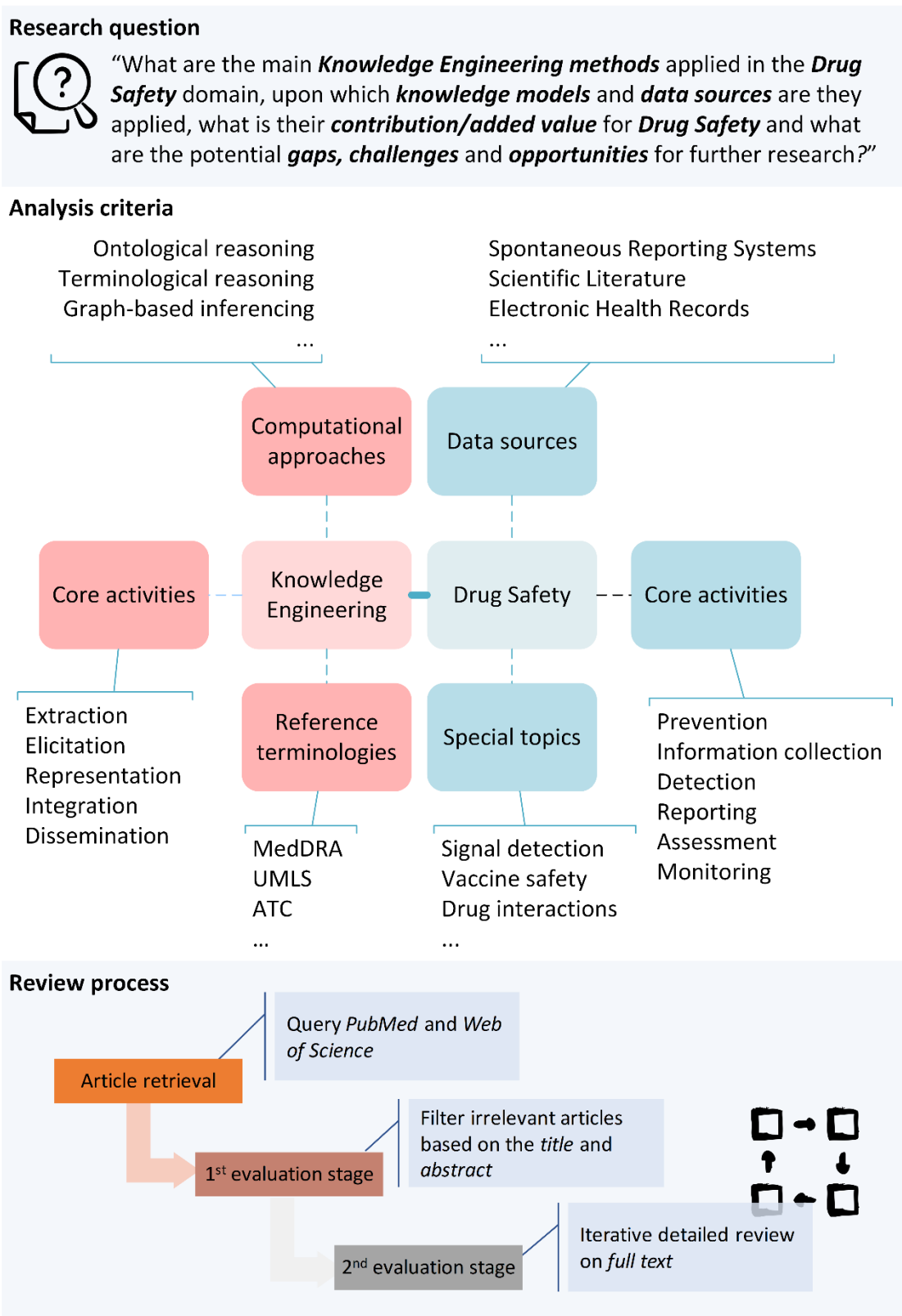


Figure 3: Rationale of the review methodology

The review was conducted by the authors of the paper. In the retrieval stage, we defined and executed two queries (provided as Supplementary Material²⁰) and imported the obtained citations in BibReview²¹, a tool that was used throughout our study enabling collaborative review of bibliographic data (Lamy et al., 2015). The queries included two core parts (linked with the logical operator AND), each comprising of synonym terms describing the domains of interest, i.e. KE and DS. We considered articles written in English and published in scientific journals between 2006 and 2017. 2006 was selected as the starting year of our review, since there was no much activity on KE for DS until then and a key study regarding the use of MedDRA has sparked an interesting discussion about the use of formal semantics, highlighting the prospects and the need for further research (Bousquet et al., 2005b).

In addition, the current study relied on the following inclusion and exclusion criteria:

- 1) Inclusion criteria: (a) articles exploiting clearly KE methods/technologies; (b) articles referring to algorithms exploiting formal mathematic structures (e.g. graphs), as these can be considered knowledge representation schemes, and (c) articles in which NLP was employed to extract information from free-text sources combined with other KE processes, e.g. ML algorithms using reference terminologies/ontologies.
- 2) Exclusion criteria: (a) articles referring to “inference” through plain statistics; (b) articles referring to ontologies (e.g. Gene Ontology (GO)) as simple data sources, without exploiting their underlying semantics; (c) articles not reporting the use of at least one knowledge source, e.g. a terminology, a thesaurus, an ontology, etc.; (d) opinion or review papers not providing concrete suggestions or designs, and (e) articles from the same authors with a high degree of overlapping²².

Table 2 partially presents the analysis criteria employed in the overall mapping process. These were based on established knowledge in the domain, experiences and tacit knowledge of the authors, and the outcomes obtained as the review progressed. While other systematic reviews related with KE were considered for criteria definition (e.g. (Wnuk and Garrepalli, 2018), (Bjørnson and Dingsøyr, 2008)), to a great extent these were found irrelevant for our study. In order to reduce the subjectivity of the review process, specific enumerations of answers for each review criterion were defined. The authors iteratively examined the possible

²⁰ <https://www.frontiersin.org/articles/10.3389/fphar.2019.00415/full#supplementary-material>

²¹ <https://pypi.org/project/BibReview/>

²² In such cases, only the most representative article was considered in our review.

answers for each criterion, to make sure that these are orthogonal (not conceptually overlapping) to the extent possible. Furthermore, specific explanations for each criterion value were added in a spreadsheet file used for data gathering and analysis²³, in order to avoid ambiguities for the reviewers.

Table 2: Analysis criteria and indicative answers

Criterion	Indicative answers
<i>DS core activities</i>	ADE information collection, ADE detection, ADE assessment, ADE monitoring, ADE prevention, ADE reporting
<i>DS special topics</i>	Comparative drug analysis, Drug interactions, MoA identification/analysis Personalized drug safety, Signal detection, Specific (class of) disease, Specific (class of) drug(s), Specific adverse effect, Vaccine safety
<i>Data source categories</i>	ADE databases, Bibliographic databases, Clinical narratives, Clinical trials, Drug information databases, EHRs, Genetics and biochemical databases, HL7 messages, Manually annotated corpora, mHealth apps, Patient summaries, PHRs, Social media, Structured Product Labels, Spontaneous Reporting Systems
<i>Data source(s)</i>	Absorption, Distribution, Metabolism, and Excretion Associated Proteins database (ADME-APs), ADE Corpus, ADEpedia, ADRMine Corpus, AEOLUS, AERS-DM, etc.
<i>KE core activities</i>	Knowledge dissemination, Knowledge elicitation, Knowledge extraction, Knowledge integration and Knowledge representation
<i>Computational method(s)</i>	Data mining, Disproportionality analysis, Graph-based inferencing, Information extraction (e.g. Natural Language Processing), Machine Learning, Ontology reasoning, Rule-based inferencing, Simulation, Terminological reasoning, Vector-based similarity identification
<i>Challenges/weaknesses</i>	Commercial tools, Competing interests, Evaluation against small dataset, Evaluation restricted on a narrow scope, Evaluation with simulated data, Knowledge model not available, Knowledge model not validated for completeness, No evaluation regarding knowledge modelling quality criteria, No statement regarding competing interests, Not applying formal DL semantics, Not using a knowledge representation standard, Proprietary datasets, Significant dependence on manual work
<i>Reference terminologies/ontologies</i>	Adverse Event Reporting Ontology (AERO), Anatomical Therapeutic Chemical Classification System (ATC), Basic Formal Ontology (BFO), British National Formulary (BNF) Dictionary, ChEBI, etc.
<i>Knowledge formalism</i>	DAML+OIL, Frame-based ontology, OWL, RDF, Relational, SWRL, XML
<i>Country</i>	e.g. Australia, Belgium, Canada, China, Denmark, France, etc.
<i>Organization type</i>	Academia/Research, Healthcare, Industry, DS Monitoring

In order to mitigate the risk for various kinds of bias, we applied the guidelines provided by (Drucker et al., 2016) and (Altman et al., 2011) (further discussed in subsection “Risk of bias”).

²³ The detailed review results and the overall mapping outcome is documented in the MS Excel file, which is provided as Supplementary Material - <https://www.frontiersin.org/articles/10.3389/fphar.2019.00415/full#supplementary-material>

2.1.4. Results

The results are provided as supplementary material in the form of an Excel file²⁴, while they are also publicly available as online interactive analytics forms, enabling their investigation in further detail²⁵. This section presents the most important facets of these results.

Article selection

Figure 17 depicts the number of selected papers in each step of the review process, following the PRISMA guidelines (Moher et al., 2009). From the 873 articles initially retrieved, 94 articles were selected to be evaluated in full detail. 14 of them were excluded during the full-text review according to the exclusion criteria defined (section Methods). Finally, 80²⁶ articles were included in the presented review.

²⁴ <https://www.frontiersin.org/articles/10.3389/fphar.2019.00415/full#supplementary-material>

²⁵ The online analytics are available at <https://inab-certh.github.io/Knowledge-Engineering-for-Drug-Safety-Systematic-and-mapping-review/analytics> and the respective files can be accessed at <https://github.com/inab-certh/Knowledge-Engineering-for-Drug-Safety-Systematic-and-mapping-review>.

²⁶ The list of selected articles is provided as Supplementary Material - <https://www.frontiersin.org/articles/10.3389/fphar.2019.00415/full#supplementary-material>.

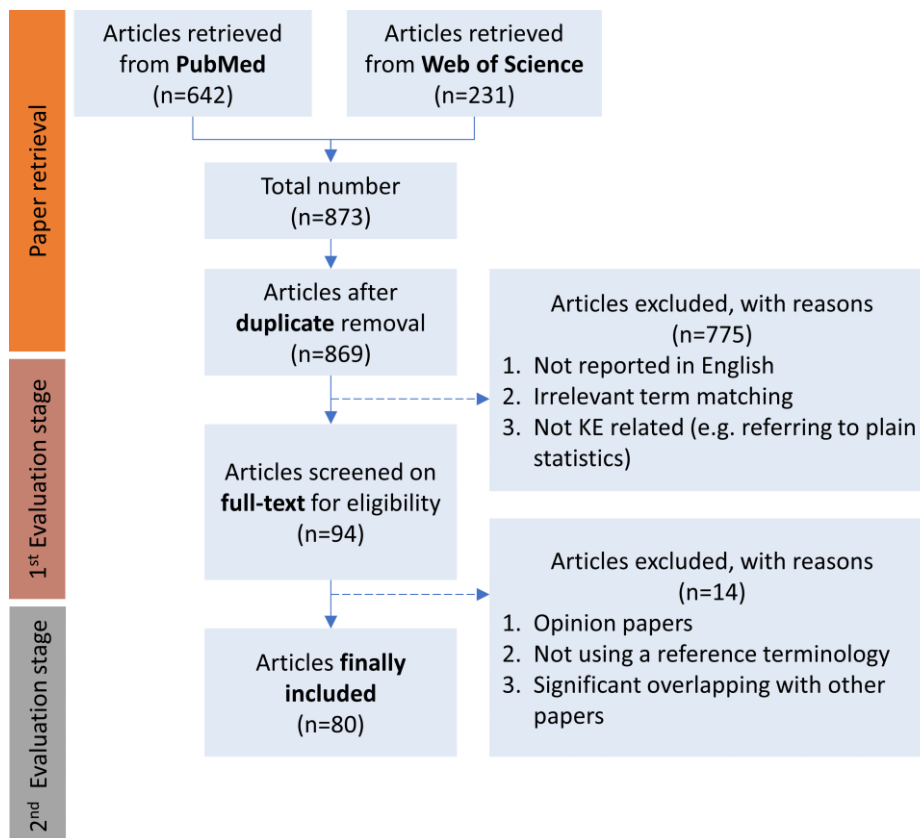


Figure 4: The PRISMA flow in the context of the current study

The “demographic” features of the selected articles are illustrated in Figure 3. In particular, Figure 5A presents the distribution of articles according to the organization category of the respective authors, highlighting that industrial, healthcare and DS monitoring organizations contributed less in the domain, compared to research organizations. As shown in the author-country distribution depicted in Figure 5B, most articles were produced by organizations located in the USA. However, China, France and Spain are also among the leading countries in researching KE for DS. In terms of time evolution, Figure 5C depicts an increasing trend in the number of publications after 2010.

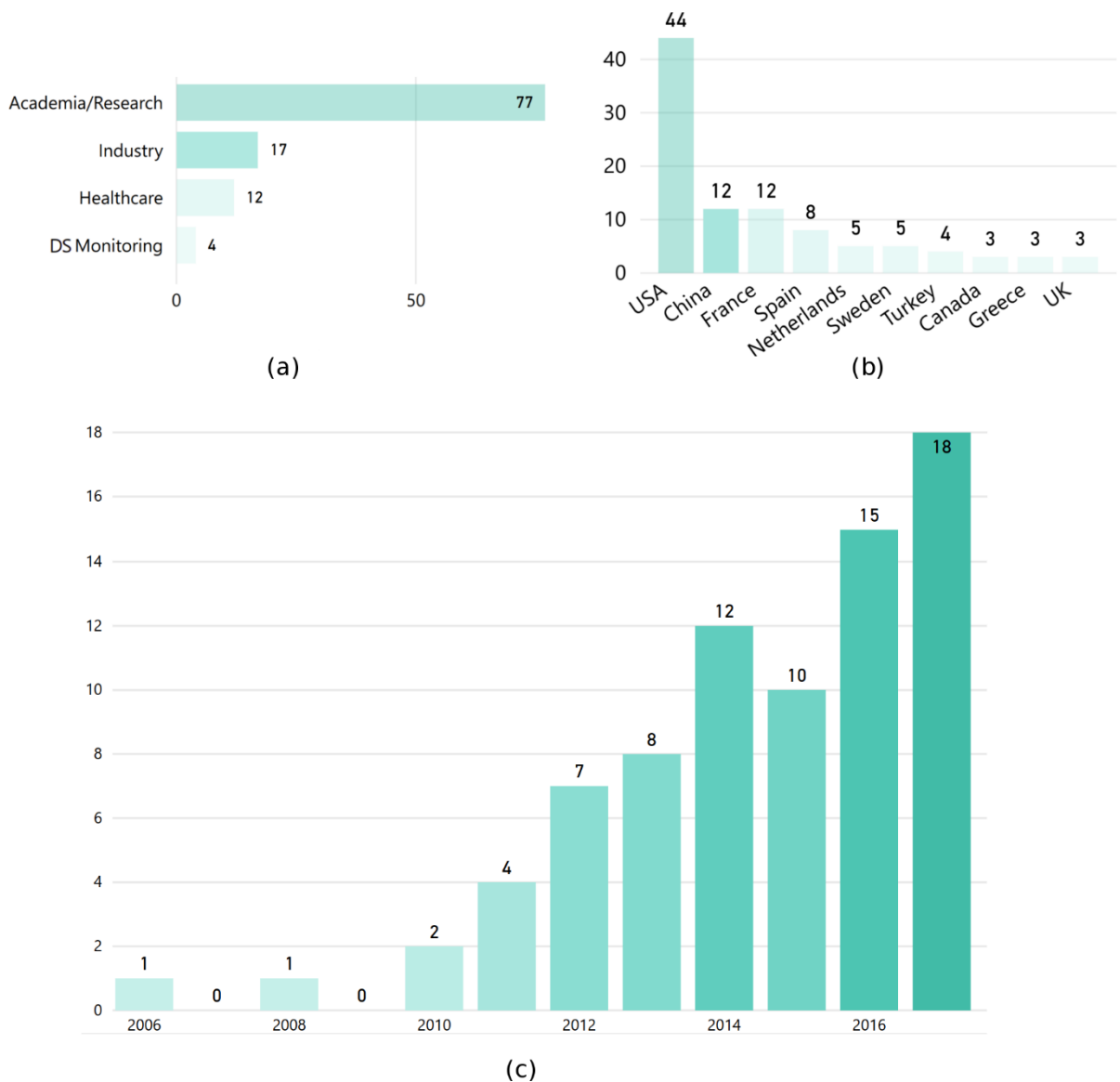


Figure 5: (A) Number of articles per authors' organization category, (B) author-country distribution (showing only $n > 3$ articles), and (C) distribution of the selected articles per year.

Synthesized findings

In this section, we present in detail the results of our quantified analysis based on the criteria presented in Table 2. Furthermore, we provide an overview of the impact of the selected papers on the main topics posed by the study research question, as described in the Introduction section²⁷.

Quantified analysis

²⁷ A catalogue with Web links to data sources, reference terminologies, ontologies, standards, technologies, and systems referred in the study is provided in the Appendix.

Figure 6 depicts the distribution of the reviewed articles, according to the DS core activities and special topics. As shown in Figure 6A, “ADE detection”, “ADE information collection” and “ADE assessment” attract most research efforts among the core DS activities. Respectively, Figure 6B depicts that signal detection, mechanism of action (MoA) analysis and drug interactions are the leading DS special topics.

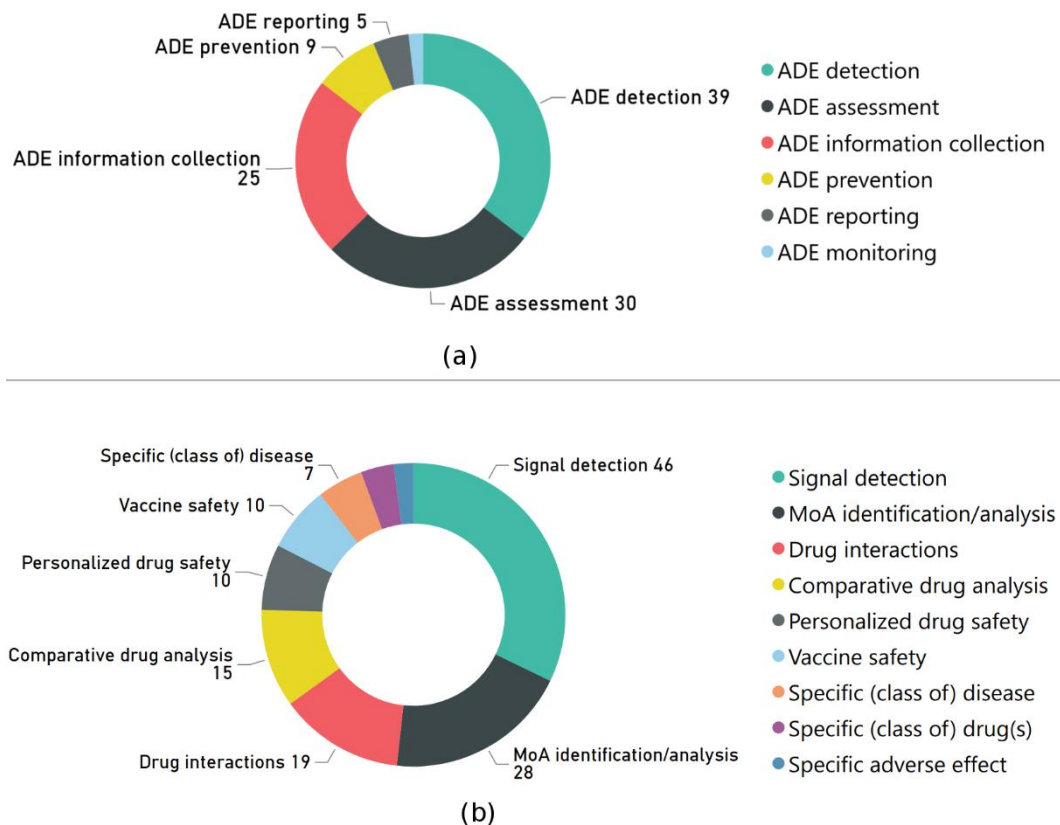


Figure 6: Number of articles related with: (A) DS core activities, and (B) DS special topics.

Figure 7 depicts the main KE activities employed in the reviewed articles and their time evolution (Figure 7C), as well as the number of articles related with the most prominent computational approaches (Figure 7A). Knowledge extraction, representation and elicitation were the main focus, mostly through the application of NLP, terminological reasoning, ontological reasoning and vector-based similarity identification using ML algorithms, e.g. Support Vector Machines (SVMs). Typically, more than one KE core activities were employed in each article. As shown in Figure 7B only knowledge extraction seems to be a standalone approach employed in a significant number of papers. This overlapping between the use of more than one KE core activities outlines the complexity of the targeted problems and the need for synthesized approaches to address them.

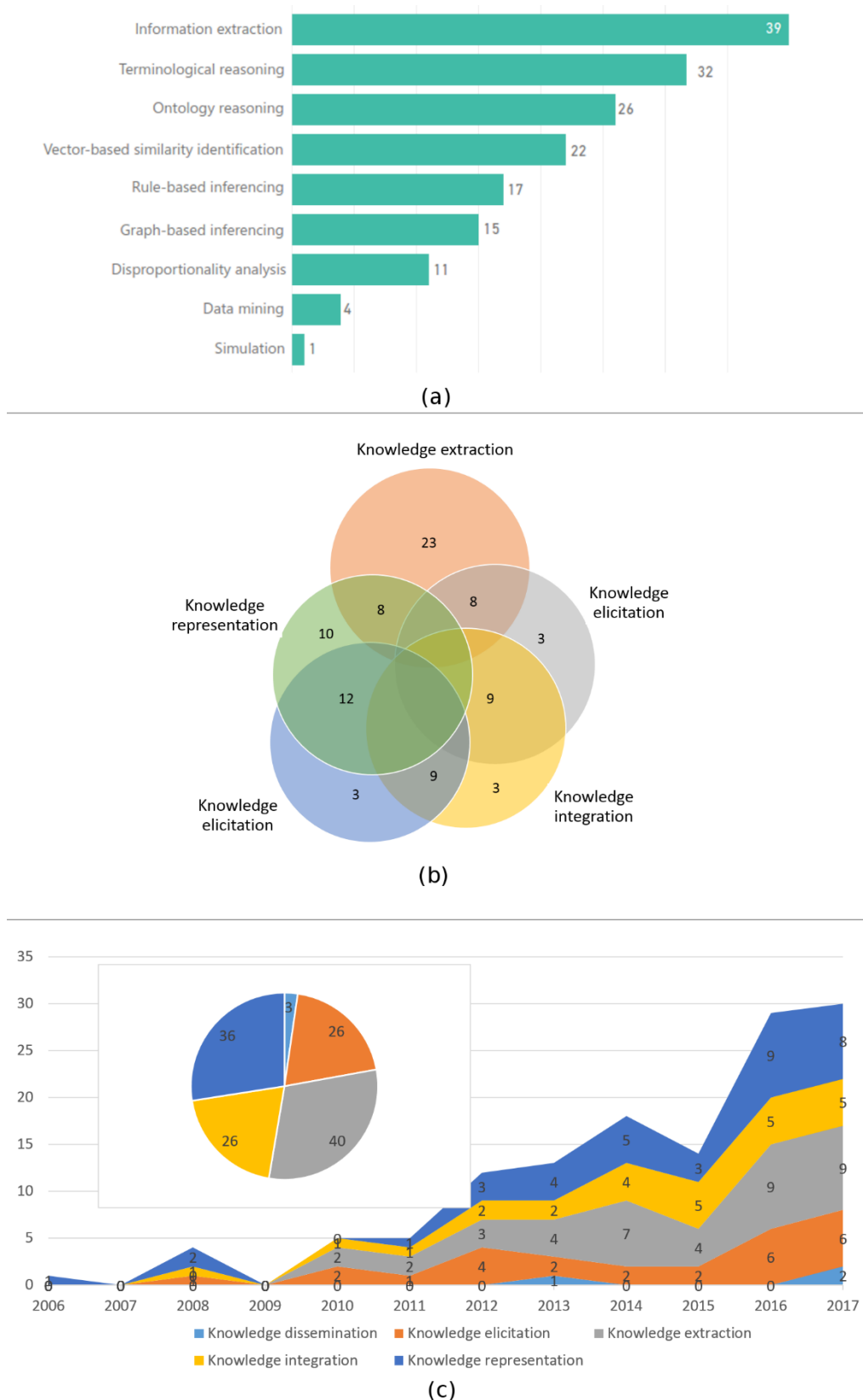


Figure 7: KE and computational approaches: (A) number of articles per computational approach, (B) overlapping of the most prominent KE activities within the selected articles, and (C) KE activities and number of respective articles across time.

Figure 8A-C present the associations between the various DS and KE core activities, the DS special topics and the data source categories, as well as the KE core activities and the data sources, respectively, in the form of chord diagrams. Figure 8D depicts a Sankey diagram presenting the most significant interconnections²⁸ among the DS special topics, the most important data source categories, and the KE core activities based on the reviewed articles. Interestingly, “signal detection”, “MoA analysis and identification” and “Drug interactions” are the three most elaborated DS special topics, exploiting a number of heterogeneous data sources, e.g. SRSs, ADE databases, etc.

²⁸ Only connections with weight greater than 5 are depicted, to maintain readability.

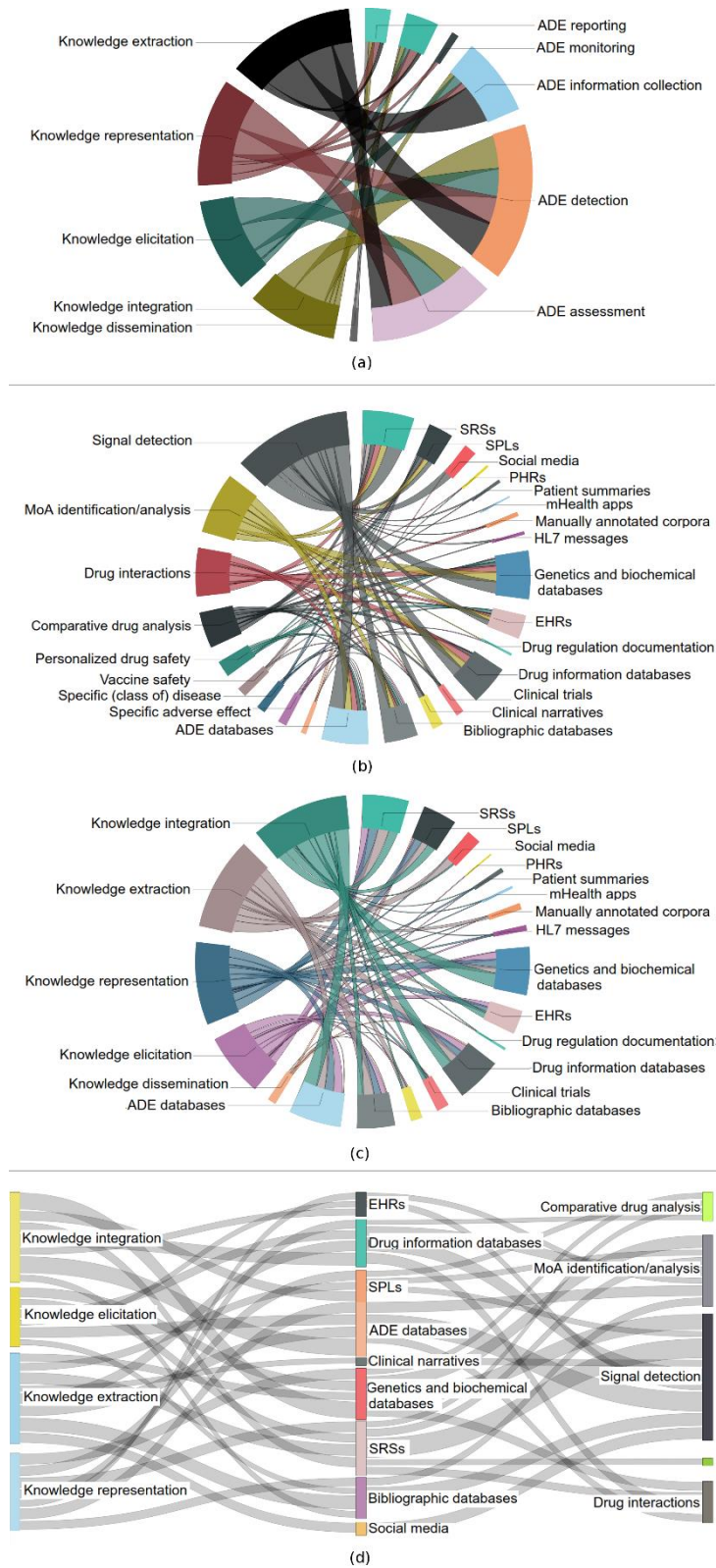


Figure 8: Links between: (A) KE core activities and DS core activities, (B) DS special topics and data source categories, (C) KE core activities and data source categories. (D) The most prominent connections among KE core activities, data source categories and DS special topics.

One of the key KE foundations is the reuse of established/reference knowledge structures (i.e. ontologies, standard terminologies, etc.). This facilitates semantic interoperability between different systems and widens the spectrum upon which KE approaches are applicable to. Figure 9 presents the most widely adopted terminologies/ontologies in the reviewed articles²⁹. Unified Medical Language System (UMLS), MedDRA, the Anatomical Therapeutic Chemical Classification (ATC) system, the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT) and the International Classification of Diseases (ICD) are the most widely used terminologies, while the Ontology for Adverse Events (OAE), the Vaccine Ontology (VO) and GO are the most widely referred ontologies.

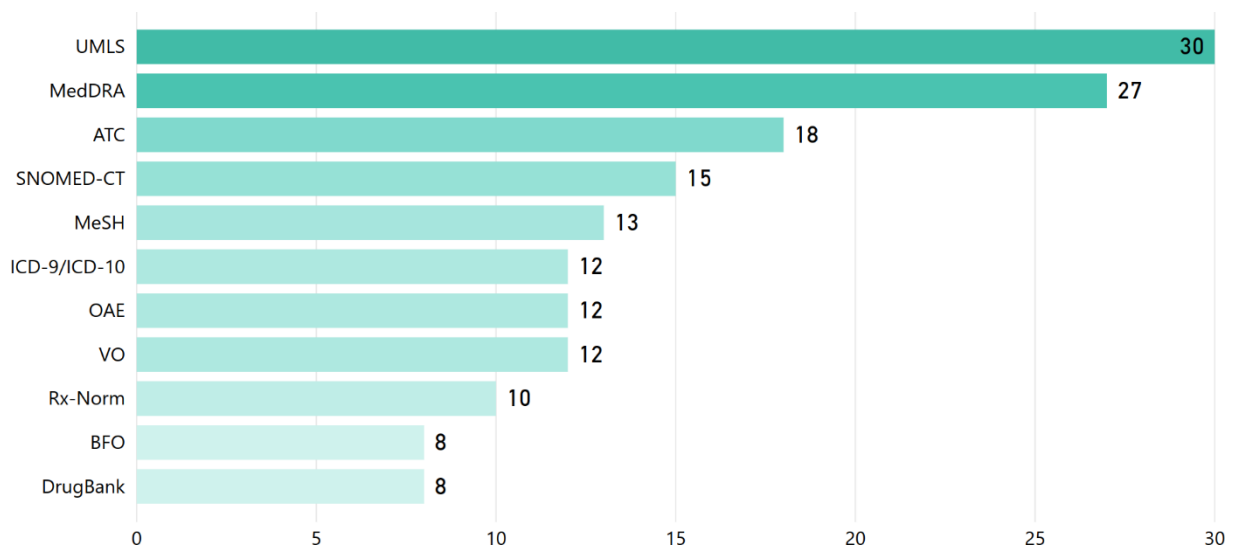


Figure 9: Reference knowledge sources (i.e., terminologies/vocabularies/thesauri and ontologies) employed in the reviewed articles.

The types of data sources employed in the reviewed articles vary significantly, highlighting the complexity of the domain and the need for advanced data integration and representation schemes based on KE (Koutkias and Jaulent, 2015). Figure 10A presents the distribution of data source categories, while Figure 10B presents the most popular data sources³⁰, as employed in the reviewed articles. SRSs (e.g. the FDA Adverse Event Reporting System (FAERS) and the Vaccine Adverse Event Reporting System (VAERS)), drug information databases (e.g. DrugBank), ADE databases (mainly the Side Effect Resource

²⁹ Not all referenced terminologies/ontologies are presented for readability purposes. The full list of referenced terminologies/ontologies can be found in the detailed analysis provided as Supplementary Material in the form of an Excel file - <https://www.frontiersin.org/articles/10.3389/fphar.2019.00415/full#supplementary-material>.

³⁰ Not all data sources identified are presented for readability purposes. The full list of data sources identified can be found in the fully detailed analysis provided as supplementary material in the form of an Excel file - <https://www.frontiersin.org/articles/10.3389/fphar.2019.00415/full#supplementary-material>.

(SIDER)), genetic and biochemical information data sources (e.g. GO and the Kyoto Encyclopaedia of Genes and Genomes - GenomeNet (KEGG)), as well as scientific literature repositories (i.e. PubMed/MEDLINE) are the most prominent ones.

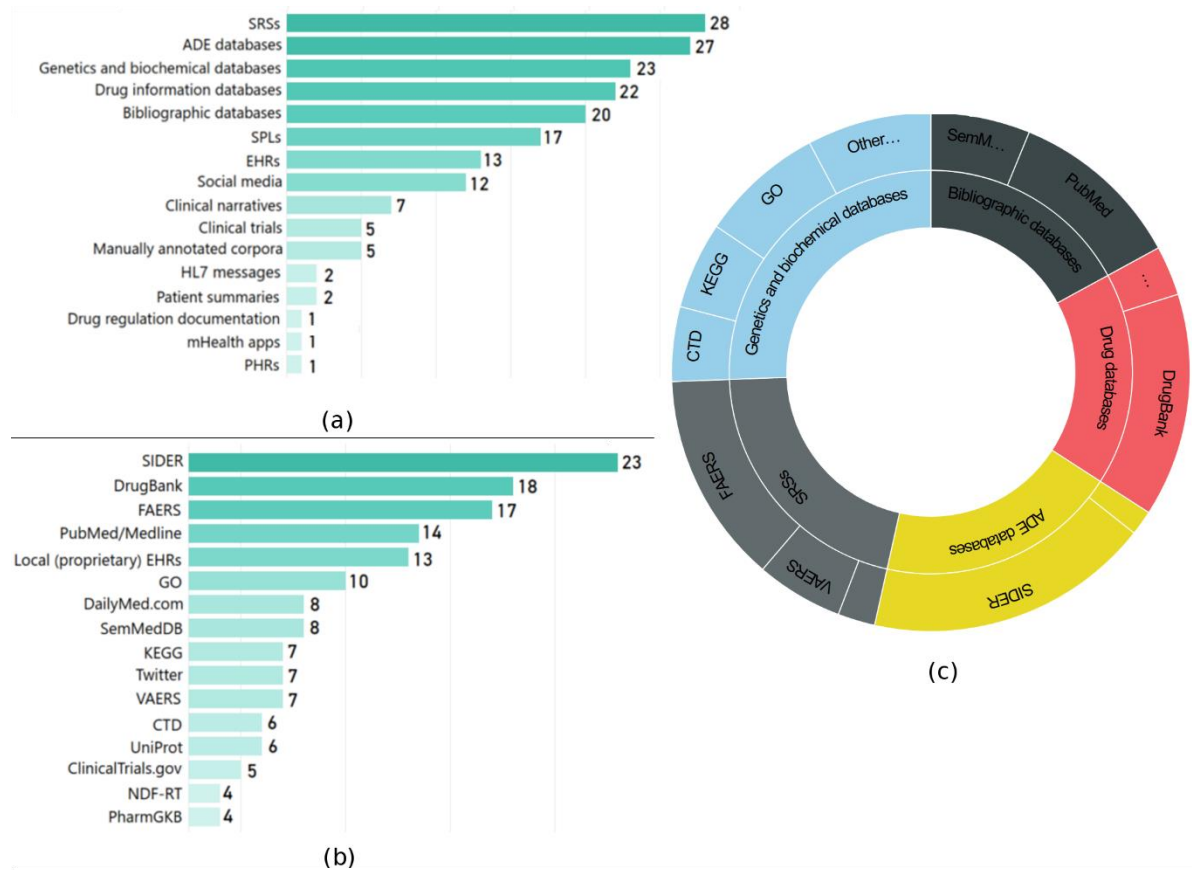


Figure 10: Use of main data sources: (A) number of articles per data source category, (B) number of articles per data source, and (C) schematic representation of main data sources used and their categories.

The selected articles were also critically reviewed to identify challenges or weaknesses and, consequently, gaps in the applied research practices. As shown in Figure 11, in many of the reviewed articles the research significantly depended on manual work (e.g. data curation, annotation, etc.) conducted by a small group of experts. Furthermore, despite elaborating on KE representation schemes like ontologies, many studies did not evaluate the proposed models regarding quality, e.g. using quality metrics frameworks like the Ontology Quality Evaluation Framework (OQuaRE) (Duque-Ramos et al., 2014). This finding may indicate a difficulty to apply the respective approaches at large-scale with real-world data. Moreover, a wide range of studies did not use an interoperable knowledge representation format (e.g. ontologies), while in

many studies the presented KE approaches were evaluated in a narrower scope than the one presented as their main use case.

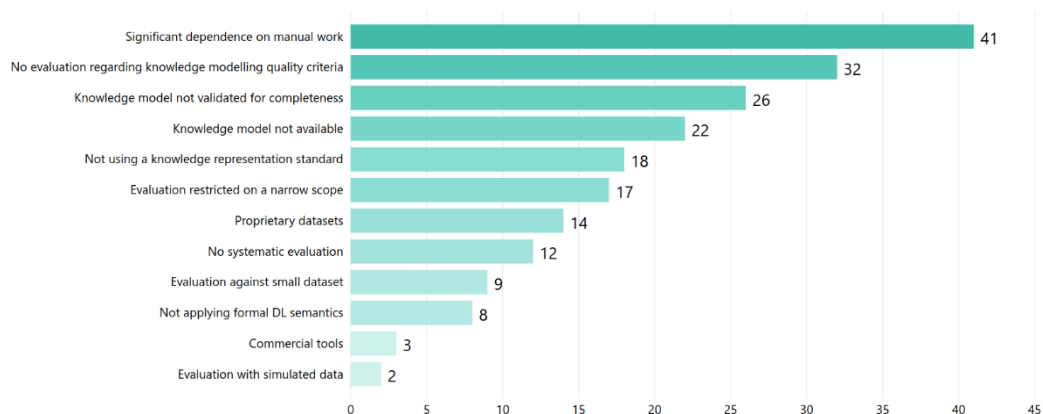


Figure 11: Identified challenges/weaknesses as reported in the reviewed articles.

Data and Knowledge sources

In this subsection, we present the main data sources used in KE for DS, as well as the employed knowledge sources, i.e. reference ontologies/terminologies, as identified in our review³¹.

Data sources

Table 3 presents the usage of data sources for specific DS applications, citing also the respective articles. We organize data sources in two main types: (a) those *established* or dominant in the domain of DS, such as SRSs, clinical trial databases, and bibliographic databases, and (b) *emerging* or quite new, such as observational healthcare databases, biochemical/genetic information databases, and social media platforms.

³¹ The special characteristics of each data source category and their possible contribution in signal detection are explicitly described in (Koutkias and Jaulent, 2015).

Table 3: Use of data sources in the reviewed articles for most prominent DS applications.

	<i>Category</i>	<i>Application in Drug Safety</i>
<i>Established data sources</i>	SRS	<p>Signal detection (Sarntivijai et al., 2012) (Tao et al., 2012) (Cheng et al., 2013) (Iyer et al., 2014) (Courtot et al., 2014) (Cheng and Zhao, 2014) (Boyce et al., 2014) (Wang et al., 2014)(Cai et al., 2015) (Dupuch and Grabar, 2015) (Liu and Chen, 2015) (Koutkias and Jaulent, 2016) (Liu et al., 2016) (Voss et al., 2017) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017) (Cai et al., 2017) (Liu et al., 2018)</p> <p>Validation (Henegar et al., 2006) (Gottlieb et al., 2012) (Iyer et al., 2014) (Courtot et al., 2014)</p> <p>Monitoring (Marcos et al., 2013)</p>
	ADE databases	<p>Signal detection (Huang et al., 2011) (Gurulingappa et al., 2012) (Cheng et al., 2013) (Iyer et al., 2014) (Cheng and Zhao, 2014) (Shang et al., 2014) (Cai et al., 2015) (Koutkias and Jaulent, 2015) (Jiang et al., 2015) (Herrero-Zazo et al., 2015) (Koutkias and Jaulent, 2016) (Kawazoe et al., 2016) (Bravo et al., 2016) (Eshleman and Singh, 2016) (Lowe et al., 2016) (Noor et al., 2016) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017) (Nguyen et al., 2017) (Abdelaziz et al., 2017)</p> <p>MoA identification/analysis (Huang et al., 2011) (Gottlieb et al., 2012) (Xu and Wang, 2013) (Cai et al., 2015) (Herrero-Zazo et al., 2015) (Guo et al., 2016) (Noor et al., 2016) (Personeni et al., 2017) (Piñero et al., 2017) (Abdelaziz et al., 2017)</p> <p>Validation (Gurulingappa et al., 2012)</p>
	Drug information databases	<p>Signal detection (Tari et al., 2010) (Huang et al., 2011) (Iyer et al., 2014) (Cheng and Zhao, 2014) (Boyce et al., 2014) (Cai et al., 2015) (Koutkias and Jaulent, 2015) (Herrero-Zazo et al., 2015) (Koutkias and Jaulent, 2016) (Zhang et al., 2016) (Noor et al., 2016) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017) (Abdelaziz et al., 2017)</p> <p>MoA identification/analysis (Lin et al., 2010) (Tari et al., 2010) (Huang et al., 2011) (Gottlieb et al., 2012) (Cai et al., 2015) (Herrero-Zazo et al., 2015) (Zhang et al., 2016) (Noor et al., 2016) (Abdelaziz et al., 2017)</p>

	Bibliographic databases	<p>Signal detection (Tari et al., 2010) (Gurulingappa et al., 2012) (Boyce et al., 2014) (Zhang et al., 2014) (Shang et al., 2014) (Koutkias and Jaulent, 2016) (Zhang et al., 2016) (Lowe et al., 2016) (Bravo et al., 2016) (Voss et al., 2017) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017) (Noor et al., 2016)</p> <p>MoA identification/analysis (Tari et al., 2010) (Hur et al., 2012) (Xu and Wang, 2013) (Zhang et al., 2016) (Piñero et al., 2017) (Cañada et al., 2017)</p>
	Clinical trials data	<p>Signal detection (Huang et al., 2011) (Boyce et al., 2014) (Koutkias and Jaulent, 2015) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017)</p> <p>MoA identification/analysis (Huang et al., 2011)</p>
Emerging data sources	EHRs	<p>Signal detection (Zhang et al., 2014) (Boyce et al., 2014) (Jiang et al., 2015) (Declerck et al., 2015) (Yuksel et al., 2016) (Voss et al., 2017) (Noor et al., 2016) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017) (Ceusters et al., 2011) (Personeni et al., 2017) (Henriksson et al., 2016)</p> <p>CDSS development (Koutkias et al., 2012) (Gottlieb et al., 2012) (Neubert et al., 2013) (Doulaverakis et al., 2014)</p>
	Clinical narratives	<p>Signal detection (Iyer et al., 2014) (Zhang et al., 2014) (Sarker and Gonzalez, 2015) (Henriksson et al., 2015) (Henriksson et al., 2016) (Iqbal et al., 2017)</p>
	Biochemical and genetic information databases	<p>Signal detection (Arikuma et al., 2008) (Tari et al., 2010) (Boyce et al., 2014) (Cai et al., 2015) (Kawazoe et al., 2016) (Noor et al., 2016) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017) (Abdelaziz et al., 2017)</p> <p>MoA identification/analysis (Arikuma et al., 2008) (Tari et al., 2010) (Gottlieb et al., 2012) (Hur et al., 2012) (Cai et al., 2015) (Noor et al., 2016) (Piñero et al., 2017) (Abdelaziz et al., 2017)</p>
	SPLs	<p>Comparative drug analysis (Bisgin et al., 2011) (Boyce et al., 2013) (Boyce et al., 2014)</p> <p>MoA identification/analysis (Gottlieb et al., 2012) (Cai et al., 2015) (Guo et al., 2016) (Abdelaziz et al., 2017)</p> <p>CDSS development (Neubert et al., 2013) (Doulaverakis et al., 2014)</p>

	Social media	ADE information collection (Sarker and Gonzalez, 2015) (Nikfarjam et al., 2015) (Liu and Chen, 2015) (Liu et al., 2016) (Eshleman and Singh, 2016) (Audeh et al., 2017) (Cocos et al., 2017) (Nguyen et al., 2017) (Liu et al., 2018)
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Established data sources

SRSs constitute the dominant data source for DS. They have been widely used in the reviewed articles for signal identification (mostly through NLP) as well as monitoring and validation. Interestingly, in order to improve the mining capacity of FAERS for signal detection and promote semantic interoperability between FAERS and other data sources, NLP techniques and normalization procedures were applied to FAERS data using reference terminologies, i.e., MedDRA, RxNorm and the National Drug File - Reference Terminology (NDF-RT) (Wang et al., 2014).

ADE databases [mostly SIDER, the Comparative Toxicogenomics Database (CTD) and MetaADEDDB), clinical trials data (from ClinicalTrials.gov), drug information databases (e.g. DrugBank) and bibliographic databases (i.e. PubMed/MEDLINE and the Semantic MEDLINE Database (SemMedDB) (Kilicoglu et al., 2012), a database of semantic relationships extracted from MEDLINE] have been employed for signal detection and MoA investigation.

Emerging data sources

Observational healthcare databases and Electronic Health Records (EHRs) in particular, gained a major interest recently for DS research. In the scope of KE for DS, structured EHRs were used for signal detection, combining the use of ontologies and NLP approaches, as well as for developing medication-related Clinical Decision Support Systems (CDSSs). Unstructured EHR data, i.e. free-text clinical notes, were also used for ADR identification.

Recent advances in high-throughput sequencing technologies enable the integration of biological information to support the new field of SP by focusing on gene-drug-disease interaction networks. An increasing number of these frameworks incorporate genetic data (most often genomic polymorphisms as described in PharmGKB) for drug-drug interactions (DDIs) and ADR in silico prediction, stressing the need to integrate such data to complement in vivo and in vitro investigations on pharmacogenomics. Information on pathways (e.g. from KEGG), proteins (e.g. from UniProt) and their annotations with GO were the most prominent data sources for ADE identification and the analysis of the respective MoA. Interestingly, the use of biomolecular functional network data improved ADR predictions (Huang et al., 2011), and suggests that such prediction could help to design new models for investigating ADRs and their

MoA, to avoid tedious and costly clinical trials, in line with the paradigms of *in silico clinical trials* and *SP*.

Structured Product Labels (SPLs) have been also used in various studies, including comparative drug analysis and the analysis of drug MoA. Furthermore, national SPL indexes were used as a data source for localized CDSSs.

Social media (mostly Twitter, DailyStrength.com and dedicated patient forums) attracted recently major interest for DS. Exploiting KE activities like knowledge extraction in social media can add a valuable new data source in the DS ecosystem, as they are characterized by three interesting aspects (Koutkias et al., 2017): (a) they provide vast amounts of data, (b) posts could be monitored across time and trends could be identified in relation with triggering events (e.g. new safety issues reported by regulatory authorities or announced in the media), and (c) user interconnections (e.g. mentions, responses, followership, etc.) could create a “social graph” which could provide useful insights through graph-based Social Network Analysis (SNA). Notably, a comparative study concerning the prevalence of ADR mentions in Twitter and other social media platforms concluded that social media can be considered as a valuable data source for DS (Nguyen et al., 2017).

Knowledge sources

Table 3 summarizes the use of the most prominent knowledge sources in the reviewed articles, citing indicative references³². We categorize them into reference terminologies, thesauri and vocabularies, spanning from simple hierarchies to ontologies which express richer semantics.

³² In the detailed analysis results (provided as Supplementary Material), all referenced knowledge sources for each paper are identified. For readability, we only refer in the manuscript to the most prominent knowledge sources used.

Table 4: Use of the most prominent knowledge sources in the reviewed articles.

	<i>Knowledge source</i>	<i>Use in the reviewed articles</i>
<i>Terminologies / Thesauri / Vocabularies</i>	MedDRA / WHO-ART	<p>Semantic annotation of concepts (grouping, classification etc.) (Henegar et al., 2006) (Neubert et al., 2013) (Courtot et al., 2014) (Jiang et al., 2015) (Declerck et al., 2015) (Guo et al., 2016) (Xie et al., 2016b) (Xie et al., 2016a) (Voss et al., 2017) (Cai et al., 2017) (Segura-Bedmar and Martínez, 2017)</p> <p>Reference terminology for data integration (Sarntivijai et al., 2012) (Boyce et al., 2014) (Sarntivijai et al., 2016) (Yuksel et al., 2016) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017)</p> <p>NLP (e.g. Named Entity Recognition) (Bisgin et al., 2011) (Gurulingappa et al., 2012) (Iyer et al., 2014) (Cai et al., 2015)</p>
	UMLS	<p>NLP (e.g. Named Entity Recognition) (Segura-Bedmar et al., 2010) (Segura-Bedmar et al., 2011) (He et al., 2013) (Kang et al., 2014) (Shang et al., 2014) (Sarker and Gonzalez, 2015) (Jiang et al., 2015) (Zhang et al., 2016) (Liu et al., 2016) (Eshleman and Singh, 2016) (Liu et al., 2018)</p> <p>Reference terminology for data integration (Henegar et al., 2006) (He et al., 2013) (Iyer et al., 2014) (Cheng and Zhao, 2014) (Boyce et al., 2014) (Cai et al., 2015) (Bravo et al., 2016) (Piñero et al., 2017) (Noor et al., 2016) (Cohen and Widdows, 2017) (Abdelaziz et al., 2017)</p>
	ATC	<p>Reference terminology for data integration (Koutkias et al., 2012) (Gottlieb et al., 2012) (Cheng et al., 2013) (Neubert et al., 2013) (Kawazoe et al., 2016)</p> <p>NLP (e.g. Named Entity Recognition) (Bisgin et al., 2011) (Henriksson et al., 2016) (Segura-Bedmar and Martínez, 2017)</p> <p>Semantic annotation of concepts (grouping, classification etc.) (Lin et al., 2010) (Iyer et al., 2014) (Doulaverakis et al., 2014) (Cheng and Zhao, 2014) (Cai et al., 2015) (Personeni et al., 2017) (Abdelaziz et al., 2017)</p>

	RxNorm	Reference terminology for data integration (Iyer et al., 2014) (Boyce et al., 2014) (Wang et al., 2014) (Jiang et al., 2015) (Voss et al., 2017) (Hogan et al., 2017) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017) (Cai et al., 2017) (Personeni et al., 2017)
	ICD-9/10	Reference terminology for data integration (Koutkias et al., 2012) (Boyce et al., 2014) (Declerck et al., 2015) (Yuksel et al., 2016) Semantic annotation of concepts (grouping, classification etc.) (Huang et al., 2011) (Zhang et al., 2013) (Doulaverakis et al., 2014) (Henriksson et al., 2015) (Personeni et al., 2017)
	SNOMED-CT	Semantic annotation of concepts (grouping, classification etc.) (Iyer et al., 2014)(Henriksson et al., 2015) (Guo et al., 2016) (Personeni et al., 2017) Reference terminology for data integration (Zhang et al., 2013) (Boyce et al., 2014) (Declerck et al., 2015) (Yuksel et al., 2016)
	MeSH	NLP (e.g. Named Entity Recognition) (Kang et al., 2014) (Henriksson et al., 2015) (Lowe et al., 2016) (Voss et al., 2017) (Piñero et al., 2017) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017) or manually (Cheng and Zhao, 2014)(Bravo et al., 2016)
Ontologies	OAE/VAE	Combined with disproportionality analysis for signal detection and comparative drug analysis (Sarntivijai et al., 2012) (Xie et al., 2016b) (Xie et al., 2016a) (Wang et al., 2017) Basis for other ontologies (Tao et al., 2012)(Marcos et al., 2013) (Lin and He, 2014) (Herrero-Zazo et al., 2015) (Guo et al., 2016) (Wang et al., 2017) (Liu et al., 2017) Enhance NLP results (Gurulingappa et al., 2012) (Hur et al., 2012)
	OntoADR	Combined with OAE to investigate MoA of Tyrosine Kinase Inhibitors (Sarntivijai et al., 2016) Secondary use of EHRs and observational studies data (e.g. signal detection and automatic report generation) (Declerck et al., 2015) (Yuksel et al., 2016) Searching, coding, and information retrieval of ADE information (Bousquet et al., 2014) (Souvignet et al., 2016)

Reference terminologies, thesauri and vocabularies

Several knowledge sources (e.g. UMLS, MedDRA, ATC, RxNorm, ICD, SNOMED-CT, and Medical Subject Headings (MeSH)) were used as reference terminologies for knowledge extraction through Named Entity Recognition (NER), which is a typical step in NLP applications. Furthermore, they provided a “light” semantic structure of concepts (i.e. a concept hierarchy), which could be exploited for automatic inference. One of their most prominent uses was the semantic normalization of heterogeneous data sources during data integration. For example, UMLS was widely used in knowledge extraction activities, i.e. as reference terminology in NER steps applied to recognize entities in free-text through the MetaMap-MMtx tool, to reduce the semantic ambiguity between the various data sources. MedDRA and the World Health Organization (WHO) Adverse Reaction Terminology (WHO-ART) were used to semantically categorize and interrelate (e.g. group) concepts regarding signals or ADE reports and also as common reference terminologies for integration purposes or NLP tasks. In US-originated studies, RxNorm was used as a reference terminology for drugs, but to a smaller extent compared to ATC overall. An interesting application of SNOMED-CT was for enhancing the semantics provided by WHO-ART (Alecú et al., 2008) and MedDRA (Bousquet et al., 2014) (Dupuch and Grabar, 2015).

Ontologies

OAE (He et al., 2014b) and VO (Lin and He, 2012) (Zhang et al., 2013) constitute reference ontologies in the domain. They were combined with statistical approaches and disproportionality analysis for the comparative analysis of drugs and ADE profiles. OAE and VO were also used to enhance the results of plain NLP algorithms, or as a conceptual base for other ontologies like the Ontology of Vaccine Adverse Events (OVAE), the Ontology of Drug Neuropathy Adverse Events (ODNAE), the Ontology of Cardiovascular Drug AEs (OCVDAE), the Ontology of Chinese Medicine for Rheumatism (OCMR), and the Ontology of Genetic Susceptibility Factors (OGSF). Furthermore, OAE has been identified as an ontology which could support a systems-based modeling approach for regulatory drug approval purposes (Sinha et al., 2016)(Zhichkin et al., 2012).

The RxNorm-based Drug Ontology (DrOn) represents the therapeutic functions of drug products, including their MoA at the molecular level and their adverse effects (Hogan et al.,

2017). However, it seems that it is not extensively employed for DS purposes, as DS was not among its main use cases.

Notably, OntoADR is an ontologized version of MedDRA (Bousquet et al., 2014), which was used in the SALUS project to integrate MedDRA in an overall ontology-based information model and support secondary use of EHR data for DS (Declerck et al., 2015) and observational studies (Yuksel et al., 2016). Similarly, OAE and MedDRA have been interlinked to investigate the biological mechanisms of Tyrosine Kinase Inhibitors (Sarntivijai et al., 2016).

Knowledge Engineering activities

In this subsection, we present how the main KE activities were employed in the reviewed articles and highlight the most prominent approaches. Thus, we emphasize on the employed KE methods, illustrating how these were employed for DS.

Knowledge dissemination

A platform aiming to facilitate knowledge dissemination regarding drug safety, efficacy, and effectiveness was proposed, overcoming the issue of outdated drug product labels (Boyce et al., 2013). The study integrated many data sources in a single knowledge graph containing information related with drug products (including ADEs and DDIs) and provided a proof-of-concept Web interface allowing to actively explore all the information related with a specific drug product. Knowledge dissemination approaches were also employed to support comparative drug analyses regarding ADEs and contraindications, using visual analytics combined with ontological reasoning (Lamy et al., 2017).

Knowledge elicitation

Knowledge elicitation activities are typically related with rule-based inferencing combined with ontological reasoning methods. For instance, a conceptual model relying on the Drug Interaction Ontology (DIO) to identify DDIs was developed based on two rule-based inferencing modules (Pathway object constructor and Drug interaction detector) (Arikuma et al., 2008). Drug-Drug Interactions Ontology (DINTO) combined Description Logic (DL) (Baader et al., 2004) based reasoning with rules formed in the Semantic Web Rules Language (SWRL) to identify DDIs and investigate their MoA (Herrero-Zazo et al., 2015), upon a conceptual model exploiting Pharmacokinetics and Pharmacodynamics related knowledge. The

Drug Enzyme Interaction (DEI) ontology was combined with a rule-base to investigate drug MoAs (Zhang et al., 2016). Similarly, ProLog was used to encode rules regarding drug metabolism and conduct reasoning to identify potential DDIs (Tari et al., 2010). In addition, SPARQL queries following specific patterns regarding temporal inference were used to identify ADRs upon HL7 messages integrated in one large Resource Description Framework (RDF) graph (Kawazoe et al., 2016). Rules referring to four levels of interaction mechanisms, namely, pharmacokinetic, pharmacodynamic, pharmacogenetic, and multi-pathway interaction, were employed to identify DDIs and their underlying MoAs upon a large RDF knowledge graph integrating 15 DDI databases (Noor et al., 2016).

Inferencing methods based on graph theory were also extensively applied. Graph clustering coefficient analysis was used to identify similar ADE clusters (Lin et al., 2010). Node closeness in a protein–protein interaction graph was used to infer DDIs (Gottlieb et al., 2012), while network centrality was investigated in a gene-gene interaction graph as a metric of gene importance in terms of causing fever (Hur et al., 2012). Several graph-based metrics (i.e. connectivity, betweenness and clustering coefficient) were used to predict ADEs in a knowledge graph built upon MetaADEDDB (Cheng et al., 2013). Graph shortest paths were used to identify the weight of relationships in a vaccine-related network extracted from SemMedDB, to confirm the structural validity of VO (Zhang et al., 2013). A similar approach was used to identify relationships between drugs and ADE terms presented in the UMLS Metathesaurus semantic network, in order to extract ADEs from biomedical text (Kang et al., 2014). A graph kernel based ML approach was used to extract drug-enzyme relationships from the literature, using UMLS as reference terminology (Zhang et al., 2016). Graph-based metrics combined with terminological reasoning were employed to calculate the semantic distance between MedDRA terms and cluster them to improve Standardized MedDRA Queries (SMQs) (Dupuch and Grabar, 2015). The relationships of drugs and their effects were modelled in the form of the so-called Drug Effect Graph and used topological characteristics to identify ADE relations in Twitter (Eshleman and Singh, 2016).

DL-based reasoning upon ontologies was applied in various cases (Vandervalk et al., 2013) (Zhang et al., 2013) (Courtot et al., 2014) (Herrero-Zazo et al., 2015) (Souvignet et al., 2016) (Lamy et al., 2017). In particular, combining the use of ontology reasoning (upon OAE and VO) with more traditional disproportionality measures like the Proportional Reporting Ratio (PRR) was used to analyse already identified ADEs and interrelate the statistic properties

of each signal with the categorical information provided by the respective ontologies (Sarntivijai et al., 2012) (Xie et al., 2016b) (Wang et al., 2017). A similar approach, combining ontology reasoning upon OAE interlinked with MedDRA and disproportionality analysis of SRS data (i.e. FAERS and VAERS) was presented in (Sarntivijai et al., 2016) and (Xie et al., 2016a).

Terminological reasoning was combined with ontologies and other statistical approaches, including disproportionality analysis. For example, an advanced association rule mining approach was presented for identifying causality between drugs and ADEs in FAERS (Cai et al., 2017). In particular, the Relative Reporting Ratio (RRR) was used to model confidence as defined in association rule mining, combined with terminological reasoning based on RxNorm and MedDRA upon FAERS data.

ML was also identified as a prominent paradigm employed for knowledge elicitation. SVMs were used in several classification schemes (Huang et al., 2011) (Zhang et al., 2016) (Henriksson et al., 2016), while association rules were elicited and contextualized in (Koutkias et al., 2012) for ADE prevention based on EHR data. Vector-based similarity mechanisms were also extensively used, mostly for content-based document classification (Henriksson et al., 2015) (Nikfarjam et al., 2015) (Cocos et al., 2017). For example, SemMedDB predicates (i.e., triplets in the form of subject-predicate-object) were modelled as vectors and used an SVM to classify concepts (Cohen and Widdows, 2017), while deep-learning neural networks were used to identify ADEs in Twitter (Cocos et al., 2017). A vector-based approach implemented pattern structures, in combination with the class hierarchies of three medical ontologies (ICD-9-CM, SNOMED-CT, and ATC), to mine association rules that characterize ADEs occurring in distinct patient subgroups (Personeni et al., 2017).

Finally, a large-scale DDI prediction system relying on a large RDF knowledge base was developed upon vector-based as well as graph-based similarity metrics combined with terminological reasoning (Abdelaziz et al., 2017).

Knowledge extraction

The most widely used knowledge extraction approach refers to the use of NLP techniques applied on unstructured data, i.e. free-text, originated from biomedical literature, social media, clinical notes, etc., using various computational methods (including ML-based).

Relying on core NLP methods, the DrugNerAR system demonstrated its ability to identify drug mentions in biomedical literature for DDI identification (Segura-Bedmar et al., 2010), and drug-gene relationships, extracted from MEDLINE (Xu and Wang, 2013). NLP was also used upon bibliographic data sources, storing a structured representation of plain text in a “parse tree database” for further elaboration and reasoning to identify DDIs (Tari et al., 2010). Notably, an alternative approach targeting social media took into account the 3 previous and the 3 next tokens to analyse each token in its context for identifying ADR mentions (Nikfarjam et al., 2015). Context-based semantic analysis across sentences improved the identification of ADRs in patient forums, using the NegEx tool and drug indications to filter out negated ADEs and drug indications, respectively (Liu and Chen, 2015). NLP was also applied on clinical notes to identify DDIs based on drug-gene relationships extracted from SemMedDB (Zhang et al., 2014), while SemMedDB was also exploited for Literature Based Discovery aiming at signal assessment (Shang et al., 2014). Similarly, NLP was applied on the clinical notes of a large dataset, taking into account contextual information (i.e. temporal information and categorization in factual, hypothetical or negated sentence), to detect ADEs specific to antipsychotics and antidepressants (Iqbal et al., 2017). NLP was also applied on Wikipedia to identify drugs and conditions in the title of its articles, as well as links to other pages related to drugs, conditions and ADRs, aiming to construct a lexicon of ADR terms (Lowe et al., 2016).

An alternative approach used topic modelling on free-text drug leaflets to generate novel hypotheses regarding DS (Bisgin et al., 2011). Topic modelling and sentiment polarity were used as contextual information regarding the identification of ADEs in Twitter (Eshleman and Singh, 2016). Ontology-assisted NLP was used to identify ADE mentions in free-text sources, i.e. medical case reports and literature, targeting at signal identification (Gurulingappa et al., 2012). Finally, SPLs were used to extract information and integrate it in a large RDF graph (Boyce et al., 2013).

On exploiting ML-based approaches, the SSEL-ADE framework relied on an SVM employing n-grams and graph-based metrics to identify ADE mentions in social media (Liu et al., 2018). N-gram models were used combining 3 SVM kernels and stacked generalization to improve the identification of DDIs in biomedical literature (He et al., 2013). An ensemble of ML methods was employed to identify DDIs in clinical narratives, taking into account contextual information for the analysis of each term (i.e., negation, speculation and temporality) (Henriksson et al., 2015) (Henriksson et al., 2016). Notably, third-party data sources were

integrated in one knowledge base combined with ML to identify ADEs in biomedical literature (Bravo et al., 2016). Interestingly, crowdsourcing was used to manually annotate a corpus of free-texts (in a reasonable time and without bias) to train the ML model.

Knowledge integration

WHO-ART and SNOMED-CT were mapped based on synonymy in the UMLS Metathesaurus to automatically generate definitions of WHO-ART terms in a DL formalism, i.e. the Web Ontology Language (OWL), aiming to identify WHO-ART terms that may be grouped together (Alecú et al., 2008). As the same medical condition may be coded with different terms in DS databases, it was assumed that such approach would enable to group similar terms and improve signal generation. As a next step in the same line of work, SNOMED-CT was used to convert MedDRA to an OWL ontology, namely, OntoADR, which combined the semantics of MedDRA and SNOMED-CT (Bousquet et al., 2014), through a relational database implementation (Souvignet et al., 2016).

Koutkias and Jaulent investigated the limitations of computational signal detection methods when applied on single data sources, and elaborated on multiple heterogeneous signal detection methods, data sources and other drug-related resources under a common, integrated framework (Koutkias and Jaulent, 2015). The framework relied on the Pharmacovigilance Signal Detection Ontology (PV-SDO) and a multiagent system, implementing a comprehensive workflow comprising of method selection and execution, as well as outcomes' aggregation, filtering, ranking and annotation (Koutkias and Jaulent, 2016).

Declerck et al. proposed an ontology-based abstraction layer called Common Information Model – CIM (Declerck et al., 2015). CIM was populated through software “bridges” based on mappings of local EHR databases to CIM, thus accommodating the dependencies of the overall framework on the local EHR data schemas.

Furthermore, various data sources (SPLs, ADE information, clinical trials data, etc.) were integrated in a single knowledge graph based on common-terms matching and mappings to reference terminologies, in order to provide a unified and semantically enhanced knowledge base for information regarding drug products (Boyce et al., 2013).

Considering the integration of biochemical data for DS, several sources such as UMLS, DrugBank, CTD and UniProt were integrated in one large RDF graph for ADR detection

(Abdelaziz et al., 2017). Several heterogeneous data sources were also integrated to interrelate biochemical and phenotypic information for predicting ADEs through an SP approach (Huang et al., 2011) (Cheng and Zhao, 2014). Furthermore, the Adverse Drug Reaction Classification System (ADReCS) combines a hierarchical structure of concepts (similar to the MedDRA structure) and integrates information from a large number of ADE and biochemical data sources, explorable through a Web interface for signal assessment (Cai et al., 2015). Similarly, DisGeNet is a comprehensive centralized repository created by integrating data from curated databases and two datasets obtained by mining the scientific literature (Piñero et al., 2017). It focuses on the associations between genes/variants and diseases. DS is one of DisGeNet's main use cases and can also be considered as a large knowledge graph as it is also available in RDF format (Queralt-Rosinach et al., 2016).

Regarding medication-based CDSSs, Koutkias et al. integrated various knowledge sources using the Computerized Interpretable Guideline (CIG) formalism (Koutkias et al., 2012); they used meta-rules to integrate these sources and well-defined communication interfaces, in order to satisfy both performance requirements and also the need to obtain knowledge from third-party sources. In the same context, a combination of rule-based and ontology-based knowledge representation was developed to accommodate the need for integrating various data sources and also providing effective DSS support to prevent ADEs in a computationally effective manner (Doulaverakis et al., 2014).

The D3 (Drug-drug interactions Discovery and Demystification) system aimed to infer MoAs for DDIs based on an integrated RDF schema of 12 biomedical resources and 15 DDI databases (Noor et al., 2016). Some data sources included data in RDF format obtained from Bio2RDF, which were semantically aligned through the use of UMLS and a set of specific relationships (e.g. "has indication"). Non-UMLS compatible data sources were also integrated via explicit database cross-references.

The LAERTES knowledge base which was built in the context of the Observational Health Data Sciences and Informatics (OHDSI) collaborative (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017), integrated multiple data sources into a common knowledge schema for signal investigation, in compliance with the OMOP Common Data Model (CDM) (Boyce et al., 2014) (Voss et al., 2017).

Knowledge representation

Ontologies are the most commonly used knowledge representation formalism and, therefore, several ontologies were introduced targeting the domain of DS, mostly using OWL and RDF.

As regards the ADE representation, OAE is the most prominent ontology. OAE is a community-based outcome, widely used to semantically categorize ADEs (He et al., 2014b). Respectively, VO is a community-based ontology used to semantically categorize vaccines (Lin and He, 2012) (Hur et al., 2012) (Zhang et al., 2013), typically used in combination with OAE. VO was also used in combination with the Time Event Ontology (TEO) which was developed to formally represent the time-oriented aspects of an ADE report (Tao et al., 2012), as time has been recognized as an important aspect of ADEs (Personeni et al., 2017) (Iqbal et al., 2017). VO and OAE were also used as the conceptual base of OVAE to depict relationships between vaccines, adverse events, and patient age groups (Marcos et al., 2013), in the context of the VIOLIN vaccine safety analysis system (He et al., 2014a), and to classify and update data regarding ADEs of Hepatitis vaccines (Xie and He, 2017). VO and OAE were referenced by OGSF, aiming to model the genetic susceptibility (or predisposition) to vaccine adverse events (Lin and He, 2014). Furthermore, ODNAE extends OAE to facilitate the analysis of drugs causing neuropathy adverse events (Guo et al., 2016). Similarly, OCVDAE extends OAE to facilitate the analysis of ADEs caused by cardiovascular drugs (Wang et al., 2017), and OCMR extends OAE to facilitate the comparative analysis of traditional Chinese drugs regarding rheumatism (Liu et al., 2017).

Henegar et al. modelled MedDRA using DAML+OIL (OWL's predecessor) to support automatic signal generation (Henegar et al., 2006). The same group created an OWL ontology to enrich the formal definitions of WHO-ART terms with associative relations provided by SNOMED-CT to support grouping of WHO-ART terms related to the same medical condition (Alecu et al., 2008) and, as a further step, presented an ontologized version of MedDRA, exploiting SNOMED-CT semantics (Bousquet et al., 2014). OWL was also used to model ADEs focusing on the patient's medical history concepts and their time-related aspects (Ceusters et al., 2011). Moreover, the Adverse Event Reporting Ontology (AERO) was proposed by modelling case definitions related to adverse events following immunization to support the respective information processing workflow (Courtot et al., 2014).

In the scope of representing drug interactions, DIO models drug metabolic pathway related concepts, including information from organ to molecular level, supporting SP approaches (Arikuma et al., 2008). DEI models the interactions of drugs and enzymes, used to infer potential DDIs from biomedical literature (Zhang et al., 2016). DINTO provides a DDI classification schema and a conceptual model taking into account both the pharmacokinetic and pharmacodynamic aspects of DDIs (Herrero-Zazo et al., 2015). DINTO references OAE and integrates knowledge from other data sources (i.e. ChEBI, DrugBank, and SIDER) with no manual curation, following the NeOn KE methodology (Suárez-Figueroa et al., 2012).

In a few cases, the RDF representation formalism was used without aiming to formulate a specific conceptual model; for example, HL7 messages were converted to RDF and integrated to a large RDF model to confirm that they could be used in the context of ADR detection (Kawazoe et al., 2016).

Alternatively, relational databases were used as a knowledge base storage formalism, since they provide a mature data storage paradigm, able to support vast data storage in a computationally effective manner that is widely used in real-world enterprise systems. Compared to ontologies, relational databases are not specifically designed to support KE activities (e.g. automatic reasoning). On the other hand, while ontologies can support formal semantics and automatic reasoning given their underlying robust mathematical background, i.e. DL, the respective data storage systems are not yet mature enough and the automatic reasoning process is computationally expensive for large knowledge graphs, making relational databases a competing alternative for large knowledge bases. To this end, MEDLINE abstracts were used to extract knowledge on drug metabolism and interactions (storing the corresponding structured representation into a database in the form of a tree-structure representation) and queried to identify DDI mentions (Tari et al., 2010). SemMedDB contains statements in the form of triples (subject-predicate-object) extracted from MEDLINE and stored in a relational format (Zhang et al., 2014). MetaADEDB relies on a relational schema to integrate several heterogeneous data sources for DS (Cheng et al., 2013).

Hybrid data storage approaches have been also proposed, using both relational and RDF formalisms. For example, LAERTES used relational databases as its basic data storage paradigm (Boyce et al., 2014) (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative, 2017). However, it also employs the Web Annotation Data Model (WADM), to enable “drill-down” into evidence supporting a statistic

measure of association between a drug and a Health Outcome of Interest (HOI) (e.g. a count, PRR, etc.). DisGeNet is also available both in relational and RDF version, accompanied by an ontology which defines its conceptual model.

Impact of Knowledge Engineering on Drug Safety

In this subsection, we highlight the contribution that the employed KE approaches have in DS core activities (Table 2). In particular, the emphasis is given on illustrating the value of adopting KE approaches for DS and their potential application in current DS practice.

ADE information collection

Currently, information collection methods to support routine DS activities (e.g. signal identification) are mostly focusing on SRS, bibliographic, and clinical trial data. In particular, bibliographic search is typically conducted manually by experts, requiring the formulation of the respective query (i.e. define the terms of interest, expand the query through synonyms, etc.), and the manual evaluation of the returned results based on expert tacit knowledge. On the other hand, via the formalization of knowledge in an explicit way, the use of KE tools can automate this process, facilitate the exploitation of new/emerging data sources, and reduce errors in the process.

Bibliographic data sources were used to extract DDIs (Segura-Bedmar et al., 2010) (Tari et al., 2010) (He et al., 2013) and ADE mentions (Gurulingappa et al., 2012) (Kang et al., 2014). NLP combined with disproportionality analysis was used to identify DDIs in free-text clinical notes, concluding that the narrative part of EHRs can complement existing sources for post-marketing DDI surveillance (Iyer et al., 2014). Similarly, clinical narratives were exploited for ADE identification (Zhang et al., 2014) (Henriksson et al., 2015). Notably, psychiatric clinical notes were used to identify ADEs achieving an F-score of 0.83 (Iqbal et al., 2017). EHR data were also used to generate ADE reports automatically, aiming to address ADE underreporting by clinicians (Declerck et al., 2015).

Various studies exploited social media with promising results³³. In particular, they were used to identify ADE mentions using various NLP techniques (Sarker and Gonzalez, 2015)

³³ A relatively updated list of studies working on ADE extraction upon social media is presented in (Liu et al., 2018), regardless if they employ KE techniques or not.

(Nikfarjam et al., 2015), concluding that since the language used is highly informal, the use of context and sentiment analysis could further improve the results. A combination of statistical learning and semantic filtering improved the recognition of known ADRs in patient forums with precision ranging between 75% and 82% and recall between 56.5% and 65.3% (Liu and Chen, 2015). High accuracy in recognizing ADE mentions in two MedHealth forums and Twitter were also reported, with area under the curve (AUC) values of 84.5%, 77.3%, and 84.5%, respectively (Liu et al., 2016). Finally, a graph-based inference approach combined with topic modelling and sentiment analysis identified adverse drug effect mentions in Twitter with precision exceeding 85% and F1 exceeding 81% (Eshleman and Singh, 2016).

ADE detection

Systematic approaches for knowledge extraction, integration and further processing (e.g. based on DL reasoning) demonstrated promising results on ADE detection. An exemplar implementation of *in silico* DDI prediction incorporating drug metabolic pathways and molecular events enabled the quantitative evaluation of drug interactions (Arikuma et al., 2008). A prototype implementation was able to quantitatively examine the effect of irinotecan-ketoconazole interactions using numerical simulations. The extension of this method for other drug pairs as well as multiple drug interactions showed the potential to support computational DDI predictions using DIO. As a result, four potential drug interactions that involved cytochrome p450 (oxidation by CYP3A4) and drug binding reaction to albumin were automatically detected via DIO, while two of them had not been reported in the literature. DDIs were successfully identified (>75% according to the presented evaluation scheme) by modelling the behaviour of regulatory elements, particularly enzymes (Tari et al., 2010). Furthermore, live attenuated influenza vaccines were found to have lower chance of inducing Guillain-Barre Syndrome and paralysis than trivalent (killed) inactivated influenza vaccine (Sarntivijai et al., 2012).

Integrated knowledge bases created with the support of KE processes demonstrate remarkable results regarding ADE detection. The ability to identify ADEs through large-scale data integration in one knowledge base was demonstrated using MetaADEDDB (Cheng et al., 2013). Using FAERS as the gold standard during the evaluation process, MetaADEDDB facilitated ADE detection (AUC value reported more than 0.9 by 10-fold cross validation and 0.912 for external validation). Furthermore, the LAERTES knowledge base (Knowledge Base workgroup of the Observational Health Data Sciences and Informatics (OHDSI) collaborative,

2017) was evaluated including positive and negative controls, illustrating an AUC value of 0.92 (Voss et al., 2017).

Notably, INferring Drug Interactions (INDI) inferred both pharmacokinetic and pharmacodynamic DDIs upon EHR data by applying ML on drug MoA similarity and their biochemical properties (Gottlieb et al., 2012). Its validation confirmed one of the predicted CYP-related DDIs using hospital data in Israel. Finally, Tiresias, a DDI prediction system relying on a large integrated RDF knowledge base, was successfully used to predict DDIs, identifying 68% of all DDIs found after 2011, using only information about DDIs present in the January 2011 version of DrugBank (Abdelaziz et al., 2017).

ADE assessment

ADE assessment mostly refers to the analysis of the underlying MoA as well as the comparative analysis of drugs. These activities typically require the integration of heterogeneous data sources, including biochemical and genetic information databases.

Dynamic reconstruction of drug metabolic pathways from primitive molecular events using information modelled in DIO was conducted, showing that unknown potential pathways can be inferred through the combination of ontologies and rule-based inference (Arikuma et al., 2008). Similarly, drug target information was used to identify clusters of similar DDI cases reported in FAERS and provide explanations for their MoA (Lin et al., 2010). The ability to interpret the MoA of the respective DDIs was demonstrated by exploiting drug metabolism knowledge encoded in the form of rules linking proteins and drugs via four types of relationships (i.e. metabolizes, induces, inhibits, regulates) (Tari et al., 2010). For each DDI identified, the respective triggered rules could be considered as a description of the respective MoA. Alternatively, a gene interaction graph regarding vaccines was built based on bibliographic data, and provided a method to identify genes potentially related with the ADE of fever (Hur et al., 2012). DIO drug-enzyme relationships were used to model the mechanism of drug metabolism for DDI detection in biomedical literature, achieving an F-measure of 84.97% for drug-enzyme relationships recognition and 83.19% for DDI recognition against the “in vivo” dataset used for evaluation (Zhang et al., 2016). Finally, in the context of the eTOX project a Web application was presented, aiming to facilitate the exploration of a knowledge base regarding drugs, genes and compounds’ toxicity associations for investigating liver toxicity (Cañada et al., 2017).

An interesting contribution was the development of a semantics-enabled Web analytics tool, namely, the Case Series Characterization Tool (CSCT) (Yuksel et al., 2016). CSCT has been used to conduct observational studies and comparative drug analyses, exploiting the integration of semantically and syntactically heterogeneous data sources, addressed by an ontology-based data information model. The CSCT deployment was validated by PV researchers from both UMC and the Lombardy Regional Pharmacovigilance Centre. The main advantages of the presented approach are: (a) easier definition of analysis rules (since CIM semantics were independent of the underlying data sources' syntactic or semantic schema), and (b) scalability of the proposed integration model due to semantic mediation of CIM as *“whenever a new source or target content model is to be added, the required mapping to the CIM is added in linear time, without affecting the existing resources”*.

Another notable contribution of the reviewed studies concerns the semantic enhancement of widely used terminologies like MedDRA. OntoADR (semantically) enhanced MedDRA using knowledge from sources such as SNOMED-CT (Bousquet et al., 2014) (Souvignet et al., 2016). The “ontologization” of MedDRA could significantly benefit disproportionality analysis, data mining or other techniques used for post-marketing DS surveillance, since MedDRA taxonomic limitations can decrease the sensitivity and specificity of signals computed by automatic approaches (Bousquet et al., 2005a) (Bousquet et al., 2005b) (Yokotsuka et al., 2000).

Furthermore, the use of ontologies and the reasoning capabilities that they offer facilitated ADE profiling. In particular, the semantics provided by OAE and VO or their extensions combined with statistical approaches (i.e. disproportionality analysis) against various DS data sources (i.e. FAERS, VAERS, drug package insert documents from the China Food and Drug Administration Website) were employed, in order to extract ontology-assisted ADE profiles and investigate the underlying MoAs (Wang et al., 2017) (Lin and He, 2012) (Guo et al., 2016) (Xie et al., 2016a) (Xie et al., 2016b). Some profiles were identified as novel, since they were not previously reported in the literature (e.g. ADE profiles regarding the M. bovis strain Bacillus Calmette - Guerin (Xie et al., 2016a)). Using this approach, two drug ingredient classes and three cardiovascular drug MoA classes were found to have statistically significant class effects on 13 AEs (Wang et al., 2017). The fact that valid, novel ADE profiles were automatically inferred and linked to specific MoAs through the use of ontologies, highlights the significance of adopting KE-based approaches in the context of DS.

Another significant contribution of the reviewed KE approaches regarding ADE assessment concerned the prioritization of ADE signals according to their importance. A normalized AERS dataset and the Common Terminology Criteria for Adverse Events (CTCAE) were used to prioritize DDI-induced ADEs identified in FAERS (according to their severity), as well as occurrences of medications and problems extracted from clinical notes from Mayo Clinic's EHR (Jiang et al., 2015). This ontology-based approach facilitated automatic prioritization of DDIs related to Warfarin, Clopidogrel and Simvastatin, three frequently prescribed cardiovascular drugs.

Finally, regarding the investigation of ADE MoAs, the D3 system uses a rule-base with 9 rules corresponding to 9 different interaction mechanisms divided into 4 levels (Noor et al., 2016): pharmacokinetic (protein binding, metabolic inhibition, metabolic induction, transporter inhibition, and transporter induction); pharmacodynamic (additive-enhancement and competition); pharmacogenetic (SNPs that may alter drug exposure); and multiple pathway interactions (MPIs). For example, when both drugs x and z share at least 1 enzyme y and 1 transporter y2, then an MPI mechanism could be inferred and the rule would be "x metabolized_by y; x transported_by y2; z metabolized_by y; z transported_by y2". The results of using such an inference mechanism included 85% recall rate and 61% precision rate in terms of the inference or lack of inference of DDI MoA explanations, for a random collection of interacting and noninteracting drug pairs, respectively.

ADE prevention

In the context of the ReMine project, an ontology was developed to support adverse event prevention and mitigation, in addition to detection and monitoring, based on the patient's medical history (Ceusters et al., 2011). While the ReMine project aimed to better document adverse events and facilitate the development of mitigation and prevention strategies on the long term, others were aiming at real-time interventions. For example, in the context of the PSIP (Koutkias et al., 2012), Panacea (Doulaverakis et al., 2014) and E-pharmacovigilance (Neubert et al., 2013) projects, knowledge-based DSSs were developed for preventing ADEs in the clinical environment, taking into account hospital data and also focusing on the clinical context to address aspects such as over-alerting.

A novel Web analytics platform aimed to facilitate clinicians to conduct comparative drug analysis for ADE prevention (Lamy et al., 2017). The proposed tool was based on

ontological reasoning, in order to classify information and highlight important relationships between drugs and ADEs. The tool was evaluated by 22 General Practitioners, demonstrating high rates of user acceptance.

Interestingly, few works focused on “personalized” ADE prevention. In particular, an automatic technique to identify genes and drugs relationships was presented (Xu and Wang, 2013), as well as a prototype implementation of a Web browser plugin providing personalized warnings for DDIs based on ontologies and Personal Health Record (PHR) data (Vandervalk et al., 2013).

ADE monitoring

ADE monitoring concerns the process of tracking the evolution of an ADE through time, mostly for epidemiological reasons. As this process is mostly relevant with statistical metrics, KE approaches are not expected to significantly contribute in that and, therefore, ADE monitoring was not one of the main focuses in the reviewed papers. Notably, only one of the selected papers explicitly referred to ADE monitoring as one of its key objectives, through secondary use of EHR data (Yuksel et al., 2016).

ADE reporting

ADE reporting can be defined as a bidirectional activity: (a) patients and healthcare professionals (HCPs) reporting potential ADRs to regulatory agencies and the pharma industry, and (b) drug monitoring organizations or regulatory agencies communicating DS-related information (e.g. new signals or confirmed ADRs) to HCPs and patients. Both reporting channels pose challenges, e.g. under-reporting towards drug monitoring agencies, ambiguity and vast amount of information communicated to patients and HCPs, etc. These reporting processes could significantly benefit from KE approaches; however, it seems that this DS activity does not receive much attention and can be identified as a “research gap” with a lot of room for progress.

An open Web platform based on SPL information and other interlinked data sources was developed to support the dissemination of information regarding DS by exploiting comparative drug effectiveness among other information (Boyce et al., 2013). The targeted users were primarily clinicians and researchers.

An ontology-supported methodology for reporting adverse events following immunization to regulatory agencies according to the Brighton case definition was presented based on the AERO ontology (Courtot et al., 2014). The study demonstrated the feasibility of confirming automated diagnosis and concluded that a logical formalization of existing guidelines could improve reporting by identifying missing elements and enforcing consistency through standardization. The approach allows medical experts to prioritize reports and, therefore, such formalization may accelerate the identification of vaccine-induced ADRs and the response of regulatory agencies.

Interestingly, the SALUS project developed an ontology-based approach to automatically generate ADE reports from EHR data in the E2B format (Declerck et al., 2015).

Risk of bias

Bias is defined as a “*systematic error, or deviation from the truth, in results or inferences*” (Altman et al., 2011). Risk of bias can refer to multiple aspects of the systematic review process and can be related with various causes (Drucker et al., 2016). For example, “*evidence selection bias occurs when a systematic review does not identify all available data on a topic*” and this “*can arise from publication bias, where data from statistically significant studies are more likely to be published than those that are not statistically significant*”. It should be clarified that bias does not refer to imprecision (e.g. due to the reviewing process inherent subjectivity, further discussed in subsection Limitations), but only refers to *systematic error* introduced by the systematic review protocol.

Table 5 depicts the main bias sources and the way that our study protocol has mitigated the respective risks. It should be noted that bias risks have been investigated mostly in the context of clinical trials or similar interventions and this has also affected the widely accepted risks of bias as well as their reporting or mitigation mechanisms. As the presented review does not refer to a medical intervention, the respective bias risks and their effect on the presented study have been adapted accordingly.

Table 5: Analysis of bias risks and mitigation measures employed in the current study.

<i>Bias risk</i>	<i>Application in current study</i>	<i>Reporting/Mitigation</i>
<i>Selection bias: missing important research</i>	Our systematic review focuses on qualitative criteria which cannot be	We employed two bibliographic repositories (namely, PubMed and Web

<i>because it was not published due to bias (e.g. due to lack of statistical significance)</i>	statistically measured. Therefore, criteria like statistical significance could not affect our study and reporting tools like funnel plots are not applicable. However, indexing errors in the systematic review initial data source(s) could lead to missing potentially relevant articles.	of Science), in order to mitigate the risk of missing articles due to indexing errors.
<i>Primary study bias: reviewed studies could be biased regarding the evaluation mechanism used, the presented findings, conclusions, etc. (a.k.a. reporting bias)</i>	Since there is no widely accepted methodology to publish the results of KE practices on DS application, the reviewed studies report results in an arbitrary manner that could indeed affect overall conclusions.	Identified specific evaluation and reporting weaknesses that could imply bias in the systematic review evaluation criteria. The reviewed studies that have been identified to suffer from such reporting weaknesses correspond to 62.5% of the selected articles.
<i>Competing interests: reviewed studies (or even the presented systematic review) could be sponsored by companies or have other ties to industry</i>	The authors of the presented systematic review do not have ties with industry or any other kind of relationship which could imply competing interests. Some reviewed articles originate from companies and, therefore, this kind of bias could have an implication in their reported outcomes.	The industrial participation in the studies was identified as a specific evaluation criterion. More specifically, these studies correspond to 30% of the selected articles.

2.1.5. Discussion

Drug safety encompasses all data gathering and processing activities related with the detection, assessment, understanding and prevention of adverse effects throughout the entire lifecycle of drugs (World Health Organization, 2002). In a pre-market setting, clinical trials of newly developed drugs constitute the main procedure for identifying ADRs resulting from their use. However, due to time constraints, the limited population size as well as potential bias, clinical trials do not enable the detection of all possible ADRs. Consequently, post-marketing surveillance is necessary to identify new or incompletely documented ADRs throughout the time a drug is actively prescribed (World Health Organization, 2008).

Recently, several studies argued that data employed for DS should be extended from the traditional data sources, i.e. SRSs and bibliography, to observational healthcare databases and even social media platforms, while linkage with biochemical and genetic information would be desirable to provide MoA and may allow to identify more unexpected AEs. In order to achieve this advancement and take into account these requirements, DS monitoring organizations have to face new challenges, both scientific and technical, given that the above sources are not designed to serve DS aspects per se. In particular, there is an emerging need for high-throughput

computational methods that will enable, from the one hand, efficient data analysis and interpretation and, on the other hand, knowledge extraction, representation, exploitation and management (Koutkias and Jaulent, 2015).

Up to now, the emphasis in computational DS surveillance was mostly given on data-driven and statistics-based approaches. The current review focused on KE, a discipline of Computer Science which exploits methods for acquiring, representing and exploiting knowledge, having as its cornerstone well-defined formalisms and structures. The study illustrated the methods employed and the impact that current KE-based approaches have in DS, while also highlighting trends, limitations, as well as opportunities for further research.

Summary of main findings

The number of studies exploiting KE for DS increased constantly between 2006 and 2017 (Figure 5C). The reviewed articles illustrated the interest in exploiting diverse data and knowledge sources as well as the application of various KE methods, spread across the entire spectrum of the core KE activities as defined in our study (in many cases targeting multiple KE activities). Interestingly, these studies targeted diverse DS aspects as well, including both core DS activities (i.e. ADE information collection, assessment, etc.) and DS topics of special interest (e.g. vaccine safety, drug interactions, etc.), according to our study context (Table 2).

The distribution of authors across the globe (Figure 5B) illustrated an international interest in KE for DS. However, the relatively low contribution from DS monitoring organizations as well as healthcare organizations in research studies in the field (Figure 5A), could be attributed to the lack of the required KE-oriented technical expertise and, perhaps, to the reluctance in adopting technological paradigms that are not directly related with familiar approaches, e.g. statistical inference, disproportionality analysis, etc. This may also indicate a significant challenge for KE researchers in the domain to illustrate a major “success story”, which would disseminate the value of KE approaches in the context of DS and, therefore, facilitate their wider adoption. The reviewed studies illustrated mostly proof-of-concept outcomes, indicating that KE for DS is still in its infancy, especially regarding its application in routine DS activities.

While wide interest in exploiting diverse as well as emerging data sources is apparent, it raises many challenges and room for further research. For example, the biological knowledge

underlying drug metabolism and pharmacological mechanisms has not been adequately elaborated to infer new causal relationships among drugs and effects. Besides polymorphic sites and alterations to gene expression, other molecular mechanisms, such as regulatory elements and epigenetic modifications, may have direct or indirect relationship with medication and consequently ADEs. Furthermore, standardisation of observational healthcare data is an issue (Koutkias, 2019). Common data models relying on reference terminologies, such as the OMOP CDM (Voss et al., 2015), may scale-up the applicability and the reproducibility of computational analysis methods in the domain. Despite the inherent noise and complexity in analysing social media content, this data source cannot be neglected due to its wide penetration in everyday life and its capacity to provide insights especially for rare health-related events (Klein et al., 2018).

To a great extent, the reviewed studies relied on publicly available data, provided, for example, via PubMed/MEDLINE and FAERS. Nevertheless, important, systematically curated and rather new Linked Data infrastructures such as the EBI-RDF platform³⁴ and OpenPHACTS³⁵ are available, which were not adequately considered in the reviewed studies. In terms of knowledge sources, UMLS, MedDRA, ATC, SNOMED-CT and ICD were the most widely used terminologies, as these constitute reference and well-curated resources with varying granularity. With respect to ontologies, OAE, VO and GO were the most widely used, due to their rich content and relevance with DS.

In terms of KE activities, knowledge extraction and knowledge representation were extensively elaborated, while the focus on knowledge dissemination was quite limited (Figure 8). Similarly, ADE detection, information collection and assessment attracted most research efforts among the DS core activities, while signal detection, MoA analysis, and identification of drug interactions are the three most focused DS special topics. Contrariwise, the focus on ADE reporting is limited, and it can be identified as a gap for further research (Natsiavas et al., 2018a).

Regarding the employed KE methods, NLP-based as well as graph-based inference were employed in many studies, while DL-based inferencing was quite limited. Interestingly, few studies exploited temporal modelling or analysis, despite the fact that time is extremely useful

³⁴ <https://www.ebi.ac.uk/rdf/>

³⁵ <http://www.openphactsfoundation.org/>

in the assessment of potential DS signals. In addition, very few studies employed holistic KE methodologies based e.g. on ontology patterns, quality control frameworks, etc. Adopting methodologies such as MIRO (Matentzoglou et al., 2018), NeOn (Suárez-Figueroa et al., 2012), OQuARE (Duque-Ramos et al., 2014) and XOD (He et al., 2018), could reinforce the credibility and the completeness of future contributions in the domain. Furthermore, the lack of focus on knowledge dissemination approaches is also evident.

Interestingly, some studies jointly exploited multiple data sources, illustrating, for example, the added value of KE methods regarding integration (Koutkias and Jaulent, 2016), as well as the interest for systematic linkage/modelling between the phenotype and elements of the genome/proteome that interact with the drug, and activated pathways to investigate the MoA. This need for a systematic approach facilitating the integration of low-level biochemical and genotypic information with phenotypic models applying the SP paradigm has been already identified as a research opportunity (He, 2016) (Herrero-Zazo et al., 2016) (Mager and Kimko, 2016). While such models illustrated remarkable results, they were not fully exploiting the power of ontologies, as they are typically based on rules (at least partially) in order to model physiological, biological, or pharmacodynamic/pharmacokinetic processes, and not using reference ontological models depicting Systems Biology or SP concepts in a systematic manner. While such models were implemented with remarkable results, they were either not fully exploiting the power of ontologies as they were partly rule-based (e.g. (Noor et al., 2016)), or they partially relied on known drug MoA/SP models (Herrero-Zazo et al., 2016). Therefore, the holistic modelling of ADRs, combining the power of ontologies and DL reasoning with the mathematical or empirical models of pharmacokinetics and pharmacodynamics is a topic of open research. Such an approach could enable the integration of big data sources (via ontologies) with SP multi-scale models, to facilitate *Precision Medicine*. Well-promising results were obtained by combining statistical-based inference on report data and ontology-based modelling and inference upon ADR characteristics and categories (Xie et al., 2016b); thus, this approach enhanced with SP models shall be considered also as a research opportunity and further elaborated by future studies.

With respect to technical challenges, reasoning performance constitutes an important issue, especially when considering large-scale knowledge models. For example, in order to avoid multiple inheritance, OAE (a quite big, reference ontology in the domain) asserts only one parent term and allows the other parent term(s) to be obtained automatically by reasoning

(Xie et al., 2016b). Another example of compromising knowledge modelling in the sake of performance is the case of DINTO (Herrero-Zazo et al., 2015), where the ontology had to be simplified in order to be processed by existing reasoners. Thus, performance issues in DL reasoning software may be considered as a bottleneck for the real-world adoption of complex/large ontology models.

In terms of evaluation, the results presented in many of the reviewed articles significantly depended on manual work (e.g. data curation, annotation, etc.), or they were obtained by engaging a small group of experts. In addition, many of the presented KE approaches were evaluated focusing on a narrower scope than the one presented as their main use case. Overall, shortcomings related to evaluation were the most frequent in the reviewed studies (Figure 11).

Besides weaknesses/challenges, some remarkable outcomes reported in the reviewed studies include:

- 1) An improvement in ADR prediction by exploiting biomolecular functional network data in the context of clinical trials (Huang et al., 2011).
- 2) An ontologized version of MedDRA which can facilitate grouping of ADRs that correspond to the same medical condition (Bousquet et al., 2014).
- 3) The successful incorporation of contextualized, medication safety related CDSSs in commercial products (an EHR and a Computerized Physician Order Entry (CPOE) system) (Koutkias et al., 2012).
- 4) A semantic interoperability platform automatically generating ADE reports from EHR data, aiming to address underreporting by clinicians (Declerck et al., 2015) (Yuksel et al., 2016).
- 5) The successful identification of adverse drug effect mentions in Twitter with precision exceeding 85% and F1 exceeding 81% (Eshleman and Singh, 2016).
- 6) The automatic detection of two novel drug interactions involving cytochrome p450 (CYP3A4) and albumin as potential drug interaction proteins from DIO (Arikuma et al., 2008).
- 7) The conclusion that live attenuated influenza vaccines have lower chance of inducing Guillain-Barre Syndrome and paralysis than trivalent (killed) inactivated influenza vaccine (Sarntivijai et al., 2012).
- 8) The extraction of novel, ontology-assisted ADE profiles regarding the M. bovis strain Bacillus Calmette – Guerin (Xie et al., 2016b).

- 9) A Web analytics platform relying on ontological reasoning, facilitating clinicians to conduct comparative drug analyses based on advanced and user-friendly analytics regarding ADEs and contraindications (Lamy et al., 2017).
- 10) An ontology-supported methodology for reporting ADRs to regulatory agencies, demonstrating automated diagnosis confirmation (through standardization) and improvement in the reporting process (Courtot et al., 2014).

To this end, Figure 12 illustrates the identified advancements of the data-driven perspective in DS through KE with respect to methods, enabling technologies, and exemplar applications.

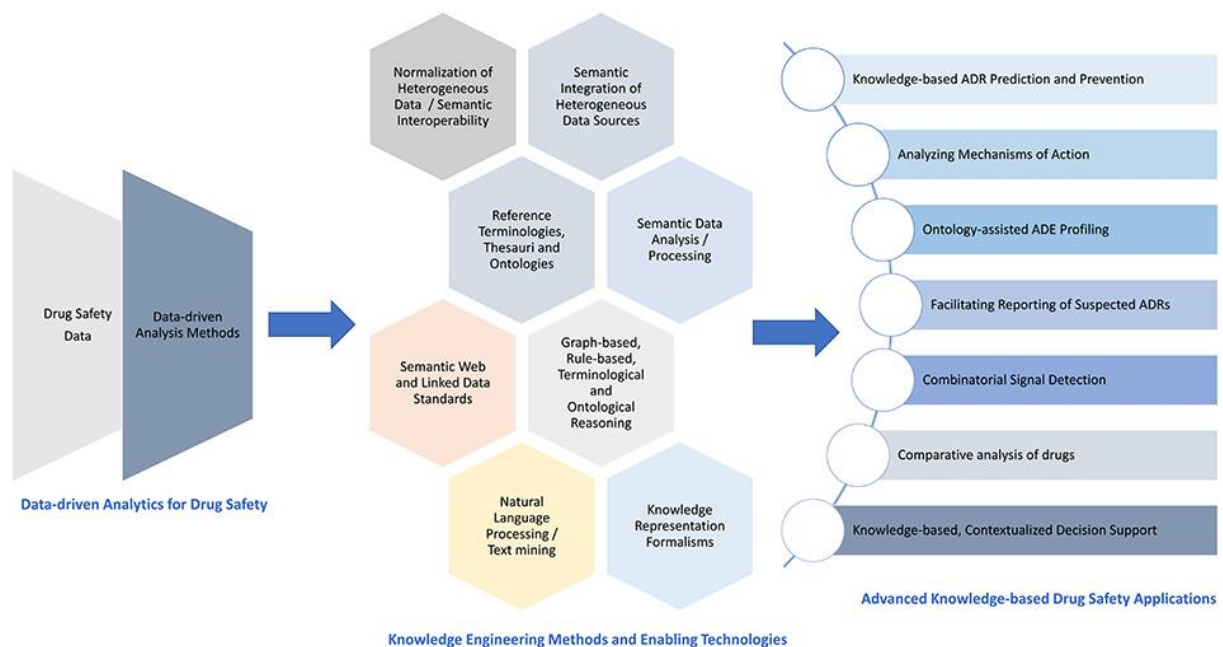


Figure 12: Advancing the data-driven perspective in DS through KE: methods, enabling technologies, and exemplar applications.

Applications in routine DS practice

Employing ICT tools in routine DS practice conducted by hospitals, pharmaceutical companies, Contract Research Organizations (CROs) as well as drug regulatory organizations, imposes major challenges (Lu, 2009). In this subsection, we highlight the reviewed studies explicitly focusing on practical applications engaged with real-world environments as part of their pilot or validation phase.

The knowledge components of the CDSS developed in the PSIP project were based on EHR data obtained from three European countries (Koutkias et al., 2012). The CDSS was connected to the respective Hospital Information Systems (HIS) to identify and prevent potential ADEs. PSIP elaborated on contextualizing the CDSS knowledge in the particular local setting, such as the hospital/clinic and the targeted users. For example, in order to avoid over-alerting, alert generation was based on thresholds considering the statistical significance of each ADE rule in each particular clinical site. In addition, clinicians (both hospital pharmacists and medical doctors) were engaged in the system design and evaluation. The electronic service for DDI and ADE prevention during medication prescription of the Panacea CDSS was evaluated using patient data from a public hospital in Thessaloniki, Greece (Doulaverakis et al., 2014). Similarly, the E-pharmacovigilance system was deployed through a Web interface to present DS data to treating physicians (paediatric and internal medicine inpatient clinics from the University Hospital of Erlangen-Nurnberg) within the local HIS (Neubert et al., 2013).

The SALUS project focused on a practical implementation to automatically produce ADE reports based on real-world clinical data in two pilot sites (a regional clinical data warehouse maintained in Lombardy Region, Italy and the commercial EHR system in Uniklinikum Dresden, Germany) (Declerck et al., 2015). Notably, SALUS developed a signal analysis tool, which was validated by DS experts in pragmatic cases (Yuksel et al., 2016). Finally, a visual analytics platform to support comparative drug studies was deployed and evaluated by clinicians to assess the physician's decision whether to consider the new drug for future prescriptions (Lamy et al., 2017).

It is clear that most KE approaches are currently in an experimental phase and have not yet entered routine DS practice beyond pilots, due to technical challenges (e.g. automated reasoning upon big data volumes is computationally ineffective), or procedural/organizational challenges (e.g. need of clear evidence regarding CDSS performance, need to validate the respective knowledge data sources, etc.). The DS-related routine procedures which could be improved via KE-oriented applications can be summarized as follows: (a) DS procedures applied in the clinical environment to report and/or prevent ADEs, (b) DS-related information assessment and dissemination from the drug regulatory organizations point of view, and (c) assessment of potential signals in clinical trials of new drugs. The practical challenges of these processes in each context have already been highlighted. Notably, clinicians do not feel confident about the currently applied DS procedures (Vallano et al., 2015), while the need for

better and more active DS surveillance has been identified by both drug regulatory organizations (Weaver et al., 2008) and the industry (Lu, 2009).

The use of KE technologies like the use of the Semantic Web and Linked Data paradigms could significantly facilitate information and knowledge extraction, integration, elicitation and dissemination and, therefore, accommodate the imposed challenges on routine DS tasks. The main advantages of using KE approaches in real-world DS applications could be summarized as following:

- (a) *Information linking* could be significantly improved and automated, reducing the need for manual data exploration through automatic processing.
- (b) *Semantic enhancement* of already established information processing workflows (typically based on statistical measures like disproportionality analysis). The already established statistical processing could be combined with well-defined knowledge sources and their semantics to improve outcomes (e.g. regarding causality assessment).
- (c) *Error prevention* could be facilitated by integrating different data sources to be used as control sources, in order to prevent false positives, over-alerting etc.
- (d) *Process acceleration* as KE approaches could save a lot of time via (semi)-automatic data retrieval and interlinking.

The above advantages advocate for more intense research in the domain, in order to increase the level of maturity, which is necessary to employ KE approaches in routine DS practice.

Limitations

The main source of limitation for the current study concerns the risk of bias. As explained in subsection Risk of bias, our analysis considered such risks and followed specific mitigation actions to eliminate them. Subjectivity in the review process as well as in the definition of the domain is a significant issue for review studies. We believe that the participation of domain experts in our study, the employment of an appropriate conflict resolution protocol, as well as the adoption of reference definitions (e.g. to establish the analysis criteria) significantly reduced this issue. However, some risk inevitably remains; for example, in the paper submission phase we realized that one relevant paper was not included in our study (Bean et al., 2017), because we did not include the term “Knowledge Graph” (a term recently

coined in the domain of KE) in our query terms. In addition, given that our query for article retrieval was focused on DS per se, some interesting resources that could be of wider scope, and not explicitly targeting or being used for DS, have not been considered in our study.

Conclusions

Computational methods in the domain of DS have been primarily data-driven. However, in the era of big data, data heterogeneity and complexity hamper the application of these methods at large scale and across data sources. In order to overcome these shortcomings, an increasing number of studies employ KE methods and tools. Especially as semantic technologies and standards evolve and KE approaches gain awareness, the potential of enriching the traditional data analytics approaches for DS with knowledge-based components becomes stronger.

Along this perspective, this review highlighted exemplar research efforts by presenting a variety of knowledge-intensive activities applied in the DS field, such as normalization of DS data, integration of data from heterogeneous sources, the use of semantic models and terminologies to facilitate signal detection, and semantic processing of DS data, to name a few. In addition, we referred to a number of knowledge-based tools and platforms that have been employed to reinforce DS and support ADR detection, contextualized ADE prevention, and large-scale, semantically-enriched combinatorial signal detection. Through the conducted analysis, our study illustrated the contribution, the complementarity as well as the advances that KE-based approaches may bring to traditional data analytics applied in DS.

Despite the increasing number of studies exploiting KE for DS, the lack of a major “success-story” – beyond proof-of-concept – is apparent. This constitutes a significant challenge for researchers in the domain, that have to respond to, if they wish to foster the value of KE approaches in the context of DS and, therefore, facilitate their wider adoption by DS stakeholders. Although few studies reached or explicitly focused on routine DS practice, we argue that engaging KE methods in established DS processes can substantially contribute in the development of an advanced, continuous learning health system (Friedman et al., 2015), which is necessary for efficient DS surveillance. Finally, we suggest that the use of KE approaches, e.g. ontologies, in combination with *pharmacokinetics* and *pharmacodynamics* models could facilitate the construction of an SP framework able to provide a pathway towards *Precision Medicine* exploiting real-world evidence (Helmlinger et al., 2017) (Caudle et al., 2016).

2.1.6. Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

2.1.7. Author Contributions

VK and MCJ conceived the study in the scope of the SAFER project. VK supervised the study, defined the search protocol and executed the queries against the two data sources (i.e. PubMed and Web of Science). PN and VK defined the inclusion/exclusion rules. PN, VK and AM independently reviewed all the obtained articles, while CB and MCJ contributed in conflict resolution. The analysis criteria were initially defined by VK, progressively refined by PN and reviewed by AM, CB and MCJ. PN performed the data analysis and published the online interactive analytics graphs. AM provided expertise on biochemical/genetic data sources. All the authors contributed in the interpretation of the study findings and in writing the manuscript. All the authors reviewed and approved the content of the manuscript.

2.1.8. Funding

This research has been co-financed by the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneurship and Innovation, under the call RESEARCH – CREATE – INNOVATE (project code: T1EDK-03789).

The study relied also on material and research outcomes supported by a Marie Curie Intra European Fellowship project awarded to the corresponding author within the 7th European Community Framework Programme FP7/2007-2013 under REA grant agreement 330422 – the SAFER project.

2.1.9. References

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2.1.10. Appendix

Table A: Abbreviations used in the study

Abbreviation	Full text	Abbreviation	Full text
ADE	Adverse Drug Event	IT	Information Technology
ADR	Adverse Drug Reaction	KE	Knowledge Engineering
AUC	Area Under the receiver operating characteristic Curve	ML	Machine Learning
CDM	Common Data Model	MoA	Mechanism of Action
CDSS	Clinical Decision Support System	MPI	Multiple Pathway Interactions
CIG	Computer Interpretable Guidelines	NER	Named Entity Recognition
CSCT	Case Series Characterization Tool	NLP	Natural Language Processing
CIM	Common Information Model	PHR	Personal Health Record
CPOE	Computerized Physician Order Entry	PRR	Proportional Reporting Ratio
DDI	Drug-drug interaction		
DEI	Drug Enzyme Interaction ontology	RRR	Relative Reporting Ratio
DIO	Drug Interactions Ontology	SNA	Social Network Analysis
DL	Description Logics	SNP	Single Nucleotide Polymorphism
DS	Drug Safety	SP	Systems Pharmacology
DSS	Decision Support Systems	SPL	Structured Product Label
EHR	Electronic Health Record	SRS	Spontaneous Reporting System
FDA	Food and Drug Administration	TEO	Time Event Ontology
HCP	Healthcare Professional	UMC	Uppsala Monitoring Centre
HIS	Hospital Information System	XOD	eXtensible Ontology Development

Table B: catalogue with Web links to data sources, reference terminologies, ontologies, standards, technologies, and systems referred in the study.

<i>Abbreviation</i>	<i>Full text (if applicable) and link</i>
ADReCS	Adverse Drug Reaction Classification System (http://bioinf.xmu.edu.cn/ADReCS/)
ATC	Anatomical Therapeutic Chemical Classification system (https://www.whocc.no/atc_ddd_index/)
Bio2RDF	http://bio2rdf.org/
CheBI	Chemical Entities of Biological Interest (https://www.ebi.ac.uk/chebi/)
CTD	Comparative Toxicogenomics Database (http://ctdbase.org/)
D3	Drug-drug interaction Discovery and Demystification (https://scholar.colorado.edu/csci_gradetds/106/)
DAML+OIL	https://www.w3.org/TR/daml+oil-reference/
DINTO	Drug-Drug Interactions Ontology (http://www.ontobee.org/ontology/DINTO)
DrOn	Drug Ontology (https://www.ebi.ac.uk/ols/ontologies/dron)
DrugBank	https://www.drugbank.ca/
E2B	http://www.ich.org/products/electronic-standards.html
FAERS	FDA Adverse Event Reporting System (https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugs/ucm082193.htm)

GO	Gene Ontology (http://www.geneontology.org/)
ICD	International Classification of Diseases (http://www.who.int/classifications/icd/en/)
INDI	INferring Drug Interactions (https://www.cs.tau.ac.il/~bnet/software/INDI/)
KEGG	Kyoto Encyclopaedia of Genes and Genomes – GenomeNet (https://www.genome.jp/kegg/)
LAERTES	Large-scale adverse effects related to treatment evidence standardization (https://github.com/OHDSI/KnowledgeBase/tree/master/LAERTES)
MedDRA	Medical Dictionary for Regulatory Activities (https://www.meddra.org/)
MeSH	Medical Subject Headings (https://www.nlm.nih.gov/mesh/)
MetaADEDDB	http://lmmd.ecust.edu.cn/online_services/metaadedb/
MIRO	Minimal Information for Reporting of an Ontology (https://zenodo.org/record/398804)
NDF-RT	National Drug File - Reference Terminology (https://www.nlm.nih.gov/research/umls/sourcereleasedocs/current/NDFRT/)
OAE	Ontology for Adverse Events (http://www.oae-ontology.org/)
OCMR	Ontology of Chinese Medicine for Rheumatism (http://www.ontobee.org/ontology/OCMR)
OCVDAE	Ontology of Cardiovascular Drug Adverse Events (http://bioportal.bioontology.org/ontologies/OCVDAE)
ODNAE	Ontology of Drug Neuropathy Adverse Events (http://www.ontobee.org/ontology/ODNAE)
OGSF	Ontology of Genetic Susceptibility Factors (https://www.ebi.ac.uk/ols/ontologies/ogsf)

OHDSI	Observational Health Data Sciences and Informatics (https://www.ohdsi.org/)
OVAE	Ontology of Vaccine Adverse Events (http://www.violinet.org/ovae/)
OWL	Web Ontology Language (https://www.w3.org/OWL/)
OQuaRE	Ontology Quality Evaluation Framework (http://miuras.inf.um.es/oquarewiki/index.php5/Main_Page)
PharmGKB	Pharmacogenomics Knowledge Base (https://www.pharmgkb.org/)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses (http://prisma-statement.org/)
PV-SDO	Pharmacovigilance Signal Detection Ontology (http://safer-project.eu/SignalDetectorsOntology.owl)
RDF	Resource Description Framework (https://www.w3.org/RDF/)
RxNorm	https://www.nlm.nih.gov/research/umls/rxnorm/
SemMedDB	Semantic MEDLINE Database (https://skr3.nlm.nih.gov/SemMedDB/)
SIDER	Side Effect Resource (http://sideeffects.embl.de/)
SMQ	Standardized MedDRA Queries (https://www.meddra.org/standardised-meddra-queries)
SNOMED-CT	Systematized Nomenclature of Medicine-Clinical Terms (https://www.snomed.org/)
SPARQL	SPARQL Protocol and RDF Query Language (https://www.w3.org/TR/2013/REC-sparql11-overview-20130321)

SWRL	Semantic Web Rules Language (https://www.w3.org/Submission/SWRL/)
UMLS	Unified Medical Language System (https://www.nlm.nih.gov/research/umls/)
UniProt	https://www.uniprot.org/
VAERS	Vaccine Adverse Event Reporting System (https://vaers.hhs.gov/)
VO	Vaccine Ontology (http://www.violinet.org/vaccineontology/)
WADM	Web Annotation Data Model (https://www.w3.org/TR/annotation-model/)
WHO-ART	World Health Organization Adverse Reaction Terminology (https://www.who-umc.org/vigibase/services/learn-more-about-who-art/)

2.2. Beyond the paper: Where does this thesis stand in terms of the recent Knowledge Engineering advances in the context of Drug Safety

Attempting to cover the time gap between the publication of the review paper presented in the previous subsection and the time of this thesis writing, several interesting projects should be highlighted. For example, the PraktikPharma project³⁶ aims to construct a Knowledge Graph named PGxLOD, integrating various data sources to support pharmacogenomics studies (Monnin et al., 2019). Furthermore, the DOMINO project³⁷ organized in the context of the DRUGS-SAFE initiative, aims to analyse data from discussion forums to identify messages regarding drug safety (Bigéard et al., 2018). To the same end, depicting prominent works regarding the analysis of social media data for PV purposes, the WEB-RADR project published a recommendations paper, concluding that “social media channels may provide a useful adjunct to pharmacovigilance activities” even though “Facebook and Twitter, are not recommended for broad statistical signal detection” (van Stekelenborg et al., 2019).

As depicted in the presented Systematic Review paper, several research gaps were identified regarding the use of KE approaches for DS purposes. These were clearly enumerated in terms of technical approaches and missing data, e.g. lack of focus on Systems Pharmacology approaches and the need to use KE (e.g. ontologies) with low level pharmacology models.

Furthermore, it was highlighted that while KE approaches are actively investigated, they are not yet adopted by IT systems used in the everyday clinical practice. For example, while the value of integrating heterogeneous emerging data sources (e.g. social media, observational data etc.) and consolidate them with data traditionally used for PV (e.g. ICSRs) is widely recognized, yet it is still far from being part of standard practice. To this end, alternative approaches could also be investigated (e.g. integrating analysis results instead of raw data) as they could substantially contribute to the development of an advanced continuous learning health system (Friedman et al., 2015a) hence, in principle, facilitating to close the “loop” of information between clinicians, patients and researchers.

³⁶ <http://praktikpharma.mystrikingly.com/>

³⁷ <https://drugssafe.fr/2019/09/12/domino/>

To this end, the key issue of identifying the challenges hindering the integration of “intelligent” systems (i.e. systems based on AI paradigms, including KE-oriented systems) in real-life operational healthcare environments was early identified as a critical issue. Thus, while the use of KE-based analytics and advanced User Interfaces might be extremely useful, the need to elaborate on the respective BPs and UGs in order to identify potential gaps in the applied processes was also identified as a priority setting the main context for this thesis.

3. Regulatory context and Management aspects

In this chapter, the BPs related with pharmacovigilance are depicted. More specifically, a paper presented in ICIMTH 2020 provides an overview of the regulatory context in European Union which sets the baseline for all European countries and depicts the identified BPs (Natsiavas et al., 2020). Furthermore, in the “Beyond the paper” section, a brief introduction of the various stakeholders engaged in AP processes is provided. It should be highlighted that the analysis of these BPs might seem trivial for PV experts however it is far from obvious for other professional domains, aiming to support the overall AP vision (e.g. software engineers, IT researchers etc.).

3.1.Supporting Active Pharmacovigilance via IT tools in the clinical setting and beyond: Regulatory context and Management aspects

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3.1.1. Abstract

Information Technology (IT) could have a prominent role towards the “Active Pharmacovigilance” (AP) paradigm by facilitating the analysis of potential Adverse Drug Reactions (ADRs). PVclinical project aims to build an IT platform enabling the investigation of potential ADRs in the clinical environment and beyond. In this paper, we outline the respective EU regulatory framework and the related Business Processes (BPs), elaborated based on input from clinicians and PV experts as part of the project’s “user requirements analysis” phase, highlighting their potential pivotal role in the design of IT tools aiming to support AP.

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Keywords. Active Pharmacovigilance, Drug Safety, Business Processes

3.1.2. Introduction

Adverse Drug Reactions (ADRs) are detrimental regarding public health and cost (Formica et al., 2018) and therefore, preventing them is critical both during drug development, as well as during clinical practice (Ferner and McGettigan, 2018). To this end, Pharmacovigilance (PV) is defined as the science and activities related with all aspects of the detection and management of ADRs (World Health Organization, 2002).

The investigation of potential new or partially documented ADRs (a.k.a. “signals”) is based on the collection of Individual Case Safety Reports (ICSRs) via Spontaneous Reporting Systems (SRSs), based on “Disproportionality Analysis” (DA) approaches (Montastruc et al., 2011).

Recent breakthroughs in Information Technologies (IT) enable the use of new, emerging data sources expanding the real-world evidence space used to explore potential PV signals. The “Active Pharmacovigilance” (AP) paradigm refers to the “hot pursuit” of all possible data sources, instead of “passively” waiting for ICSRs to be submitted (Gagne et al., 2012).

PVclinical project³⁹, develops a Web-based platform exploiting Knowledge Engineering (KE) technologies to facilitate the investigation of potential ADRs, by clinicians, as well as PV experts and researchers. A preliminary design of the platform, i.e. a first set of “User Goals”/design objectives and its main information workflow was presented in (Natsiavas et al., 2019a). This paper focuses on the PV regulatory and procedural context and also discusses its key impacts on the design of novel IT tools aiming to support AP.

3.1.3. Methods

The employed “user requirements analysis” process is based on the approach described in (Natsiavas et al., 2018c) (Figure 13) aiming to consolidate various information, including end-user input, to identify “*User Goals*” (UGs). UGs are “abstract user requirements, not directly referring to specific technical approaches” (Natsiavas et al., 2018c), directly attributed

³⁹ <https://pvclinical-project.eu>

to user “roles” or “actors”. UGs’ definition aims to highlight “gaps” in the currently applied Business Processes (BPs) and the resolution of potential conflicts between actors and BPs, to provide input in the overall system design. In this paper, we emphasize on the results of two parts of the overall process: (a) a “Regulatory framework overview” which was based on a thorough review of European legislation that pertains to PV and input from partners (including Pharmassist which is a Contract Research Organization conducting PV activities on behalf of pharma companies and therefore legally bound by this regulatory context), and (b) “BP identification and elaboration”. To this end, we discuss some key conclusions and their impact on the design of IT systems supporting AP paradigm. Noting a potential limitation of the applied approach, we conducted an exploratory review which was empirically validated, rather than a systematic review of literature/legislation.

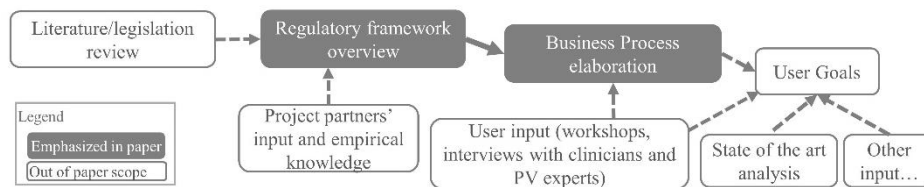


Figure 13: Overall methodology rationale

3.1.4. Results

Regulatory framework

Drug Safety Monitoring Organizations (DSMOs) play a crucial role in both the pre- and post-market stages of a drug life cycle, i.e. from clinical trials and marketing authorization to post-marketing surveillance, and typically, they also maintain SRS. For example, the U.S. Food & Drug Administration maintains (FDA) maintains the FDA Adverse Event Report System and European Medicines Association (EMA) maintains EudraVigilance. Notably, the Uppsala Monitoring Centre (WHO-UMC) is the WHO PV reference centre and maintains the largest database of ICSRs in a global scale, VigiBase.

Emphasizing on the EU context, the directive 2010/84 (applied on July 2012 via regulation No 520/2012 and Good Pharmacovigilance Practices – GVP - Modules I to XVI), marked a major policy update regarding the safety requirements for the human drugs. Regarding post-market surveillance, it instructed the deployment of national SRSs also enabling citizen

reports. Furthermore, pharma companies were obliged to maintain and regularly update Risk Management Plans (RMPs) and provide Periodic Safety Update Reports (PSURs). All the stakeholders were instructed to actively exchange data and finally, all the collected information are evaluated by the EMA Pharmacovigilance Risk Assessment Committee (PRAC), responsible to assess drug risks in EU (Santoro et al., 2017).

Business Processes

Table 6 and Table 7 depict the relevant BPs as they resulted after workshops and interviews with clinicians and PV experts. For each of these BPs, the potential benefits of using IT tools were elaborated to identify and prioritize the relevant User Goals.

Table 6: BPs related with PV in the clinical environment

<i>Name</i>	<i>Description</i>	<i>Actors</i>	<i>Data</i>
BP1: Visit to outpatient clinics	BP1 could include the registration of the patient and its medical history in the hospital EHR, clinical examination, ePrescription, etc.	<ul style="list-style-type: none"> • Doctor • Nurse 	Demographics, Medical history, Lab result, diagnosis, ePrescription
BP2: Hospitalization	BP2 includes BP1 steps and also clinical procedures (e.g. an operation), computerized physician order entries (CPOE), clinical notes maintenance and patient discharge.	<ul style="list-style-type: none"> • Doctor • Pharmacologist • Nurse 	BP1 data and also clinical notes, CPOE data, discharge notes
BP3: Service evaluation	BP3 does not refer to clinical practice but is regularly applied in hospitals to evaluate clinically relevant metrics (ADRs, in-hospital infections, errors etc.).	<ul style="list-style-type: none"> • Doctor • Pharmacologist • Nurse • IT scientist • Manager 	EHR statistics, prioritized lists of adverse events of interest, comparison with other data sources

Table 7: BPs related with PV out of the clinical environment

<i>Name</i>	<i>Description</i>	<i>Actors</i>	<i>Data</i>
BP4: Clinical trials	BP4 includes the design of a study/intervention, the definition of patient cohorts, data collection and	<ul style="list-style-type: none"> • Doctor 	Demographics, medical history, genetic profiling, lab results, clinical notes,

	curation, comparison with other clinical trials and also results reporting	<ul style="list-style-type: none"> • PV Expert 	safety and efficacy reports
BP5: Update of Periodic Safety Reports	BP5 includes the review and the statistical analysis of ICSRs, literature review, clinical trial data processing and reporting to regulatory authorities	<ul style="list-style-type: none"> • Doctor • PV Expert 	Drug safety data, statistics, documentation /reports, prioritized lists of adverse events of interest
BP6: Weekly literature review	BP6 refers to literature reviews including the shaping of queries based on keywords and synonyms against various literature sources	<ul style="list-style-type: none"> • Doctor • PV Expert 	Documentation/reports
BP7: Risk management	BP7 includes literature review, relevant clinical trial data review, and also the calculation of risk factors	<ul style="list-style-type: none"> • PV Expert 	Drug safety data, statistics, documentation/reports

3.1.5. Discussion

In this paper, we provide an overview of the PV regulatory context, and the identified BPs, resulted as part of the PVClinical “user requirements analysis” phase. In this section, we discuss their impact on the design of IT tools aiming to support AP.

PV regulatory context highlights the need for IT tools which could support the robust analysis of heterogeneous data sources. To this end, KE technologies can accelerate and qualitatively improve tasks regularly conducted by PV experts, pharma industry and DSMOs (e.g. compilation of RMPs, PSURs etc.). The need to integrate various data sources is also supported by the analysis of the relevant BPs, identifying a gap regarding the use of automatic reasoning capabilities, and therefore further supporting the potential of KE. It is obvious that IT tools should have the capacity to retrieve, analyse and depict succinctly metrics of DA emphasizing prowess on advanced analytics features. Furthermore, it should be considered that in the clinical setting BPs might overlap and potentially conflict. For example, while potential ADR prevention is important, more urgent duties exist and they should not be interrupted or obstructed. Notably, the engagement of various actors with different educational and operational contexts, i.e. pharmacists and nurses apart from PV experts and medical doctors, also depicts the overall complexity of the clinical setting. For instance, while complex DA analytics are useful for a PV expert focusing on risk management, they might be irrelevant or

even obscuring for a clinician. Thus, the need to focus on usability is highlighted for IT tools supporting AP, both in the clinical context and beyond.

3.1.6. Acknowledgements

This research has been co-financed by the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneurship and Innovation, under the call RESEARCH – CREATE - INNOVATE (project code: T1EDK-03789).

The authors would also like to highlight the major contribution of the recently deceased Dr Vassilis Koutkias, Coordinator/Principal Investigator of PVClinical project.

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3.2. Beyond the paper: Stakeholders description

In this section, the stakeholders engaged in PV processes are briefly described, as these could play a pivotal role in terms of the AP vision. More specifically, the role of the most prominent DSMOs and regulatory authorities is discussed, using the respective Greek National Drugs Organization as an example of a national DSMO/regulatory organization.

3.2.1. Regulatory Organizations and Drug Safety Monitoring Organizations

The bodies that control the legality of the circulation of medicines and their safety are referred to as Regulatory Organizations (ROs). ROs can operate at national level (e.g. the Greek National Drugs' Organization - NDO) or internationally (e.g. the European Medicines Agency - EMA). Although the tasks of each RO may differ depending on its mission and the legislation, an indicative list of tasks of a RO could be:

- Supervision of clinical trial procedures for the preparation of new formulations (eg in terms of bioethics).
- Checking the marketing legality of a preparation (e.g. granting a marketing authorization).
- Check or define a formulation booklet that describes the identity of the formulation, as well as various information about its use (e.g. ADRs).
- Providing counselling and dissemination of knowledge in case of emergencies (e.g. occurrence of serious ADRs that must be treated as urgent).

(Huang et al., 2014) present a useful overview and a partial comparison of the main systems for data collection and analysis on PV internationally. In this section, we provide a brief description of the most prominent ROs/DSMOs and the respective Greek organization as an example of a local/national RO.

Greek National Drugs Organization

The Greek National Drugs Organization (NDO) was founded in 1983 by Law 1316 and is a Legal Entity under Public Law of the Ministry of Health and Social Solidarity. The

institutional mission of NDO is: *"The promotion and safeguarding of public health by ensuring appropriate standards of safety, quality and efficiency for all products under the responsibility of EOF that circulate in the Greek market. Also, the implementation of relevant controls, the inspection and surveillance of the market and the provision of information that will contribute to the safe and effective use of these products by the citizens."*

In particular, its mission can be described as "the protection of Public Health" related with:

- medicinal products for human and veterinary use
- organic products for human and veterinary use
- food supplements
- special diet foods and nutritional supplements
- biocides
- medical devices
- cosmetics

In the framework of its mission and in accordance with the National and European legislation, NDO in cooperation with the European Union:

- Evaluates and approves products.
- Monitors the quality, safety and efficacy of medicines while it also inspects and monitors the market for all products under its responsibility.
- Regulates the production, laboratory testing and clinical practice, distribution, marketing and advertising of the above products.
- Promotes pharmaceutical study and research.
- Informs healthcare scientists, competent bodies and the public with the latest information on the products under its responsibility, regarding their safe administration.

A large part of NDO's activity is managerial, related to the pricing of drugs, the preparation of the national prescription, etc. At the same time, NDO regulates the drug market in terms of preventing shortages.

Regarding the audit procedures followed by NDO, they are divided into Pre-Audit and Post-Audit. The pre-approval checks concern preparations that have not been re-released in Greece and include the possibility of recognizing the approval given for this preparation in other European countries or by the EMA. Accordingly, NDO is responsible for the monitoring of clinical trial procedures performed in the country. Post-approval checks include PV procedures based on the legislation applicable within the European Union. These include the collection of suspicious / potential ADR reports through the national "Yellow Card" system⁴⁰, i.e. the local SRS. The evaluation of these reports, as well as other data, is done by the NDO's ADR Committee and the resulting data are sent to the World Health Organization (WHO) and the respective EU instruments.

European Medicines Agency

One of the main missions of the European Medicines Agency (EMA) is to facilitate the development of new drugs in a way that accelerates their final delivery to patients, through an efficient and fast licensing system. At the same time, it monitors the safety of medicines in Europe, throughout their life and provides relevant information to patients and other categories of stakeholders (e.g. doctors, pharmacists, researchers, pharma industry, etc.)⁴¹.

Administratively, the EMA is the body of the European Union responsible for the scientific evaluation, and monitoring of drug safety. The application of the licensing and circulation rules is determined through the European medicines regulatory network⁴², which essentially controls the communication between the local ROs in the European countries.

In terms of PV procedures, EMA holds and supports the EudraVigilance database⁴³, which brings together reports of potential ADRs from all member countries⁴⁴. These reports are sent by the national PV authorities: EudraVigilance is a reference point for the PV in Europe, as from these reports possible "safety signals" are identified. This assessment is made by the Pharmacovigilance Risk Assessment Committee (PRAC) which is made up of public health

⁴⁰ <https://www.eof.gr/web/guest/yellowgeneral>

⁴¹ <https://www.ema.europa.eu/en/about-us/what-we-do>

⁴² <https://www.ema.europa.eu/en/about-us/how-we-work/european-medicines-regulatory-network>

⁴³ <https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance>

⁴⁴ <https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance>

experts and undertakes to assess the risk / benefit ratio of a drug. At the same time, EudraVigilance is an important tool for ADR investigation processes carried out by drug manufacturing or marketing companies. Based on EudraVigilance data, the EMA generates the corresponding reports. It is noted that the collection of reports is the responsibility of the local ROs rather than the EMA, which participates in their analysis, but is not the body receiving the report.

Uppsala Monitoring Centre – WHO Collaborating Centre for International Drug Monitoring

The Uppsala Monitoring Center - WHO Collaborating Center for International Drug Monitoring (WHO-UMC) is the World Health Organization (WHO) reference center for PV⁴⁵. It was founded in 1978 and is responsible for the WHO Program for International Drug Monitoring. This program, in which 134 countries participate, including Greece and France, maintains the largest ICSR repository globally named VigiBase⁴⁶, integrating reports from all participating countries.

WHO-UMC does not act as a RO as it does not have the legal capacity to ban the marketing of medicines or to impose changes to their instruction booklet. Nevertheless, as it provides services very important for PV, it is an international reference center for ADRs and all organizations dealing with drug safety.

The VigiBase database is the centerpiece of a tool ecosystem (e.g. VigiLyze⁴⁷), which facilitates the investigation of potential security signals. These tools include capabilities for statistical analysis of reports, as well as their analytics. At the same time, WHO-UMC maintains and provides other support services such as WHO-Drug⁴⁸. WHO-Drug is a reference dictionary for the global circulation of medicines as it is regularly updated and globally recognized as the most comprehensive index of medicines.

⁴⁵ <https://www.who-umc.org/about-us/our-story/>

⁴⁶ <https://www.who-umc.org/vigibase/vigibase/>

⁴⁷ <https://www.who-umc.org/vigibase/vigilyze/>

⁴⁸ <https://www.who-umc.org/whodrug/whodrug-portfolio/>

Finally, a very important service provided by WHO-UMC is the circulation of a quarterly newsletter (WHO Pharmaceuticals Newsletter⁴⁹) which includes information on the effectiveness and safety of medicines. Part of this newsletter is the communication of potential PV Signals, which are analyzed based on VigiBase data as well as other data sources (e.g. scientific literature). This information is analyzed by a team of experts in the field of PV (UMC Signal Review Panel) based on a specific procedure, which among other things is based on well-defined statistical metrics and algorithms (e.g. VigiRank (Caster et al., 2014)).

U.S. Food & Drug Administration

U.S. Food & Drug Administration (FDA)⁵⁰ is the RO regulating drugs in the United States of America (USA) and is perhaps the largest RO, in terms of drug safety globally. The FDA's responsibilities go beyond drug safety and include food safety.

Regarding drug safety, FDA is supported by the Office of Pharmacovigilance and Epidemiology and the Office of Medication Error Prevention and Risk Management, which are part of the Centre for Drug Evaluation and Research (CDER). FDA maintains its own ICSR collection system, the so-called FDA Adverse Event Report System (FAERS)⁵¹, as well as a similar vaccine-focused mechanism called the Vaccine Adverse Event Report System (VAERS)⁵². Individual reports submitted to FAERS are investigated by experts and combined with information from other data sources. These sources include the international scientific literature as well as information from the EHRs of the hospitals collected through the Sentinel initiative⁵³. Potential PV signals are investigated by CDER experts and potentially evaluable results published on the web⁵⁴.

⁴⁹ <https://www.who.int/medicines/publications/newsletter/en/>

⁵⁰ <https://www.fda.gov/>

⁵¹ <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/>

⁵² <https://vaers.hhs.gov/>

⁵³ <https://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm>

⁵⁴ <https://www.fda.gov/Drugs/DrugSafety/ucm199082.htm>

The collection of data and their partial communication is performed through the MedWatch program⁵⁵, which facilitates the submission of individual reports, including by citizen reports.

3.2.2. Pharma Industry and Contract Research Organizations

Contract Research Organizations (CROs) are companies that provide the pharmaceutical industry with a variety of services such as conducting and managing clinical trials, pharmacovigilance, regulatory and medical support, and quality management. As a result, more and more pharmaceutical companies outsource the above processes to CROs, due to the organized and specialized services they provide, while allowing them to reduce the time and costs required to carry out the same processes. In this sense, the PV procedures followed by CROs and pharmaceutical companies are the same.

Typically, PV departments are an integral functional department of every pharmaceutical and CRO company. Marketing Authorization Holders (MAHs), i.e. the companies holding the right to commercialize a medicine, must have a well-designed PV system that will allow them to monitor the safety of their approved medicinal products and detect changes in the risk-benefit balance. The main processes performed by the PV Departments of pharmaceutical companies and CROs can be summarized as follows:

- Collection, processing, evaluation, management, monitoring, coding and electronic submission of all serious and non-serious ADRs, coming from any source (spontaneous reports, literature, clinical trials), to the competent authorities within the legal time constraints.
- Continuous monitoring and scientific evaluation of all ADR data, coming from any source, to detect potential safety signals.
- Continuous monitoring of the safety profile and evaluation of the risk-benefit balance of medicines - Evaluation of all safety data of medicines, preparation and electronic submission to the competent authorities of Periodic Safety Update Reports (PSURs).

⁵⁵ <https://www.fda.gov/Safety/MedWatch/default.htm>

- Scientific evaluation of all information related to the risks of medicines, identification of new risks or changes in existing risks - Preparation of Risk Management Plans (RMPs) - Take risk minimization measures.
- Disclosure of safety information to health professionals and patients.

3.2.3. Hospitals

PV procedures in daily clinical practice are not standardized at any level and vary depending on the country, the hospital or the respective clinician.

For example, in some large hospitals in France, there are PV centres which have a decisive-advisory role in the evaluation of possible ADRs after a relevant request of their medical staff. However, in other countries like Greece there is no corresponding structure in hospitals. Clinicians are required to report possible indications for ADRs through the NDO's "Yellow Card" system, or alternatively report potential ADRs via direct communication with the respective pharmaceutical company. However, in practice this communication channel is also under-functioning. The small number of reports collected from the hospital environment (internationally reported to not exceed 5% of cases) can be justified as follows:

- lack of time for medical staff,
- fear for bureaucratic or other complications (e.g. legal retaliation by pharma companies),
- lack of specialized knowledge of clinical pharmacology,
- the perception that these reports are not used in practice and therefore they are pointless,
- lack of appropriate support tools for Communications and Informatics.

HCPs typically retrieve ADR information mainly through the Internet⁵⁶ and the search for the SmPC leaflets of the respective drug on online platforms. Also, information provided by reference "encyclopedias" of the genre (eg Meyler's encyclopedia (Aronson and Meyler, 2015)) is often sought. However, these sources are not updated regularly and do not include data on the valuation of new PV signals.

⁵⁶ for example, <http://www.galinos.gr> is the most prominent web site in Greece typically used by HCPs to get information about medicine

In terms of clinical practice, the possible investigation and treatment of suspected cases of ADRs is left to the practices of each clinician and the respective hospital. These practices are directly affected by the nature of the physician's employment relationship (external partner, private physician, trainee, etc.). In many cases, the nursing staff also plays an important role, as especially in cases of hospitalized patients, the patients' contact with the nurse is more frequent and the nursing staff is the one who administers the drugs and thus observes potential side effects.

3.2.4. Conclusion

As the presented paper and this section depicts, PV is a highly regulated environment engaging multiple stakeholders with varying priorities. The ultimate goal of PV is to support the process of providing safer drugs to the public; thus, the activities of the various stakeholders need to be aligned towards this goal, exploiting also the opportunities provided by the new “intelligent” technological paradigms and the emerging data sources. This alignment process is far from trivial due to both technical and organizational barriers and to this end, the respective BPs were analysed, in order to support the mining of the UGs which could ultimately support the design of IT systems and the revision of the application of PV activities in the clinical context and beyond.

4. User goals and challenges regarding the integration of “intelligent” IT systems in the clinical environment

This chapter elaborated on the identified UGs and the main information workflow designed as part of the integration process of a KE-based IT platform designed in the context of the PVClinical project. A preliminary version of these UGs was presented in the conference Medinfo 2019 (Natsiavas et al., 2019a), and this paper is presented as is in the following subsection. Moreover, as the definition of UGs was iteratively refined, the “Beyond the paper” subsection presents the UGs as they were finalized, after the respective paper was published.

4.1.A Knowledge-based Platform for Assessing Potential Adverse Drug Reactions at the Point of Care: User Requirements and Design

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4.1.1. Abstract

Even though Adverse Drug Reactions (ADRs) constitute a significant public health issue, there is a lack of Information & Communication Technologies (ICT) tools supporting Pharmacovigilance (PV) activities at the point of care. In this paper, we present the rationale of a Web-based platform to address this need. The driving user scenario of the proposed platform refers to a clinician who investigates information for a possible ADR as part of a specific patient treatment. The goal is to facilitate this assessment through appropriate tools for searching various relevant data sources, analysing the acquired data, aggregating the obtained evidence, and offering follow-up ADR monitoring over time in a systematic and user-friendly way. In this regard, we describe the adopted user requirements engineering methodology and we illustrate the use of Knowledge Engineering (KE) as the platform's main technical paradigm to enable heterogeneous data integration and encounter the complexity of the underlying information processing workflow.

Keywords:

Pharmacovigilance; Drug-Related Side Effects and Adverse Reactions; Knowledge Management

4.1.2. Introduction

Pharmacovigilance (PV) is defined as “the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems” (World Health Organization, 2002). As Adverse Drug Reactions (ADRs) cause a significant social and financial burden (Formica et al., 2018), PV is widely recognized as an important public health priority. An estimation by the US Office of Disease Prevention and Health Promotion has recently calculated that Adverse Drug Events (ADEs)⁵⁷ are responsible for 1 in 3 of all hospital adverse events, related with about 2 million hospital stays each year and increased hospitalization by 1.7 to 4.6 days⁵⁸. Thus, the detection and prevention of ADRs at the point of care rises as a major clinical issue as the probability of benefit should balance the possibility and cost of potential harm (Ferner and McGettigan, 2018).

The assessment of potential new or incompletely documented ADRs (called “signals”) is typically performed by national and international drug monitoring/regulatory organizations (e.g. the Food and Drug Administration (FDA) in the US, the Uppsala Monitoring Centre (UMC), World Health Organization collaborating centre for international drug monitoring, etc.). These organizations perform statistical analysis of individual case safety reports (ICSRs) gathered in Spontaneous Reporting Systems (SRSs), in order to identify indications of a causal relationship between the drug administration and the adverse effect based on measures of disproportionality (Montastruc et al., 2011), taking also into account other sources of evidence (e.g. scientific literature, clinical trial databases, etc.).

While SRSs are the dominant data source for PV, recent advances in Information and Communication Technologies (ICT) enable the exploitation of new, emerging data sources that can expand the real-world evidence base for PV (e.g. observational healthcare databases, social media, internet search logs, etc.). Thus, the need for comprehensive and knowledge-intensive ICT tools supporting the systematic and efficient exploitation of diverse data sources for PV is evident, in order to accommodate the entailed big data challenges (Koutkias and Jaulent, 2015).

⁵⁷ ADEs include side-effects that may or may not have a causal relationship with the respective drug, also referring to cases of adherence failure. ADRs refer only to side-effects caused after legitimate drug use, therefore implying a possible causal relationship between the drug and the adverse effect (Lindquist, 2007).

⁵⁸ <https://health.gov/hcq/ade.asp>

To this end, we develop a Web-based platform aiming to facilitate the early identification and assessment of potential ADRs at the point of care. The main objective is to contribute at “active”, post-marketing drug safety surveillance (Gagne et al., 2012), focusing on the timely assessment of potential drug safety risks, supporting clinicians (as well as PV experts and researchers) to explore diverse data sources of interest and obtain actionable insights via knowledge-intensive analytics (Koutkias et al., 2017). The proposed platform is currently in its “user requirements analysis” and “design” phase, which is driven by the real-life scenario according to which a clinician investigates information for a possible ADR as part of a specific patient treatment. The ultimate goal is to facilitate the integration of ADR assessment in routine clinical practice (Figure 14), by introducing tools which facilitate the search of diverse data sources, the analysis of the acquired data, the aggregation of the evidence to conclude with ADR assessment, and follow-up ADR monitoring over time in a systematic and user-friendly way.

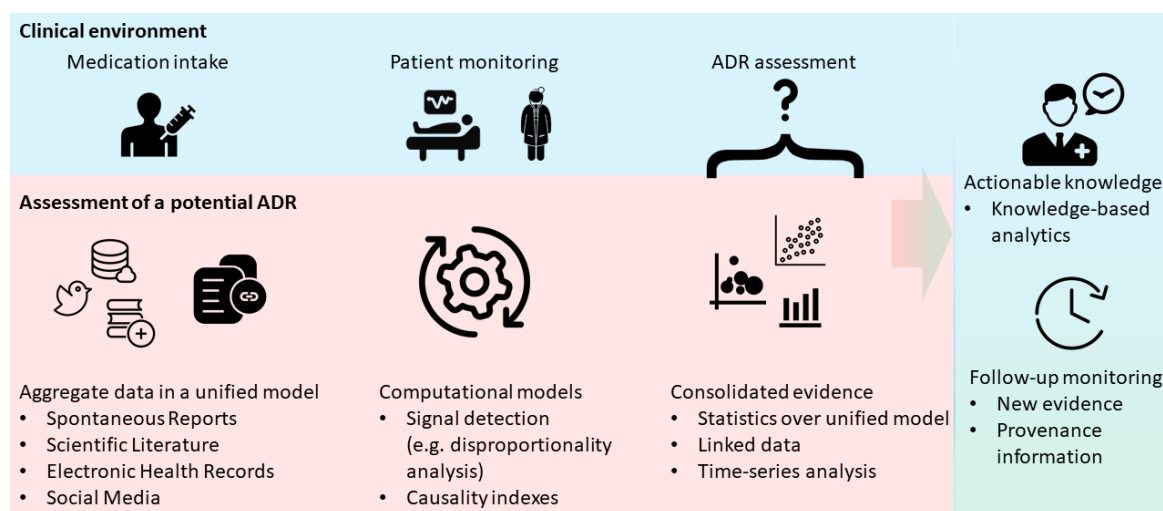


Figure 14: Integrating the ADR assessment process in the clinical context.

In this paper, we present the methodology applied and the main challenges identified during the “user requirements analysis” phase of our development, which were in turn mapped to relevant user goals. We also illustrate the main elements of the platform design through the respective information processing workflow. In this regard, we elaborate on how a Knowledge Engineering (KE) based approach can accommodate the respective design and development challenges. We further discuss practical implications of our work and outline directions for future work, aiming to support a comprehensive learning health system for active, post-marketing drug safety surveillance at the point of care (Ramsey et al., 2017).

Compared to relevant works, like the SALUS platform (Yuksel et al., 2016), which focused on exploiting Electronic Health Records (EHRs) for ADR detection, or the platform developed in Web-RADR (Ghosh and Lewis, 2015), which exploited social media for new insights on drug safety, our work relies on multiple, diverse data sources, increasing the search space for real-world evidence with an explicit focus on the clinical environment.

Methods

The employed “user requirements analysis” process is an adjusted version of the methodology described in (Natsiavas et al., 2018b) and it can be summarized as follows:

1. Analysis of the currently applied *Business Processes* (BPs) based on the respective user scenarios.
2. Definition of *User Goals* upon the elaborated BPs based on end-user input.

A *Business Process* (BP) is defined as a collection of relevant and ordered structured activities/tasks aiming to produce a specific outcome (Weske, 2012). ADR assessment can also be considered as a BP conducted in the context of a hospital, as part of other parallel BPs (e.g. patient treatment, administrative processes, etc.). We envisage that the use of the proposed platform could reform the current process of ADR assessment, typically conducted manually and with no systematic ICT support, to a well-defined sequence of information processing steps, supporting the overall clinical treatment processes. The ultimate goal is to optimize this BP model by satisfying the so-called *User Goals*. User goals are defined as “abstract user requirements, not directly referring to specific technical solutions or components” (Natsiavas et al., 2018b), associated with specific user actors or roles and facilitating timely identification and resolution of potential conflicts between actors. For the optimization of the ADR assessment process, user goals were elaborated based on feedback provided by clinicians and PV experts in the “user requirements analysis” and the “design” phases.

Regarding the presented platform design, the main BP of interest refers to the assessment of a potential ADR by a clinician. However, other BPs could also interact with it, e.g. concerning the patient’s treatment. Given that patient treatment is the topmost priority in the clinical environment and that it is a personalized process, highly dependent on the local context (e.g. the way the specific clinic/hospital is organized), the modelling of these “interacting” BPs is very important and could be rather complex. The proper modelling and

early identification of such BP interactions could be critical as they may substantially affect the identified goals and, thus, the platform design.

We model the identified BPs using flowcharts based on a notation similar to Business Process Management Notation (BPMN), in order to identify decision points, possible information processing bottlenecks, interactions with other BPs, etc. These flowcharts are further refined collectively by ICT experts, healthcare professionals (i.e. clinical doctors) and PV professionals (i.e. scientists who investigate potential ADR signals). Furthermore, interviews and workshops among researchers and end-users were conducted as part of the overall “user requirements analysis” phase to analyse the established BPs, identify the *User Goals* and refine the platform’s information processing workflow accordingly. Meetings were also held in the clinical environment (i.e. in the two hospitals which will host the platform in its pilot phase) to validate these goals and also address deployment issues in practice.

All types of current and emerging data sources considered in PV [6], were found interesting to explore by the end users. These include the local EHR systems, national and international SRSs, reference bibliographic databases as well as social media. From a technical viewpoint, programmatic data access is considered of high priority, as it enables systematic data gathering (e.g. spontaneous reports from the FDA Adverse Event Reporting System via openFDA (Kass-Hout et al., 2016), articles via the PubMed Central Application Programming Interface, etc.).

In order to successfully accommodate the imposed challenges regarding the synthesis and analysis of the vast data available, *Knowledge Engineering* (KE) is adopted as the main technical paradigm for our platform development. KE refers to methods, tools and theories for developing knowledge-intensive applications (Schreiber, 2008), and includes *knowledge extraction*, *knowledge integration*, *knowledge representation*, *knowledge dissemination*, and *knowledge elicitation* as its subdomains.

In the scope of our work, which concerns the systematic exploitation of all the available evidence from multiple PV data sources for the assessment of possible ADRs, we employ two technology artefacts tightly related with KE, namely, “*Linked Data*” (Heath and Bizer, 2011) and “*Semantic Web*” (Shadbolt et al., 2006). Linked Data refer to a group of standards which facilitate the interconnection of data over the existing Internet infrastructure, while Semantic

Web refers to the vision of semantically annotated publicly available data interlinked via Linked Data standards.

The use of Semantic Web and Linked Data standards provides two main technical benefits: (a) *Interoperability*: The use of the Linked Data paradigm provides syntactic and semantic interoperability tools to interlink heterogeneous data sources and unify them in one processing realm. (b) *Reasoning capabilities*: The well-defined semantics upon a robust mathematical infrastructure, i.e. Description Logics (Baader et al., 2004), enable automatic reasoning through specific software, a.k.a. “reasoners”.

4.1.3. Results

Based on this methodology and the choice of KE as the main technical paradigm, several challenges were identified from the end-user perspective, leading to concrete user goals and the design of the platform’s information processing workflow. In particular, given the characteristics of the clinical environment, the following challenges (enumerated with Cx) regarding the adoption of an ICT-based ADR assessment process were identified:

C1 | *Lack of time*: While the assessment of potential ADRs is identified as an important task, it is often neglected by clinicians due to lack of time.

C2 | *Lack of expertise*: PV entails specialized knowledge, which may not be available in clinical settings. While this argument supports the need for ICT-based support tools, it could also be conceived as a barrier for their adoption as their value might not be evident for the end-users.

C3 | *Adaptation to the clinical workflow*: Workflow diversity among various clinical environments (different hospitals, or even different clinics in the same hospital apply different BPs) could hinder the definition and the adoption of a “one-size-fits-all” workflow of PV information processing.

C4 | *Inadequate evidence*: While spontaneous reports are the dominant source of evidence for PV, other data sources such as EHRs, bibliographic databases, and even social media platforms are interesting for clinicians during ADR assessment. However, systematic access to multiple data sources shall be facilitated through appropriate tools.

C5 | *Coping with “big data”*: Expanding the search space for PV does not only provide a broader evidence space, but it also imposes “big data” challenges.

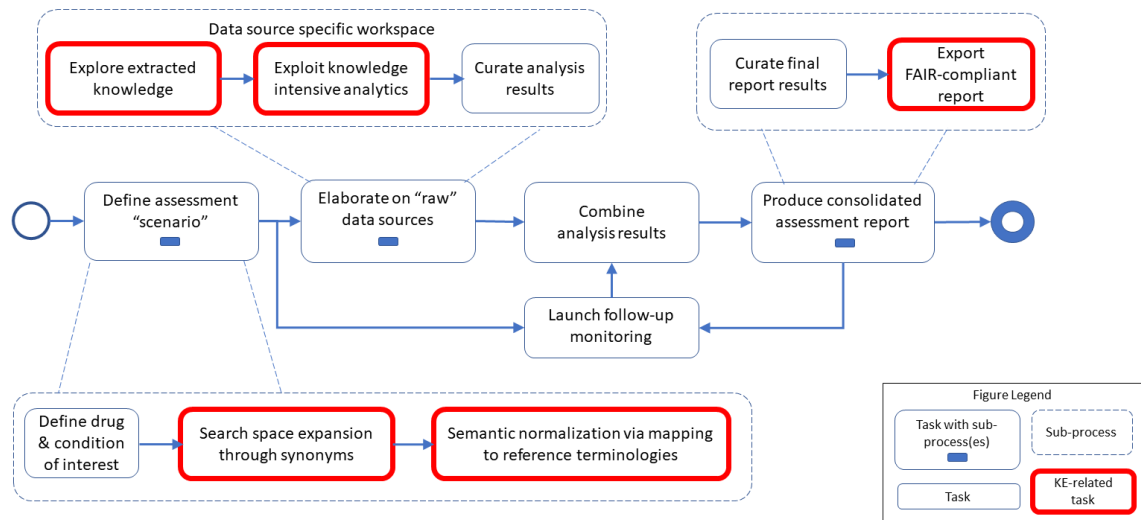


Figure 15: Outline of the main information processing workflow supported by the proposed platform (tasks related with Knowledge Engineering are highlighted in red).

Overall, challenges C1-C5 have been discussed in the conducted workshops and the following user goals (enumerated with Gx) were identified and mapped to the respective challenges:

G1 | *Flexibility and Unobtrusiveness (mapped to C3)*: The ADR assessment process should be flexible and tolerant to interruptions by tasks directly related with patient treatment. Thus, an important feature would be the ability to easily recover from such interruptions. Practically, this can be interpreted as the need to “save” the ADR assessment workflow and continue later. In addition, clinicians stressed that the patient’s treatment should not be disrupted. Thus, the designed process should be as unobtrusive as possible, minimizing “alerts”/ “warnings”.

G2 | *Balance between assessment depth and speed (mapped to C1 and C5)*: As the clinician’s time is valuable, the platform should enable both “in depth” assessment capabilities, while also supporting a “quick look” which could provide rigorous information. Although the information provided this way would obviously be more superficial than an “in depth” assessment, it could still provide value for clinicians.

G3 | *Semantic enhancement (mapped to C1, C2 and C5)*: Since the expression of the drug and condition of interest can be ambiguous (e.g. active substances, trade names, synonyms etc., could be used as drug terms), the overall process should be supported by curated standard terminologies and lexicons (e.g. with automatic synonym matching) to accelerate and facilitate information search and synthesis.

G4 | *Heterogeneous data synthesis (mapped to C4 and C5)*: Clinicians identified the need to synthesize various and heterogeneous data sources (e.g. scientific literature, drug-information databases, clinical trial information, SRS data, observational healthcare databases, etc.). Overloading the end-user with incomprehensible data was identified as a major risk and, thus, the need for knowledge-based analytics emerged.

G5 | *Data sharing (mapped to C2)*: The need to share data to further elaborate on the collected ADR information and assessment results was also identified. Moreover, the value of data provenance was highlighted, especially for the process of reporting assessment outcomes to regulatory organizations.

G6 | *Follow-up monitoring over time (mapped to C4)*: Typically, an ADR assessment produces a report with the conclusion and the supporting evidence. However, the time dimension is critical in PV, especially regarding new marketed drugs. Thus, a follow-up mechanism for monitoring potential ADRs over time is important and is currently missing.

The main information processing workflow supported by the proposed platform (Figure 15) that was defined based on the abovementioned challenges and user goals is organized in 5 steps. These steps are summarized next, describing the use of the KE methods that are applicable in each case:

Step 1 | *Definition of “ADR assessment scenario”*: When the user launches an ADR assessment, the platform shall support the definition of the drug and the condition of interest by automatic suggestions of synonyms and relevant terms obtained from reference terminologies, e.g. the Anatomical Therapeutic Chemical (ATC) classification for drugs, and the Medical Dictionary for Regulatory Activities (MedDRA®) and the International Classification of Diseases (ICD) for the conditions of interest. The use of such well-defined knowledge structures expands the search space, enables the semantic normalization of the overall process, prevents ambiguities, and facilitates automatic information interlinking in the next analysis steps.

Step 2 | *Browse/analyse raw data from each data source*: Each raw data source has its own characteristics. For example, SRS data could be used for disproportionality analysis, while EHR data could be explored through observational healthcare data analytics (Kass-Hout et al., 2016). KE approaches will be exploited for the analysis of each data source, e.g. text mining techniques can be used to extract and semantically annotate information from unstructured data sources such as the literature or social media. Thus, the end-user can browse or analyse the respective data source in a dedicated workspace, providing suitable features and analysis capabilities.

Step 3 | *Combine analysis results from raw data sources*: The results/analysis outcome obtained from each data source workspace shall be integrated in one common processing realm, where all the analysis results could be integrated, compared and evaluated by the end-user. Knowledge integration is based on semantic annotations produced in the previous steps and the use of Linked Data standards. Moreover, semantic reasoning can be applied to further elicitate knowledge from the already extracted analysis results.

Step 4 | *Produce a consolidating assessment report*: The overall analysis outcome shall be generated as a consolidated report, facilitating further analysis in collaboration with other clinicians, or even reporting to PV regulatory agencies. The produced report shall be available in both human-readable (e.g. in text form as a pdf document) and machine-readable (e.g. an RDF document) formats. Knowledge dissemination approaches can be used to facilitate the respective information exchange in a way that could promote the automatic reuse of this information. For example, the recently developed OpenPVSignal model (Natsiavas et al., 2018a) could be used in this regard, to enable compliance with the FAIR data principles (Wilkinson et al., 2016).

Step 5 | *Launch follow-up monitoring*: The end-user can launch a monitoring follow-up process, in order to receive potentially new information regarding the assessed ADR from the available data sources. This process would notify the end-user based on his/her notification preferences to avoid over-alerting. Ontology models such as the *Time Ontology* (Cox et al., 2017) and the *PROV-O Ontology* (Gil et al., 2013) can be used to enrich the obtained information with semantically enhanced time and provenance annotations, and thus, facilitate further processing/reasoning regarding the time aspects and the origin of the information collected regarding the ADR under assessment.

It should be noted that the presented workflow defines an independent BP, which can be adapted to each organizational context. Furthermore, in each assessment process, the end-user may decide the time spent on each BP step, either selecting to use the automatically retrieved information, drill-down to investigate further or manually curate the produced outcomes, and save or share his/her work with others at any time.

4.1.4. Discussion

Drug safety is an important issue in the clinical environment. Among the common tasks that are routinely performed in PV centres/departments in hospitals is the collection and review of all the available data for a potential ADR of interest. However, there is a lack of comprehensive tools to support PV activities, specifically tailored for use at the point of care. For example, a clinician may ask for a timely evaluation of the respective patient case after a new drug administration, and the PV centre/department shall provide a documented answer with a medical advice about the case, after assessing the eventuality of an ADR (Koutkias et al., 2017). To respond to this challenge, currently available sources of information about the drug–event pair have to be searched by PV experts separately and in many cases without using appropriate support tools.

To address this need, we are currently developing a Web-based, knowledge-intensive platform aiming to support the assessment of potential ADRs, experienced during routine patient treatment. In the current paper, we presented the entailed challenges and the goals for such a development from the user perspective. We also presented the platform’s main information processing workflow (Figure 15). Its design relies on exploiting various KE-based methods, employed in each step of the workflow.

In particular, the use of Linked Data and Semantic Web technologies provides the following key benefits:

Information linking can be improved and automated by reducing the need for manual data exploration and discovery as data could be automatically retrieved.

Rich *semantics* enhance information processing capabilities, which are typically limited in the PV domain to statistical measures of disproportionality. The already established statistical methods could be combined with semantically-enhanced knowledge sources to improve outcomes via automatic reasoning capabilities (e.g. regarding causality assessment).

Evidence can be strengthened through the knowledge-intensive, concurrent exploitation of multiple data sources, eliminating false positive findings (Koutkias and Jaulent, 2015).

KE-based automatic information linking enables the use of *provenance information* to annotate the generated analysis outcomes. This is important as full supporting evidence shall be explicitly available, e.g. when reporting results to regulatory organizations.

Despite the abovementioned benefits, the implementation of KE-oriented techniques entails complex challenges, both in methodological and technical terms, e.g.:

- Automatic reasoning capabilities based on the Description Logic defined semantics are one of the most prominent features of Semantic Web technologies. However, “reasoners” require significant computational resources and their efficient use in large datasets remains a challenge.
- Various reference knowledge sources (e.g. terminologies/thesauri/vocabularies) are available and can be applicable in the scope of this work. However, since these sources are constantly evolving and refined, their alignment is a complex task as it can lead to semantic inconsistencies.
- Integrating all the collected evidence under one unified knowledge model can be very challenging. This process engages many heterogeneous data sources, which could be available via standard data exchange interface or not. For example, using proprietary EHRs to retrieve observational healthcare data would typically require specific interface implementations.

To this end, besides the ultimate goal of delivering a robust and evaluated ADR assessment platform, our mid-term goals are: (a) the design of a unifying semantic model enabling the integration of heterogeneous data sources in one information processing realm, and (b) the modelling of ADRs in one ontological model, facilitating advanced reasoning operations upon the collected information.

4.1.5. Conclusions

There is a clear need for comprehensive tools to support PV activities at the point of care. The proposed platform aims to support the assessment of potential ADRs in routine clinical practice, relying on the concurrent exploitation of multiple data sources for appropriate

evidence. This entails the analysis of the acquired data, the aggregation of the obtained evidence, and the support of follow-up ADR monitoring over time in a systematic and user-friendly way. In this paper, we presented the main challenges and the goals from the end-user perspective for such a development, identified during the “user requirements analysis” phase of our development. We also presented the main elements of the platform design, i.e. its main information processing workflow, and illustrated the use of KE as the platform’s main technical paradigm. Our work contributed to the development of a learning health system for active, post-marketing drug safety surveillance at the point of care.

4.1.6. Acknowledgements

This research has been co- financed by the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneur-ship and Innovation, under the call RESEARCH – CREATE - INNOVATE (project code: T1EDK-03789).

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4.2. Beyond the paper: User goals refined and challenges identified regarding the integration in the clinical environment

As explained in the Methodology subsection, the main outcomes of the thesis were iteratively refined. To this end, the final list of the identified UGs is summarized in Table 8, also taking into account the analysis regarding BPs, presented in “Regulatory context and Management aspects”. Furthermore, the challenges of integrating systems based on “intelligent” technical paradigms are discussed in this subsection.

Table 8: Finalized list of User Goals

ID	Title	Description	Reference to BPs
UG1	<i>Use of drug synonyms should be encouraged</i>	Retrieval of drug information either by using the active substance, empirical or commercial name should be supported	All BPs are relevant, but this feature would be especially useful for BP5, BP6 were complex queries are formed
UG2	<i>Graphical components with conceptual hierarchy should be applied</i>	Conceptual levels/hierarchies and concept groupings provided by well-defined encodings (e.g. MedDRA and WHO-ATC levels), could facilitate the formulation of search queries by users in a more succinct way, exploiting the semantics provided by the respective encodings as part of the User Interface.	All
UG3	<i>Well-defined unambiguous concepts should be used based on widely accepted thesauri, dictionaries and medical ontologies</i>	The use of well-defined terms is expected to enhance the formulation of queries by reducing semantic ambiguity and to improve access to pertinent well-standardized data sources.	All BPs are relevant, but this feature would be especially useful for BP5, BP6 were complex queries are formed
UG4	<i>A multitude of data sources should be used, including but not restricted on ICSRs</i>	Both well-established sources (i.e. sources widely used in everyday practice), as well as emerging sources that are being thoroughly researched for their potential merit in drug safety studies should be used	BP2, BP3, BP4, BP5, BP6, BP7
UG5	<i>Statistical evaluation of possible signals and computational causality assessment</i>	The use of statistical metrics based on disproportionality analysis techniques is the main approach for the detection and the ensuing prioritization of potential safety signals and these should be heavily employed.	BP3, BP4, BP5, BP7
UG6	<i>Exploit the special characteristics provided by each data source</i>	Each data source provides data of different types with different features, exploitable in terms of drug safety signal investigation. For example, while DA statistics (e.g. PRR, ROR etc.) might be extremely useful in ICSR databases, these metrics might be irrelevant for social media and therefore each data source's special features should be taken into account.	BP2, BP3, BP4, BP5, BP7

UG7	<i>Advanced visual analytics features should be integrated</i>	In addition to statistics-numerical data, visual aids could facilitate the in-depth investigation of potential safety signals	BP2, BP3, BP4
UG8	<i>Long term/"pausable" processes for investigating a drug-safety signal should be available</i>	A "save for now and resume later" feature is critical, because such processes are time-consuming and laborious. Especially in the clinical environment where PV is not HCPs' top priority, such a feature would be of the highest importance.	BP2, BP3, BP4, BP5, BP6, BP7
UG9	<i>Capability for long term monitoring of a signal should be provided</i>	Many safety signals may entail the investigation of longitudinal studies or the long-term monitoring of a drug and thus they could span long periods of time. By the same token, analysis of clinical trials or the provision of clinical services are also considered lengthy processes.	BP3, BP4, BP5, BP6
UG10	<i>Investigation "scenarios" should be identified as the main usage paradigm</i>	Albeit the proven value of direct searches for signal detection, the formulation of investigation scenarios could be even more beneficiary due to the deeper analysis with enhanced capabilities that they offer. Notwithstanding, a certain "quick search/investigation" feature can be also included.	BP2, BP3, BP4, BP5, BP6, BP7
UG11	<i>Role-Based Access control for the users</i>	This control can enable simultaneous analysis of multiple PV signals. Users can create, edit or delete scenarios, depending on the specific permissions granted to each one of them. Furthermore, collaboration and teamwork can be encouraged and thus mistakes can be prevented	All
UG12	<i>Comprehensive report generation from each investigation scenario</i>	An investigation scenario report would be very useful in order to disseminate the investigation results to other clinical experts or other stakeholders (e.g. regulatory agencies etc.).	BP2, BP3, BP4, BP5, BP6, BP7
UG13	<i>Access to information for each individual patient case</i>	Due to inter-patient variability, the investigation of suspected ADRs demands access to as much detailed information available. This could pertain for example, to the genetic profile of a patient affected by an ADR during clinical trials or to the original form of ICSRs that document a signal.	BP2, BP4, BP5, BP7
UG14	<i>Ability to trace back to original raw data source</i>	Reliability can be assessed or proven only if the exact origin of data can be traced, a feature which might also be important for medical data-sharing.	BP4, BP5

<i>UG15</i>	<i>User-friendliness</i>	Tackling crucial challenges from the clinical setting, such as clinicians' cramped schedule, or underestimation of PV due to the higher priority of other clinical procedures	All
<i>UG16</i>	<i>Data protection and privacy</i>	Compliance with the regulatory framework and the stringent legalities (e.g. the General Data Protection Regulation GDPR)	All
<i>UG17</i>	<i>Extensibility and adaptability</i>	Being versatile with new potential pharmacovigilance data sources and operational in distinct environments (different hospitals, CROs, etc.), irrespective of the computer infrastructure used (e.g. Electronic Medical Record), or the procedures applied	All
<i>UG18</i>	<i>Interoperability</i>	Data generated (e.g. the consolidated reports) must be computationally exploitable by other information systems as well.	BP2, BP5, BP7

The following diagram qualitatively depicts the relationship of the UGs with the respective BPs. While it is clearly evident that non-clinical BPs (i.e. BP5, BP6, BP7) support the biggest portion of UGs, it is also clear that a lot of UGs are related with clinically relevant BPs (BP1 – BP4). Given the current low adoption of PV processes in the clinical context, this finding also implies that the integration of suchlike IT tools could provide value for every day clinical practice.

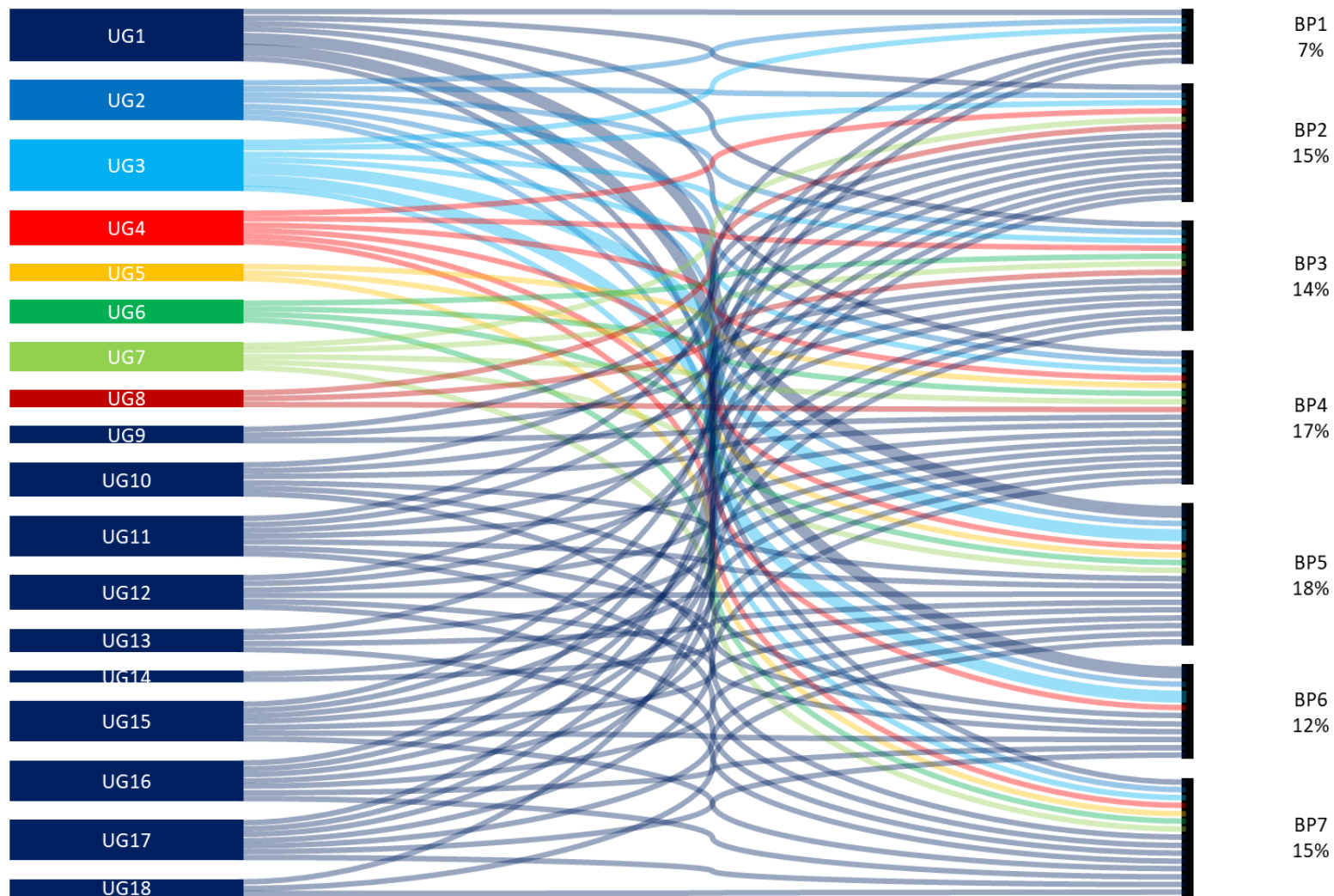


Figure 16: Relationship between User Goals and Business Processes

Advanced IT tools and ISs are expected to drive the process of shifting PV activities from a traditional, passive paradigm depending on SRSs to the paradigm of “Active Pharmacovigilance” leveraging information from all available data sources, also as part of everyday clinical practice in order to investigate or prevent potential ADRs. However, until now, the adoption of such digital approaches by PV stakeholders has been hampered due to significant limitations that are gradually coming to the forefront. The hurdles of adopting IS in PV activities focusing on the clinical context are elucidated (at least partly) by the identified UGs, however, they can be generalized referring to the adoption of ISs in the healthcare domain as a whole, beyond PV.

- *Fragmented medical datasets*: Typically the available datasets in a hospital refer to mostly unstructured, incomplete, semantically unaligned, and “siloesd” data among the various departments of a healthcare facility e.g. hospital (White, 2014). Moreover, when external datasets are available, they most frequently lack formal and computationally exploitable semantics. This special and semantic fragmentation of the available datasets prevents their aggregation; in principle their integration could be significantly facilitated by KE approaches (e.g. via the Linked Data paradigm and the use of Semantic Web technologies).
- *Inherent technical pitfalls of ISs*:
 - *Versatility* is a huge issue because in the case of ML most algorithms operate within very specific scenarios albeit the real-life demands of clinical operations entail managing a multitude of heterogeneous sources, including “dirty” or incomplete data. Increasing versatility of “intelligent” algorithms is not a trivial thing but it could be facilitated by research networks where “real-world” data would be used to validate algorithms under development (e.g. following the OHDSI initiative model⁵⁹).
 - *Validity* is also another major concern that has to be addressed considering that, typically, tools/methods etc. are systematically validated and regulated in the healthcare context (e.g. via processes including clinical trials and well-defined Risk Management approaches). Hence, the open availability of these IT tools (e.g. “intelligent” algorithms) could facilitate their wide validation (Yu et al., 2018).

⁵⁹ <https://www.ohdsi.org>

- *Interpretability* is a very important issue regarding the application of ISs in the healthcare as many times, especially ML algorithms, are viewed as a “black-box” which hides the reasoning process producing the outcomes/results. While this might be considered as a benefit for other purposes or domains, it is not acceptable in the healthcare setting, where providing a clear explanation on why an IS provides an outcome is essential.
- *Usability*: User-friendliness significantly affects ISs’ adoption in and out of the clinical setting. The pace at which doctors interact with patients and other clinical scientists is gruelling so any ISs should generate outputs rapidly, with precision, in a concise, reproducible, and validated way (Sanchez-pinto et al., 2018). To this end, a key issue identified is the need to minimize necessary user interactions which might be disrupting, as even in critical systems, alert fatigue can significantly reduce acceptance. Furthermore, focusing on the use of ISs, a major ergonomics issue is raised: How should an end user interact with (semi)automatic “intelligent” software processes (e.g. an ML algorithm or formally stated knowledge structures)?
- *Legal issues*: Legal, ethics and regulation issues also should be identified as an important factor regarding the acceptance of ISs in the healthcare. For instance, liability of clinical scientists in cases of malpractice are vague, therefore the legal framework should be elucidated, and potentially regulated as it could disrupt the processes of diagnosis, patient stratification, therapy and beyond (Yu et al., 2018). Obviously, these considerations overlap with ethics issues. For example, the concept of *consent*, one of the main legal and ethical cornerstones, needs to be adapted as getting the concept of a patient to process his/her data using ML or KE methods when he/she does not really understand how these algorithms work, is pointless and ethically questionable.
- *Information security*: ISs outcomes heavily depend on datasets, either in order to train ML algorithms or to construct computationally exploitable Knowledge Structures (e.g. ontologies). Thus, major issues are raised regarding data-based biases and potentially malicious data management. Besides technical issues, it is clear that data security defects might directly endanger patient safety, therefore, the need for a “Patient Safety Cybersecurity Framework” is clearly identified. Such a framework would map technical information security threats to patient safety threats and focus on mitigating the latter via a systematic Risk Management approach.

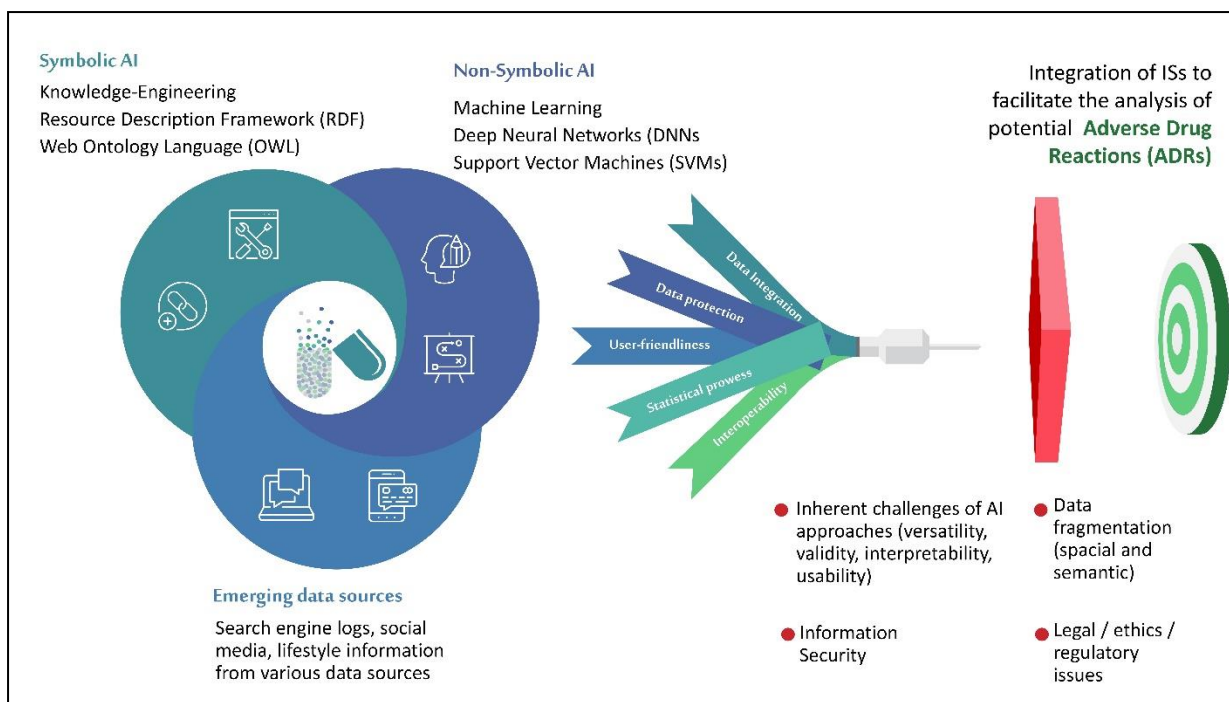


Figure 17. Combination of symbolic and non-symbolic AI technical paradigms along with the use of emerging data sources to tackle the goals of PV goals and challenges.

Based on a White Paper produced by Oracle emphasizing on the data challenges in PV (Corporation), over 60% of the PV stakeholders deploy or plan to deploy ISSs. In order to overcome the above challenges, both technical and procedural advances are required. In terms of technical approaches, many of the above challenges are imposed by the hype of using “black-box” based ML algorithms (non-symbolic AI) which provide no clear explanation of the reasoning process producing the respective outcome. We argue that KE based approaches (symbolic AI) should be more heavily employed and alternative schemes like hybrid intelligence (Computational Architectures Integrating Neural And Symbolic Processes, 1994) should also be investigated. Regarding the procedural issues, the need to move beyond data science to clinically related validation schemes is emphasized (Hauben et al., 2018). Furthermore, it is also evident that organizations need to prepare before adopting ISSs in the everyday practice (e.g. data preparation)(Bates et al., 2020a). Especially regarding the information security challenges, a threat analysis or gap analysis (Rasmussen et al., 2018) should be conducted prior to the deployment of ISSs in order to mitigate potential risks. Furthermore, the barriers and facilitators of IT systems in healthcare should also be taken into account (Natsiavas et al., 2018b).

In conclusion, we argue that the use of ISs in healthcare is moving towards the “trough of disillusionment” in terms of the Gartner hype cycle, with some prominent examples showing great promise without confirming it in real-world healthcare practice (How IBM Watson Overpromised and Underdelivered on AI Health Care - IEEE Spectrum). It should be noted that this steep disillusionment curve can also be attributed to issues which might not be directly related with technical or organizational issues. For example, ethics are a crucial factor affecting each step of the process, heavily affecting the legal context. Indicatively, while preserving patient privacy is widely accepted as a principle of utmost importance, its ethical impact becomes debatable when it hinders data processing which could potentially save lives. To this end, balancing benefits and risks of data processing in terms of ethics is crucial.

However, given the ISs advancement pace, their wide adoption in other domains and their huge potential benefits, their future use in healthcare, including for PV purposes, seems certain, in spite of the barriers and the lack of their current adoption. The development of ISs and their potential benefits and risks could be considered in analogy with the challenges imposed by the development of drugs in the 20th century. While the process of drug development changed the overall healthcare setting and the medical practice, it has also caused severe tragedies (Paine, 2017). Therefore, in order to avoid decisions which might lead to tragedies, the above challenges should be clearly identified and elaborated to maximize ISs adoption rate and their positive impact in the healthcare processes.

5. Redefining Active Pharmacovigilance in the context of the Learning Healthcare System paradigm

Based on the BPs and the UGs identified in the previous chapters, it became clear that a paradigm shift of currently applied drug safety processes should be applied, moving towards the integration of “intelligent” computational approaches and “real-world” data sources. The need to focus on a new “delivery science” focusing on the implementation of “intelligent” technical paradigms in the context of real-world healthcare processes is also discussed by a recent high profile paper (Li et al., 2020).

More specifically, providing hospitals with better IT infrastructures to support them in data collection and analysis, and interconnecting them via information exchange networks with other domains which are not strictly clinical (e.g. social services or primary care, research, drug development, lifestyle data sources etc.) could offer bidirectional benefits and also support policy decision making (Sittig and Singh, 2020). These benefits refer to healthcare processes as a whole, including drug safety and PV.

Focusing on recent developments regarding drugs development and the required safety procedures, COVID-19 led to a world-wide active pursue of a drug (European Medicines Agency, 2020) or a vaccine. In this context, myriads of technical solutions were proposed as part of an endless catalogue of worldwide or national initiatives aiming to produce or consume “big data”: from mobile apps aiming to provide diagnosis hints (Oliver et al., 2020) and blockchains used to enhance biological sample management, to multi-billion corporations (typically competitors) actively joining forces in order to provide computational infrastructure aiming to facilitate contact tracing (Oliver et al., 2020).

As humanity moves away from the first shock and its initial response to this global disaster affecting each aspect of every-day life from work practices to school (Vogel, 2020), it becomes obvious that while advanced technical solutions could be very important, their impact without an overall paradigm shift is questionable (Sharma et al., 2018)(Bhavnani et al., 2016)(Moerenhout et al., 2018)(Covid-19 has blown apart the myth of Silicon Valley innovation | MIT Technology Review). Under huge social pressure for an immediate drug development, new strategies regarding the development of potential new drugs/vaccines (or repurposing old ones) are proposed (Corey et al., 2020)(European Medicines Agency, 2020),

also emphasizing the need for thorough safety testing along with quick drug development (Jiang, 2020) and the need for better coordination in the data collection processes (Sittig and Singh, 2020). For example, the ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines) public-private partnership aims to align industry, government, and academia and their individual strengths moving towards collaborative platforms for conducting harmonized, randomized controlled vaccine efficacy trials for several candidate vaccines in parallel, so as to accelerate the licensure and distribution of multiple vaccine platforms and vaccines to protect against COVID-19 (Corey et al., 2020).

Furthermore, COVID-19 pandemic clearly highlights the need for data management transparency regarding drug safety, as vague data management practices fail to provide the necessary scientific validation and verification capabilities. This lack of data management transparency not only led to the retraction of prominent scientific publications but even worse, it also led to critical clinical trials disruption based on non-thoroughly-validated evidence (Piller, 2020).

In this new era of drug development and safety management where technologies will inevitably play a prominent role, we argue that moving towards “Learning Healthcare System” (LHS) and “Active Pharmacovigilance” (AP) paradigms could provide important benefits, for both patient safety and healthcare but also cost management, as it could facilitate quicker and better insights based on real-world data. While the administrative, financial and regulatory challenges should not be underestimated, we hold that such an approach could significantly improve the time and the overall cost burden of drug development leading to safer new drugs quicker.

5.1. The Learning Healthcare System paradigm

Currently, widely adopted CPGs play a crucial role towards the standardization and quality management of the clinical treatment procedures. Despite the undoubtable value of defining and adopting CPGs, the process of forming them can be very time consuming as it typically depends on a group of experts who thoroughly review the respective literature and other evidence to produce generally applicable CPGs. Typically, these CPGs are mostly based on clinical trial data and do not take into account “real-world” evidence. Inevitably, these “generally applicable” CPGs do not take under consideration the specific treatment process

context (e.g. special localized characteristics applying in a given country/region, features or problems regarding the specific healthcare service provider organization, patient's detailed profile etc.). Furthermore, the gaps of the overall translation of research achievements to clinical practice, including their inclusion in CPGs, also lead to huge delays regarding the adoption of potentially clinically useful practices (Morris et al., 2011). Therefore, *“care that is important is often not delivered, and care that is delivered is often not important”* (Institute of Medicine and Roundtable on Value and Science-Driven Health Care, 2015).

The LHS paradigm argues that healthcare systems need to become more agile, inclusive and learn from technical and research practice much faster than they currently do. The United States Institute of Medicine defines the LHS as the vision of a healthcare system *“... in which progress in science, informatics, and care culture align to generate new knowledge as an ongoing, natural by-product of the care experience, and seamlessly refine and deliver best practices for continuous improvement in health and healthcare”* ((IOM) Medicine, 2011). To this end, an alternative (or complementary) definition of LHS is the following: *“a learning healthcare system is one that is designed to generate and apply the best evidence for the collaborative healthcare choices of each patient and provider; to drive the process of discovery as a natural outgrowth of patient care; and to ensure innovation, quality, safety, and value in health care”* (Institute of Medicine, 2007).

A key concept for LHS is the idea of “patient centred medicine” where citizens are identified as (a) data producers, (b) service co-creators and (c) service consumers. The main policy axes typically defined in the context of LHS vision are: (a) fast adoption of research achievements in routine clinical practice; (b) culture change among various stakeholders; and (c) collaboration of patients and physicians to produce evidence. It should be noted that LHS vision emphasizes on the patient participation on the overall decision-making in order to personalize care plans instead of delivering a standard treatment designed for the “average person” moving towards the precision medicine vision.

To this end, LHS paradigm also focuses on the use of “real-world” evidence based on data collected in daily clinical practice via EHRs. EHR data are constantly updated and they constitute an evolving source of information which can be used as the basis for population-specific conclusions and knowledge, easier to use as they are already produced as part of the every-day clinical practice and more straight forward to integrate than knowledge produced via randomized controlled trials (Friedman et al., 2010a)(Budrionis and Bellika, 2016)(Friedman

et al., 2015a). Figure 18 depicts the information learning cycle envisioned as part of LHS paradigm (Friedman et al., 2017).

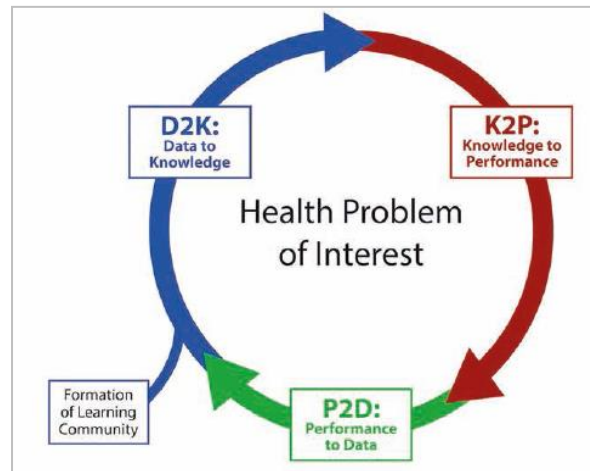


Figure 18: Learning Healthcare System, information learning cycle (Friedman et al., 2017)

Some LHS initiatives around the globe are identified in (Friedman et al., 2017). Notably, the US Office of the National Coordinator for Health Information Technology (ONC) set the achievement of rapid learning as the pinnacle goal of its 5-year strategic plans of the last decade (Office of the National Coordinator for Health Information Technology (ONC), 2011)(Office of the National Coordinator for Health Information Technology (ONC), 2015) and various initiatives take place in Europe (Eichler et al., 2018)(Keung et al., 2015)(Harnessing the potential of real world data through a ‘learning healthcare system’ | European Medicines Agency).

However, the reforms towards the application of LHS in real-world settings largely remains in theory (Budrionis and Bellika, 2016). This can be attributed to several special conditions applying in the healthcare domain, which could be summarized in the following non-exhaustive list:

- the complexity and the heterogeneity of the legislation context and the overall health systems governance model (e.g. healthcare systems are sometimes governed on a federal and other times on a state or a country level) introduce many difficulties towards the application of standardized processes, guidelines or exemplar paradigms

of healthcare processes as they have to be “translated” towards the special circumstances applying in the local environment, a far from trivial process

- the inherent complexity and need for independence and personalization of clinical practice inevitably requires subjective judgements in all the steps of the overall process, reducing the impact of guidelines, formalized or standardized processes and modern paradigms like LHS
- the heterogeneity of the various reimbursement models (both public and private) introduce various setbacks as funding is a key issue defining priorities, and therefore budgets tend to define the applied processes based on cost management
- the diversity of the various stakeholders’, their educational backgrounds and their priorities leading to contrasting budget requirements (e.g. managers focus on budgets, clinicians focus on health impact etc.)
- the lack of technical interoperability between the various data holders, both in terms of syntactic and semantic interoperability

These factors lead to a labyrinth of motives and processes where various stakeholders with different motives and ultimate goals are engaged. Thus far, the decisions taken are mostly driven by budget restrictions and requirements. In this context, the COVID-19 pandemic can be seen as a unique opportunity as it has clearly proven that quality healthcare services can be a significant factor for the overall economy (Suddenly, Public Health Officials Say Social Justice Matters More Than Social Distance - POLITICO), therefore aligning the typically contrasting motives of the various stakeholders, while also highlighting the fact that investing in the LHS will have significant benefits not only for public health, but also for the economy at large.

5.2. The vision

Information workflow in a typical health care system today is depicted in Figure 19 (adapted from (Institute of Medicine and Committee on the Learning Health Care System in America, 2013)), highlighting the gap of translating research into clinical practice. Aligning typical PV activities in the context of this information workflow, evidence is typically using “passive” approaches produced via DA based on ICSRs analysis. It should be noted that the main input from patients regarding potential ADRs comes from the submission of ICSRs which is a very weak communication channel as ICSRs are heavily underreported. Therefore, while

a lot of effort is placed on reducing the time between the occurrence of first evidence and regulatory actions for drug safety, the translational gap is still there mainly due to lack of data, heavily affecting the overall process.

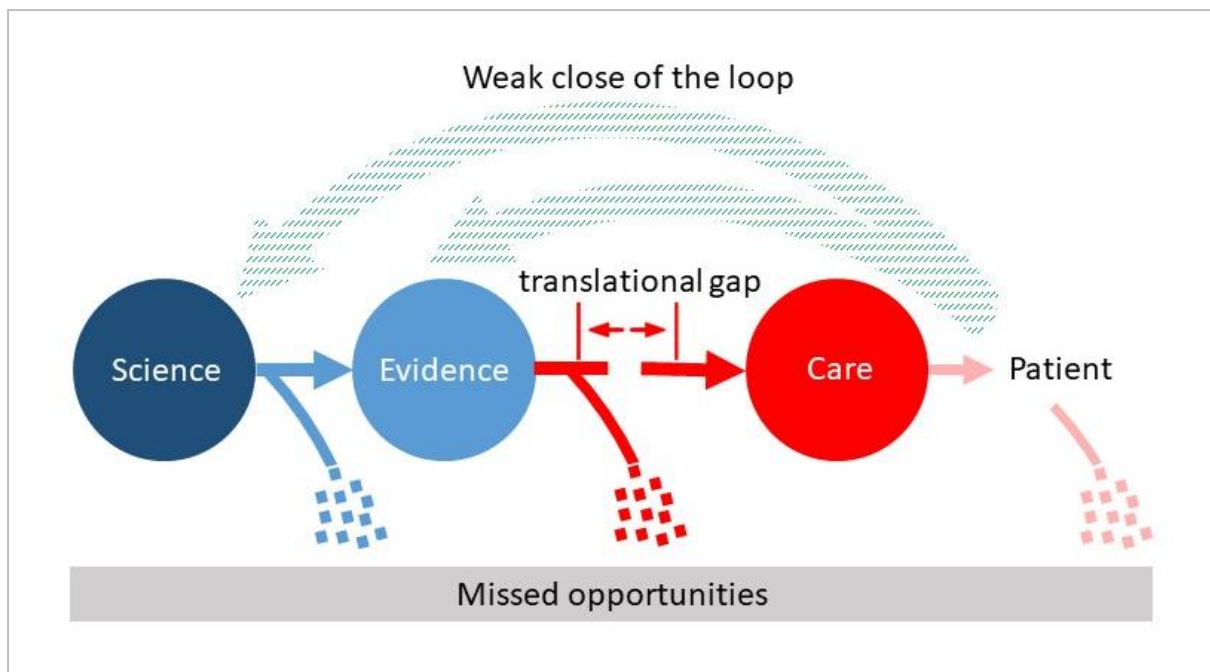


Figure 19: Informational workflow of a typical healthcare system - adapted from (Institute of Medicine and Committee on the Learning Health Care System in America, 2013)

Combining the two paradigms of LHS and AP, we propose an update on the main LHS information lifecycle, emphasizing on three concepts: (a) the need to disseminate the produced knowledge back to the community, (b) the need for transparency and (c) the need to adapt for personalized treatment. While these concepts have been elaborated to some extent in the context of LHS (Friedman et al., 2017), we highlight them as they are particularly important for AP.

Focusing on “personalized” healthcare, the evaluation of whether somebody is healthy or not should also depend on their personal input or personal lifestyle data, moving beyond simple patient stratification/clustering towards a “patient-centric” healthcare model. As PV is mostly based on the calculation of a risk-benefit ratio, the definition of this ratio in the context of the proposed paradigm should be updated accordingly, adjusted to the new data sources used and their peculiarities, including personal patient opinion and individual information (e.g. patient genetic profile), leading to Patient-Centric Benefit-Risk Ratio (PCBRR). To this end,

information flow archetypes emphasizing on personalized care/treatment (e.g. Patient-Reported Outcomes archetype) should be further adopted. It should be noted that while a personalized benefit-risk evaluation rationale has already been identified as a need and has already been discussed in context of certain research projects, however the practical outcomes to this end are not clear in terms of PV (Juhaeri, 2019).

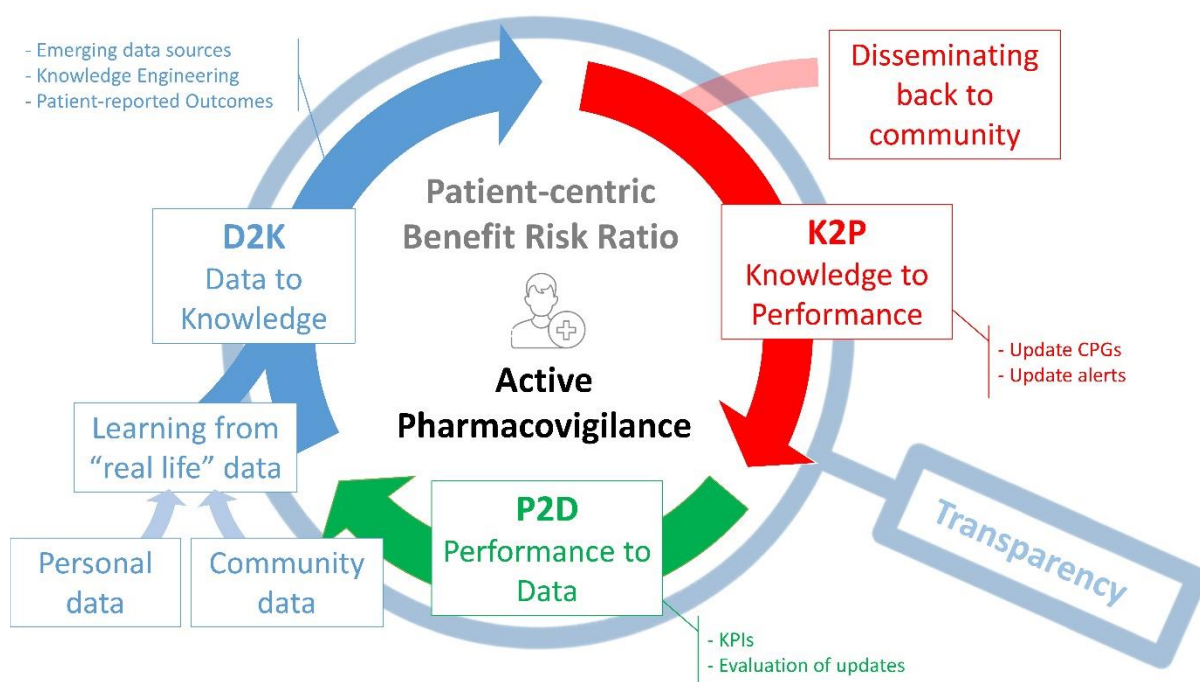


Figure 20: The AP-LHS cycle: The Learning Healthcare System information lifecycle adapted for Active Pharmacovigilance, emphasizing on the calculation of a Patient-centric Benefit Risk Ratio in parallel with the classic PV approaches

As also shown in Figure 20, the definition and the iterative calculation of a Patient-Centric Benefit-Risk Ratio (PCBRR) plays an important role as it is used in all parts of the respective AP-LHS cycle aiming to support personalized treatment. In current clinical practice, personal information is taken into account as part of the non-systematic and highly subjective HCP judgements. Supporting such information via a well-defined PCBRR could significantly improve clinical decision making. Defining or even proposing a calculation formula for PCBRR would require a thorough validation process, and as such, it is considered out of this thesis scope. However, PCBRR could be outlined via the following features:

1. Should take into account DA approaches upon community data

Patient stratification approaches and statistical analysis approaches against well-established data sources (e.g. ICSRs) and RWE (e.g. EHRs) should be part of the overall process.

2. Should take into account personal clinically related data

Personal lab tests and potentially genetic profile might be highly relevant to identify the potential risk that a drug might pose to a specific patient, for example based on pharmacogenomics information.

3. Should take into account personal lifestyle data

Food, movement, sleep patterns etc. are indicative examples of data which might influence a drug's impact and also significantly interact with the overall patient quality of life and sense of "health": as such, they might significantly impact the reporting process of potential ADRs.

4. Should take into account personal patient preferences

Patient preferences (food, lifestyle etc.) are of the utmost importance as they might significantly affect the overall sense of "health", especially regarding psychological health.

5. Should be specialized for specific ADRs

The impact of personal preferences or objective data (e.g. lab tests) is expected to vary for each ADR, taking its specific characteristics into account (e.g. its MoA). Therefore, at least in principle, the PCBRR should be specialized for each ADR.

6. The overall outcome should link to original information sources/raw data

While providing an overall PCBRR for a specific ADR would be very valuable, providing a "black-box" index would not be enough. The PCBRR should also be defined based on clear attribution relationships/links which would increase the overall transparency and enable the interpretation of PCBRR outcome for each patient further supporting clinical decision making. Using a hypothetical example, while calculating that a patient might have a PCBRR corresponding to a specific

value for a given ADR (e.g. the value 0.8) would be valuable, this calculation would provide a lot more information if it could be linked with original information/raw data (e.g. the fact that a patient genotypic characteristic increased his/her PCBRR for 0.2). Providing such interpretation links would also be crucial for the adoption of PCBRR as end-users end-users are less likely to trust computational processes whose workings they do not understand.

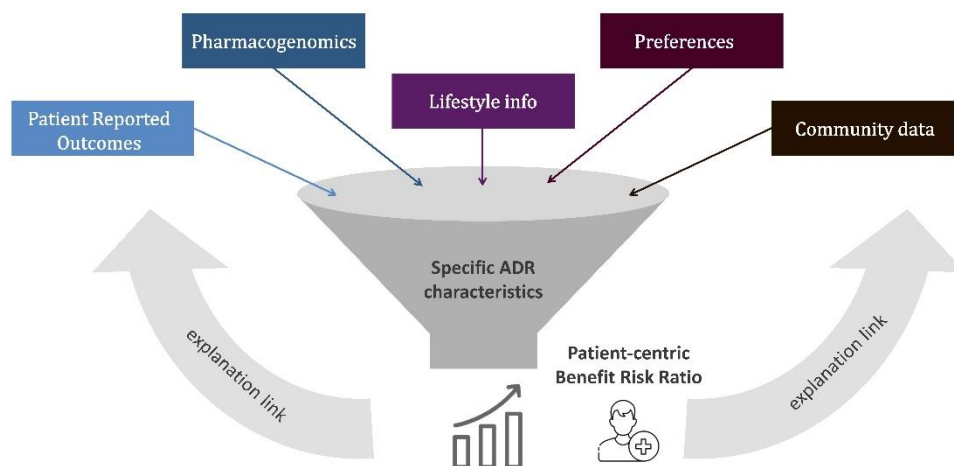


Figure 21: The Patient-Centric Benefit Risk Ratio – main information sources

Based on the above, the AP could be defined as the ‘*systematic “hot pursuit” of RWE in all possible data sources aiming to “learn” in order to support personalized clinical decision making based also on individual information, including patient as an actor of the actual decision process*’.

The vision of a patient-centric AP as part of a LHS information lifecycle is further analyzed in Table 9 where indicative real-world activities for each component of the LHS-AP information lifecycle are identified. As an indicative use case, we use the investigation of a new PV signal as part of a hospital’s PV department to support a clinical decision supporting an individual patient’s treatment. These processes could relatively easily be adjusted to support the investigation of potential new PV signals in general, as part of DSMOs. Furthermore, the relation of the presented lifecycle with the user roles, the BPs and the UGs identified in previous chapters is also depicted in Table 9.

Table 9: Interpretation of LHS-AP lifecycle components to real-world activities and their link with the identified user roles, BPs and UGs

<i>Lifecycle phase</i>	<i>Application in the context of AP</i>	<i>Exemplar information workflow</i>	<i>User roles</i>	<i>Business Processes</i>	<i>User Goals</i>
<i>Learning from community</i>	<p>A typical knowledge sharing practice among scientific communities today is the open (or via proprietary access schemes) publishing of data.</p> <p>Moving beyond this already established practice, another approach could be the formation of research or clinical “networks” which could enable the sharing of data (or analysis results) among trusted partners without requiring the open unconditional data publication.</p> <p>Finally, another more active approach could be to actively pursue direct data collection, via communication with specific patient cohorts, depending also on the severity of the investigated issue.</p>	<p>Openly available databases useful in terms of a PV signal investigation could include data provided via widely accepted ICSR databases (e.g. FAERS⁶⁰, EudraVigilance⁶¹ or VigiBase⁶²).</p> <p>An alternative would be the participation in research networks where either data or analysis results could be exchanged (e.g. the OHDSI research network⁶³).</p> <p>Direct data collection could be done either remotely (via telephone, email or electronic surveys) or even by a follow-up clinical examination of the patient, depending on the size of the target</p>	IT scientist, Manager, PV expert	BP5, BP7	UG4, UG6, UG18

⁶⁰ <https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard>

⁶¹ <https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance>

⁶² <https://www.who-umc.org/vigibase/vigibase/>

⁶³ <https://www.ohdsi.org/join-the-journey/research-network/>

		<p>cohorts, the investigated issue and the capacity of the organization</p> <p>Furthermore, lifestyle data (either structured or unstructured) could be collected using widely used devices (e.g. mobile phones).</p>			
<p><i>Learning from patient</i></p>	<p>Complementary to the process of learning from the community, identify personal relevant information is of high importance.</p> <p>Such information include patient lifestyle information, food habits, exercise habits, lab tests, pharmacogenomics information etc.</p> <p>This information could be collected via questionnaires or personal interviews, or even automatically collected using advanced IT tools (e.g. collecting data from mobile phones etc.).</p>	<p>Personal information would be valuable in order to calculate the envisaged PCBRR and finally decide if a drug should be administered/stopped/rechallenged etc.</p> <p>For example, deciding on whether a specific patient should continue taking a drug, could heavily depend on his/her genetic identity and the specific drug's pharmacogenomic profile. Furthermore, the decision should also take into account personal preferences (e.g. how he feels about the potential ADRs). These data could significantly alter the respective clinical decision compared to community based benefit-risk ratio.</p>	<p>Doctor</p>	<p>BP1, BP2</p>	<p>UG13, UG16</p>

<p><i>D2K – Data to Knowledge</i></p>	<p>D2K would include the combined processing of various data sources, either local/proprietary or openly available, on top of ICSR databases which are the main information source today. This expanded data space would include emerging and data sources primarily used for other purposes (e.g. EHRs, biochemical pathway databases, PGx data sources, social media, behavioral information sources etc.).</p> <p>Indicative related PV activities include the identification of potentially unknown PV signals, the analysis of already known PV signals, the identification of potential associations with clinically relevant values (e.g. lab test results) or patient characteristics (phenotype, social and demographic features etc.). Especially the personal data could be valuable in terms of calculating PCBRR.</p> <p>Practically, the inclusion of these new data sources would inevitably lead to the need for the development of new AI or Knowledge Engineering oriented computational approaches (e.g. Natural Language Processing algorithms, ontologies etc.), statistical tools and metrics and the development of specific guidelines (Zhuo et al., 2014)(Gagne et al., 2012)(van Stekelenborg et al., 2019), extending the ones currently deployed to support ICSR databases analysis.</p>	<p>A new PV signal would be investigated via the statistical analysis, i.e. DA, using available data sources: EHR data, openly accessible or proprietary ICSR databases, observational databases etc.</p> <p>Furthermore, via the investigation of the signal’s Mechanism of Action (MoA), suspicious biochemical pathways would be identified. The pathways would be further investigated using openly accessible pathway information databases (e.g. Reactome(Fabregat et al., 2018)) or PGx data sources (e.g. PharmGKB(Barbarino et al., 2018)).</p> <p>Regarding the management of a patient per se, the PCBRR would be calculated using his/her own personal data along community based data and could practically affect clinical decision making.</p>	<p>IT scientist, Doctor, PV expert</p>	<p>BP1, BP2, BP3, BP5, BP7</p>	<p>UG1, UG2, UG3, UG4, UG5, UG6, UG7, UG9, UG10</p>
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<p><i>K2P – Knowledge to Performance</i></p>	<p>K2P would refer to the production of data informed conclusions, based on the D2K phase. K2P would potentially include the elaboration of the outcomes of the D2K phase, in order to update the applied practices.</p> <p>For example, the locally applied CPGs could be updated based on the produced knowledge and potential inconsistencies should be early identified and resolved. Such a process could reflect special needs based on the respective clinical setting (e.g. the specific clinic, patient cohort etc.).</p> <p>Another approach could be to use an e-Prescription warning system, providing alerts in order to prevent adverse reactions. These alerts could be based on a (semi)automatically updated rule base based on the mined knowledge and the patient’s personal characteristics. As part of this workflow, novel analytic approaches could also be used to inform the clinician’s decision making process (Lamy et al., 2017).</p> <p>Finally, the calculation of PCBRR could also significantly affect clinical decision making which is obviously related with “performance”.</p>	<p>The D2K phase could identify novel features of the investigated PV signal, which could be used to update the respective drug administration/prescription practices. For example, a warning focusing on patients with specific phenotypic characteristics could be raised.</p> <p>Furthermore, measurable biochemical/genetic features which could be measured via lab tests could also be identified as relevant with the investigated PV signal, based on the use of biochemical/pathway information databases and also individual information (PCBRR calculation).</p> <p>Such an analysis could ultimately enhance the overall analysis of the specific PV signal via the use of these lab test values or identify the need to include these tests in future CPG updates.</p>	<p>Manager, Doctor, Nurse, PV expert</p>	<p>BP1, BP2, BP3, BP7</p>	<p>UG9, UG10, UG12</p>
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<p><i>P2D – Performance to Data</i></p>	<p>Hopefully, adjustments in the overall applied practices would also lead to measurable performance improvements. To this end, specific Key Performance Indicators (KPIs) could be used to quantify and evaluate the improvement of the overall performance due to the updates of the applied practices. These KPIs could be based on standard DA metrics or even provide a simple comparative statistics environment to evaluate the potential impact of these approaches.</p> <p>Furthermore, the calculated data could also feed the next iteration of the LHS circle, providing input to the D2K part.</p>	<p>Such KPIs in the case of a PV signal evaluation could include improved ADR reporting ratios using well-defined statistic metrics typically used for DA purposes (e.g. Reporting Odds Ratio – ROR, Proportional Reporting Ratio – PRR etc.).</p> <p>Regarding the use of these data as feed for the next LHS cycle iteration, as the application of a specific rule raising alerts for potential ADRs might improve metrics for a specific patient cohort, it could still worsen things for another cohort. This is crucial data/information which could be combined with other data sources and generate new knowledge as part of the following D2K step.</p>	<p>Manager, PV Expert, IT Scientist</p>	<p>BP3, BP7</p>	<p>UG7, UG12</p>
<p><i>Disseminating back to community</i></p>	<p>Communicating knowledge as it comes up needs to be done in a systematic and also an agile fashion. While the quality of the knowledge artifacts is of paramount importance, still, communicating non-validated knowledge might be crucial as it might facilitate its verification and it could also provide hints in various contexts.</p>	<p>In the case of a PV signal investigation, early publishing of DA metrics (e.g. ROR) could be of high importance. As time goes by and new data come up, these metrics and potential conclusions should be updated accordingly, enriched with contextual</p>	<p>IT professional, Manager</p>	<p>BP7</p>	<p>UG16, UG18</p>

	<p>Typically, scientific knowledge is disseminated via scientific journal publications, susceptible to various kinds of biases. In the PV context, it is sometimes also published via more informal communication channels (e.g. newsletters, web sites etc.). These communication channels need to be improved in terms of (a) time needed to publish data or conclusions, (b) enabling a systematic update of data in an iterative fashion as time goes by and the evidence get updated, and (c) highlight contextual information (e.g. special characteristics of the investigated patient cohort or the hospital producing the data etc.), while still ensuring quality.</p> <p>To this end, large “networks” of clinical or research institutions (among other communication means) might act as a bidirectional communication channel and more actively used in order to increase the produced knowledge’s value and also speed up its potential course to clinical practice. Finally, special care should be taken to include patients in this communication loop.</p>	<p>information which provide insights for the specific datasets.</p> <p>Even when information is only providing first clues and are not enough to produce verified conclusions, their early communication might be very important as they could add up in the context of “network” of institutions and therefore provide a signal for more thorough investigation.</p> <p>It should be noted that, including patients in the communication ecosystem is crucial as raising awareness among them, might (at least partly) mitigate the widely identified problem of ADE underreporting(Paudyal et al., 2020)</p>			
<p>Transparency</p>	<p>Transparency should be considered a concept that cuts through all the components of the envisioned AP information lifecycle, ensuring that all data supporting a hint or a conclusion</p>	<p>Communicating data and the relevant processes applied in order to support the analysis of a PV signal is crucial as they could make a huge difference regarding the</p>			<p>UG14, UG16</p>

	<p>could be accessible or adequately described in order to evaluate it.</p> <p>Beyond data, all the processes should also be transparently documented as they could significantly affect data quality.</p> <p>The need for transparency should be balanced using well elaborated legal and ethics frameworks, ensuring patient privacy (first of all) and considering also all potential information security threats.</p> <p>It should be highlighted that transparency is crucial for the overall acceptance of the respective computational methods, as clinicians, who ultimately take the responsibility for patient care, would not accept “black-box” approaches as they do not enable the clinical data interpretation end-users are less likely to trust algorithms whose workings they do not understand.</p>	<p>credibility of the produced conclusions.</p> <p>In the case of a PV signal, published data could include carefully anonymized EHR data and references to other data sources which have been also used in the overall analysis process. In terms of the processes applied, the respective metrics should be clearly defined and also tools used for the analysis (e.g. software applications/packages etc.) should be referenced.</p> <p>Communicating PV signal or other drug safety information to patients needs to be done based on a risk-benefit management approach in order to prevent false alerts which might cause irreversible impressions, ultimately leading to decreased patient adherence to medicine subscriptions. To this end, PCBRR should also be transparently related and clearly linked with original information sources/raw data to facilitate its interpretation.</p>			
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5.3.Challenges and steps forward

Even though the AP-LHS paradigm seems to be compatible with the UGs identified in this thesis, the challenges of the proposed paradigm shift should not be underestimated. To this end, we consider that the UGs and the BPs identified as part of this thesis could provide useful insights and facilitate the next steps toward attaining the vision of integrating AP as part of an LHS. Technically, we argue that the adoption of KE computational approaches and KE-based tools might be crucial for this vision as they could provide the technical infrastructure to support this vision.

More specifically, the identified challenges can be summarized as follows:

- *Mentality change* of the various stakeholders (doctors, nurses, patients, regulators, policy makers etc.) is necessary as they will have to adopt new tools and adapt to the respective operational processes updates.
- *Management commitment* is a top priority in the proposed paradigm shift as the identified BPs will have to be updated to include the use of new IT tools and the exploitation of new data sources. Such a change will inevitably require adaptations in everyday work; management commitment is absolutely necessary to tackle potential resistance against that and mitigate the rising risks.
- *Funding* is also a crucial parameter as investments on new infrastructures, i.e. IT enterprise systems, are required. The quantification of the return on this investment is far from trivial as this needs to be done on a, mostly, hypothetical base.
- *Biases* are ubiquitous and affect decision making processes. As explained in (Bate et al., 2018) new data sources come with new kinds of biases. These could affect various parts of the overall data analysis and therefore introduce bias in various parts of the envisioned AP circle. For example, while DA statistical metrics (e.g. PRR, ROR etc.) might have been refined for SRSs, these need to be updated or even completely rejected for observational healthcare databases or social media. Moreover, results reporting could also be challenging, especially if AI and ML are involved (Callahan et al., 2020) (Bates et al., 2020b).

- *Interoperability* is still an open technical and management issue (Shull, 2019), despite the vast development of standards, reference software implementations etc. While these initiatives can be considered (at least partially) successful, still the simple fact of retrieving the consolidated Personal Health Record of a patient or even a Patient Summary from another hospital cannot be considered standard practice, mainly due to legal issues and lack of trust between the various stakeholders.
- *Usability* of IT systems, especially regarding “intelligent” systems engaged in clinical processes is clearly identified as a challenge and as a significant priority according to the UGs described in this thesis. Integrating various heterogeneous data sources increased the risk of having end-users overwhelmed by big data. Furthermore, issues like *over-alerting* for potential drug safety issues should also be highlighted in terms of integrating modern IT tools in clinical practice.
- *Information security* could always be identified as a challenge when data sharing is involved and should be highlighted as data sharing is a crucial part of the proposed vision of AP acting as part of a wider LHS paradigm.

While no silver bullets exist, certain measures things could facilitate tackling the above challenges. The main axes of steps forward, also depicted in Figure 22, could be summarized as follows:

- *Education* and the *dissemination* of real-world success stories could play an important role in promoting the mentality update.
- *Collaborating networks* between organizations trusting each other could be an important step to potentially increase clinical data exchange. Suchlike networks (e.g. the OHDSI research network) have worked successfully towards the use of multiple hospital data for observational studies, while still respecting legal and patient privacy requirements.
- *Updated operational/business models* should be adopted focusing on both the operational as well as the funding/reimbursement aspects. For example, the adoption of finance models based on data sharing economy could facilitate the adoption of the proposed paradigm as they could potentially enhance management commitment and also provide new funding opportunities. Furthermore, operationally, new ways of work should be pursued (e.g. the

transparent and agile maintenance of “live CPGs” instead of the stiff CPG lifecycle applied today).

- A *Social Impact Analysis* could be engaged in order to evaluate the overall risk-benefit ratio based on each clinical setting’s special characteristics (e.g. type of patients, regulatory/legal context, security needs etc.).
- A *Patient Safety Cybersecurity Framework* should be defined, engaging a thorough a threat analysis process aiming to translate potential technical information security threats to patient safety threats. Such a framework should be based on widely accepted ethics and technical security analysis frameworks.
- Finally, engaging a robust *Medical Technology Evaluation Framework* in order to increase trust in the new IT tools is crucial. As explained in (Hauben et al., 2018), engineers should move beyond proving the proposed tools’ value via data science, and proceed to concrete clinical evaluation of the respective IT tools (e.g. via a clinical trial style validation) in order to prove and quantify the proposed tool’s impact.

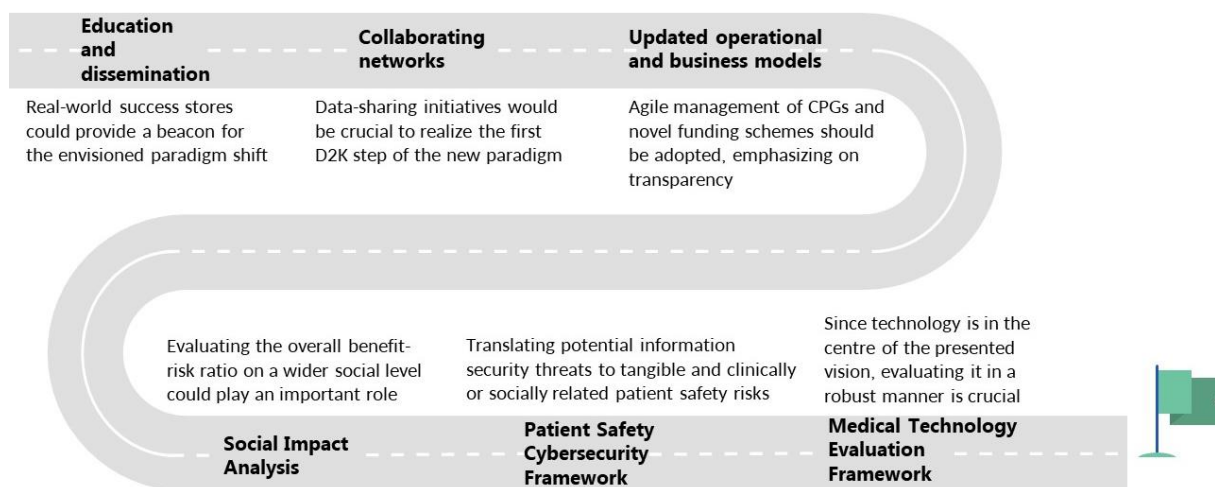


Figure 22: The steps-forward towards the realization of the envisioned AP-LHS paradigm shift

Furthermore, we argue that KE related computational approaches could provide solutions and facilitate tackling (at least partly) the identified technical challenges. For example, the Linked Data and the Semantic Web paradigms, i.e. the use of OWL/RDF ontologies, could enhance semantic interoperability. Furthermore, new data models enabling data space

expansion in a practical manner could be deployed, using ontologies (for example OpenPVSignal is an ontological model built in order to enable the integration of free-text PV signal information(Natsiavas et al., 2018a)). Similarly, ontological models could facilitate the integration of pharmacogenomics, pathway information, lifestyle information etc.

More specifically, the advantages of focusing on KE approaches for each one of the three branches of the AP-LHS circle can be summarized as follows:

- *D2K: Data to Knowledge*

KE approaches can significantly facilitate *integration* of data from various data sources in a unified computationally exploitable format. Furthermore, knowledge *extraction* methods (e.g. NLP on real-life data or other source) could (semi)automatically feed the AP-LHS circle with the required Knowledge.

- *K2P: Knowledge to Performance*

Disseminating Knowledge in a timely and interoperable manner is crucial in order to improve Performance. To this end, representing Knowledge using well defined standards, ensuring both syntactic and semantic interoperability, could have a significant impact on how this Knowledge is integrated in IT tools to increase performance and also on how it is disseminated to stakeholders (e.g. HCPs).

- *P2D: Performance to Data*

Integrating data via multiple data sources in order to measure potential impact and integrate this quantified impact in the data used to feed the next cycle of AP-LHS paradigm. Moreover, Knowledge produced as part of the K2P branch might be integrated in the whole process via specific Knowledge models (e.g. unconfirmed PV signals might feed the D2K branch via OpenPVSignal model (Natsiavas et al., 2018a)).

Finally, it should be highlighted that KE technical approaches could also enhance *transparency*, a horizontally dissecting aspect of the proposed vision which should be supported via specific organizational and technical measures in order to increase trust in the various component of the AP-LHS cycle. Indicatively, three technical approaches are presented, tightly

related with RDF/OWL technical stack and Linked Data/Semantic Web paradigms, i.e. among the most prominent KE-related technical paradigms:

1. The application of *FAIR principles* (Wilkinson et al., 2016) has been identified as a key step towards transparent data management. Practically, applying FAIR principles can be very well supported by RDF/OWL semantic models (Natsiavas et al., 2018a).
2. Data annotation using OWL/RDF semantic models using widely accepted reference terminologies/ontologies/thesauri could be crucial in terms of both technical and semantic interoperability but also transparency. This annotation could be supported also by NLP processes.
3. Technical frameworks supporting *data ownership and sharing* could also play a prominent role. For example, SOLID framework⁶⁴ enables data ownership and dynamic data sharing based also on RDF.

It should be noted that the respective KE technologies referenced here are relatively mature e.g., Linked Data and Semantic Web related technical standards which are actively supported for the last 20 years. Furthermore, Knowledge extraction techniques (e.g. NLP) are actively investigated and have already been (at least partly) successful, also for drug safety purposes (Natsiavas et al., 2019b). Therefore, at least in principle, the core KE technologies are in place, ready to support the vision of AP-LHS.

Practically, in order to quantify the impact of a potential application of the presented AP-LHS vision, a research project emphasizing on its pilot application in real-world conditions could be outlined. Such a project would focus on the following three axes:

- (a) identify and quantify the gaps towards the AP-LHS vision in localized settings

While this is (at least partially) covered in the current thesis, the gaps identified and the respective user goals need to be analyzed in greater detail and prioritized based on the local characteristics of the respective pilot sites. To this end, various pilot sites should be taken into account in order to produce generalizable results. As a whole, the application of AP-LHS paradigm could be evaluated in terms of operational benefits

⁶⁴ <https://solid.mit.edu/>: While SOLID is not built aiming specifically for health-related information management, it could very well support such data management schemes.

using a Care Delivery Value Chain (CDVC) based model (Porter and Olmsted Teisberg, 2006).

(b) provide the necessary technical toolkit to support it

While in principle the technologies exist, still tools aiming to support AP need to be built emphasizing on end-user usability. These tools, need to aim at covering the respective gaps and prioritize features based on the local needs of each site. Usability should be identified as a first class priority, hence, the barriers towards the adoption of the respective tools could be evaluated against FITT framework (Ammenwerth et al., 2006) and/or other Health Technology Assessment (HTA) methodological tools (Vis et al., 2020)

(c) create the necessary methodological tools

Definition, calculation and validation of the respective metrics (e.g. community wide KPIs, or Patient-Centric Benefit-Risk Ratio – PCBRR) is far from trivial. Therefore, special provision should be taken on how these metrics will be designed and validated, applying a “clinical trial” rationale, carefully evaluating each technical or operational intervention. For example, the application of PCBRR should be compared with advanced DA based algorithms (e.g. VigiRank (Caster et al., 2017)) in order to quantify the potential benefits.

6. Future work paths

As this thesis evolved, a number of future work paths were identified and actively investigated. These mostly refer to non-yet validated technical work which requires more time and goes beyond the scope of this PhD. More specifically, two technical work paths (i.e. (a) the building of a knowledge graph upon the OpenPVSignal model, and (b) the building of an ontology aiming to support Systems Pharmacology), were elaborated as we argue that they could provide significant value in the integration of AP vision in the clinical environment. As such, we highlight them as two clear future work paths that could highlight how to use KE approaches in order to bring AP in real-world applications.

6.1. OpenPVSignal Knowledge Graph

PV signal information is typically published by DSMOs after being thoroughly investigated by expert groups who combine information from relevant data sources and possibly from different countries (e.g. scientific literature, clinical trials, similar drugs' safety information etc.) in order to provide insights into the signal "strength" and what could potentially be the causal relationship between the drug and respective adverse effect. Obviously, this information is invaluable for drug safety activities in all stages of a drug life-cycle.

PV signal reports are typically, published in a free text "unstructured" format (e.g. in pdf files, web pages, newsletters etc.) describing the implicated drug/drugs characteristic, the respective adverse effect and reports for patients affected by the specific ADR, potentially including a statistical analysis supporting the need for specific signal investigation. They also refer to a potential "mechanism of action" which could explain the ADR and any other information that could be relevant, either "strengthening" or "weakening" the signal.

Since the current textual format of PV signals cannot be processed automatically, drug safety experts have to review the relevant PV sources manually, a laborious and potentially error prone process. As such information/data could play a significant role in drug safety activities, we argue that their publication in a format compliant with the FAIR principles could enable their systematic reuse, including (semi)automatic processing and reasoning. To address this issue, we have recently developed and published OpenPVSignal (Natsiavas et al., 2018a), to facilitate the normalization, dissemination, interlinking and verification of ADR signal

information in a FAIR compliant manner, based on Semantic Web and Linked Data paradigms also enabling automatic reasoning upon the OpenPVSignal model and Web Ontology Language (OWL) semantics.

To this end, we have started the development of an OpenPVSignal-based Knowledge Graph, modelling the PV signal information reports, produced by WHO-UMC as part of their bi-monthly newsletter for the last ten years (between 2011-2019)⁶⁵. WHO-UMC PV signal reports are based on the individual case safety reports (ICSCRs) collected in VigiBase and they are manually elaborated by expert groups⁶⁶, providing one of the most valuable data sources for PV signal information. We argue that publishing these PV signal reports in a FAIR compliant manner, while also supporting automatic reasoning upon them via the semantics of the OpenPVSignal model per se and the semantics provided by OWL, could significantly increase the value of this already highly valuable information.

The quality of finally produced KG was the main concern during the “transformation” or “mapping” process of the respective PV signal information from their original unstructured free-text format to an OWL based KG. Therefore, it has been decided that the overall process should be based on well-established KE approaches and engage at least two persons, also evaluating its completeness and quality independently. To this end, the KG construction methodology is not based on automatic processes which could be used in principal, e.g. Natural Language Processing techniques, but rather on a tedious work conducted manually.

⁶⁵ <https://www.who.int/medicines/publications/newsletter/en/>

⁶⁶ <https://www.who-umc.org/research-scientific-development/signal-detection/signal-detection-at-umc/>

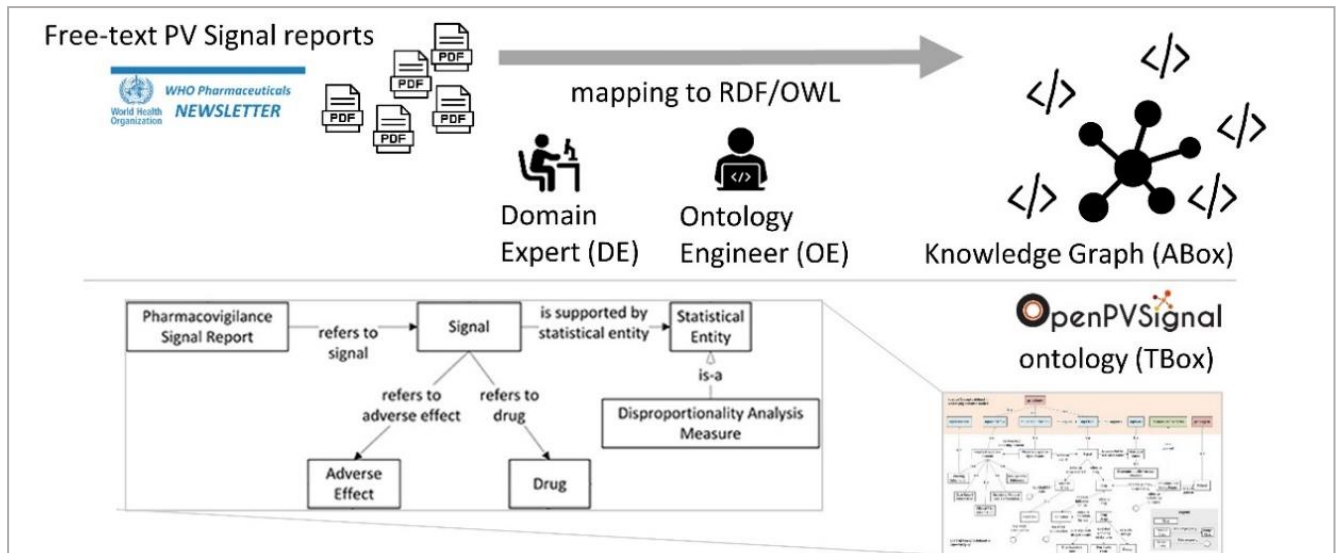


Figure 23: Overall rationale - Upper part corresponds to the building of the Knowledge Graph (ABox) presented in the paper, bottom part corresponds to the Ontology part (TBox) (out of this paper's scope)

Along the lines of modern Ontology Engineering approaches (e.g. the NeOn methodology (Suárez-Figueroa et al., 2012) and the SAMOD methodology (Peroni, 2017) the construction of the presented OpenPVSignal KG is currently done by (a) an “Ontology Engineer (OE)” with Medical Informatics background and one of the OpenPVSignal model implementers, and (b) by a Pharmacologist acting as a “Domain Expert” (DE) regarding PV.

More specifically, the methodology applied can be summarized in the following two main steps:

- Step 1 - Construction

Initially, the free-text PV signal information has been converted to a structured RDF format based on the *OpenPVSignal* ontological model, using the Protege tool (Musen and Protégé Team, 2015). This step was conducted by the DE, in order to gain both qualitative and quantitative insights into the raw data as a whole. Based on the qualitative insights gained, a set of minor modifications on the OpenPVSignal ontology was proposed by the DE and implemented by the OE. It should be noted that in order to validate the overall process of the RDF KG construction, this has been checked as an independent process per se. More specifically, 10 random free-text signal reports (out of a total of 107) have been converted to RDF independently by the OE and compared against the respective conversions produced by

the DE. While such a conversion process inevitably includes subjective decisions, these were only minor and were mostly resolved via discussion, including both DE and OE

- S2 - Quality control

The quality control of the produced KG is based on two pillars:

(a) Technical validation

Based on the insights provided via Step 1, the DE provided a list of simple validation checks focusing on the “Completion” of the KG and potential “Error detection”. These rules are further elaborated and implemented as SPARQL queries and disjoint axioms by the OE, and are run as tests upon the produced RDF data in order to validate the presented KG in line with established KE approaches (Paulheim, 2016; Peroni, 2017). Furthermore, graph-based metrics as defined in OntoQA methodology (Poli et al., 2010) have also been used to quantify and evaluate the produced KG characteristics.

(b) Qualitative evaluation

Each of the signals transformed in OpenPVSIGNAL format by the DE, has also been validated by the OE, both in terms of running the technical validation tests, but also in terms of comparing the produced RDF with the original PV signal reports, to cross check for potential errors or biases. To this end, the produced KG was also verified for interlinking with other terminologies/ontologies of the field, i.e. MedDRA and ATC.

While the building process of OpenPVSIGNAL KG is currently a work in progress and will not be completed in the context of this PhD, it is highly relevant with the presented vision of the joint AP-LHS paradigms. More specifically, such a KG could significantly contribute to the expansion of data space used for PV, enabling the “automatic” integration of a high-quality PV signal information in relevant IT tools and, as such, could be an important technical asset.

6.2. Systems Pharmacology

As identified in the Systematic Review presented in State of the Art, PV in the clinical environment could be significantly improved via the engagement of emerging data sources, including information on the pharmacological Mechanism of Action (MoA). Biochemical,

genetic, pathway information and pharmacogenomics data sources are part of this emerging data sources ecosystem. As the analysis of personal biochemical and genetic profiles is becoming cheaper and part of an overall “Personalized Medicine” vision, exploiting such data sources in the context of PV, combined with other clinically relevant data (e.g. lab test results) would support the “Personalized Pharmacovigilance” paradigm. To this end, *Systems Pharmacology (SP)* could be the knowledge link, providing the means to integrate heterogeneous data of variant granularity, via models which could be useful for computational purposes.

SP is defined as “*a hybrid, multi-scale modelling approach that seeks to combine systems or network-based structures with basic principles of pharmacokinetics and pharmacodynamics (PK/PD)*” (Mager and Kimko, 2016). The SP paradigm refers to the use of multi-scale models, i.e. from low-level biochemical information regarding the behaviour of molecular structures, to more abstract information potentially regarding PK/PD behaviour of the drug, or even its phenotypic results. These models are typically based on mathematics, systems or network-based principles, employing pharmacokinetics and pharmacodynamics and/or also empirical or experimental knowledge. The ultimate goal of SP is to facilitate the in-silico application of algorithmic approaches for enabling computational simulations regarding drug effects. Such simulations could significantly reduce necessary time, costs and patient risks, and therefore play a major role in several drug development or drug safety related scenarios (Knight-Schrijver et al., 2016) (e.g. investigation or prediction of PV signals, drug repurposing etc.). For example, SP models have been used to describe complex patterns of drug action (i.e. synergy, oscillatory behaviour) and disease progression (i.e. episodic disorders) (Danhof, 2016). It should be noted that PV has been identified as a prominent application of SP modelling approaches (Zhichkin et al., 2012) (Huang et al., 2011), also under the prism of enabling mechanism-based drug safety evaluations (Sinha et al., 2016).

In this context, several computational approaches emerge as prominent paradigms in the SP realm (e.g. Discrete Dynamic Modelling – DDM (Steinway et al., 2016), enhanced Pharmacodynamics – ePD (Bouhaddou and Birtwistle, 2016), Physiological Control Systems – PCS (Khoo et al., 2016) etc.). Most of these models are related with detailed mathematical representations of biochemical processes, typically using differential equations approximating

a PK/PD behaviour, and to this end, the use of term *Quantitative Systems Pharmacology (QSP)* is widely used, sometimes interchangeably with the term SP⁶⁷.

One of the most neglected formal modelling approaches in the context of SP concerns the use of State-based models (originating from Control Systems Theory (CST), like *State Machines (SMs)* or *Automata*. SM models are often considered a sub-domain of CST but rather than using the concept of *transfer functions*, SMs are defined upon *states* and *transitions*. In a system modeled using SMs, each new *input* potentially leads the system to another *state* via a *transition*. In general, the transitions between the various states depend on the system's last n states and the last y inputs, having $n=1$ and $y=1$ in the simple case. SM models are usually represented using transition tables or graphs (states are represented with circles and transitions are represented using arrows). Finite State Machines (FSMs), Deterministic State Machines (DSMs), Non-Deterministic State Machines (NDSMs), Fuzzy State Machines (FuSMs), Timed State Machines (TSMs) and Probabilistic State Machines (PSMs) are widely used of SM subtypes. A similar modelling paradigm (frequently considered as a subcategory of SMs) is the *Markov Model (MM)*, defined as a stochastic model describing a network of potential system states, in which the probability of the system to reach a specific state depends on the previous system states.

We argue that State-based models (SBMs) enable the representation of transitions based on **probabilistic** approaches and the use of **time** as a principal modelling dimension, and, therefore fit in the context of real-world applications regarding PV or pharmacology in general. Indeed, as the concepts of *state*, *input* and *transition* fit with the general paradigm of the administration of a drug acting as a triggering event (*input*) causing a biochemical turbulence (*transition*) leading to a new biochemical (or physiological) *state*. Typically, these sequences of various “states” in pharmacology and biology are referred to as “pathway information” and have been used to elucidate drugs’ MoA among other use cases. SBMs (e.g. SMs and MMs) have a huge advantage compared to typical QSP computational models, as they do not necessarily depend on quantitative models (e.g. differential equations) which are very difficult to produce and validate, while they could still include them as part of the overall states transition model. SBMs could use such well-defined mathematical models (when available) but could also be used to exploit non-quantitative or empirical expert knowledge regarding the

⁶⁷ In this manuscript, we explicitly and on purpose avoid the use of term *Quantitative Systems Pharmacology* as we consider it a subdomain of SP.

behavior of biological systems. Since most of the well-validated domain knowledge in pharmacology and biology (i.e. PK/PD behavior of a drug) cannot be quantified in detail and validated (or at least it is very hard to do so as it heavily depends on wet biology approaches), the use of such models in the context of SP is invaluable. As most of the prominent drug information data sources (e.g. DrugBank (Wishart et al., 2018), PharmGKB (Barbarino et al., 2018) and others) describe various aspects of the drugs' MoA without providing a detailed mathematical description, SBMs could be used to model such knowledge and use it in well-defined algorithms, without the need for quantifying the respective biochemical processes.

Furthermore, we argue that Semantic Web technologies and Ontologies used as the technological infrastructure to exploit these models could also provide significant computational advantages, especially regarding data integration and automatic reasoning capabilities.

Consolidating the above, such a model could probably be useful in the context of various applications, beyond drug safety or PV. However, PV is a good choice for an exemplar application of such a data model due to its high clinical importance and the existence of data evidence from multiple (and potentially heterogeneous) data sources.

To this end, we have started working on the so-called *States Pharmacology Ontology (SPO)* as a practical way to integrate the respective data sources in one KG and investigate the respective computational advantages. SPO enables the representation the main SBMs concepts and models in a systematic manner, thus facilitating the combination of Description Logics (DL) and SBMs in one computational framework. The ultimate goal would be to build a KG, based (at least partly) on SPO to combine the power of DL reasoning with the SM modelling to identify potential ADRs on a personalized basis, based on personal data (e.g. lab tests, genetic profile etc.) and also the ADR mechanism of action information. To this end, pathway information including Pharmacogenomics (i.e. information provided by PharmGKB) will be used as the primary data source used to instantiate the produced KG due to the following reasons: (a) it provides pathway information in an OWL format i.e. BioPax (Demir et al., 2010), and most importantly, (b) it provides a clear link with clinically applied guidelines, i.e. the ones elaborated by Clinical Pharmacogenetics Implementation Consortium (CPIC) (Relling and Klein, 2011). It should be noted that the value of PGx for clinical purposes has already been

identified and research initiatives like eMERGE network⁶⁸ already plan to develop CDSS based on PGx information (Herr et al., 2019) (Gottesman et al., 2013). In this context, ontological and automatic reasoning approaches have already been investigated to some extent, identifying both advantages and practical challenges (Samwald et al., 2015).

The process of SPO development is currently a work in progress and, similarly with the OpenPVSignal KG, it will not be completed in the context of this PhD. However, we argue that this is highly relevant to this thesis as the building of such an ontology could interlink PV in the clinical environment with the MoA information, via personal lab test values, thus enabling the building of KGs and the reasoning upon them.

⁶⁸ <https://www.genome.gov/Funded-Programs-Projects/Electronic-Medical-Records-and-Genomics-Network-eMERGE>

7. Conclusion

In this final section, the thesis contents and its main contributions are briefly summarized.

A “design thinking” based methodology was applied in the context of the PVClinical project in order to investigate the potential impact that KE computational methods could have on the revision of the PV processes in the clinical environment. More specifically, in the PVClinical project, a web platform is developed aiming to facilitate the investigation of potential PV signals, using KE as its main technical paradigm. While the technical developments of the platform development are considered to be out of scope for the current thesis, a number of objectives were identified regarding the revision and clear definition of AP and the impact the KE computational approaches could have on that. Finally, two technical pathways of work were actively investigated, outlining two future research paths in terms of employing ontologies to build KGs which could support DS and AP purposes.

Summarizing the contribution of the presented thesis, the following key points could be highlighted:

- A detailed qualitative and quantitative analysis of the research trends of the last decade regarding the use of KE for DS purposes has been depicted via a thorough Systematic and Mapping Review of the respective scientific literature.
- Based on this Systematic Review, *research gaps* have been highlighted
- A set of BPs related with the PV has been defined and elaborated, taking into account the legal and regulatory context
- A set of UGs were identified based on the respective BPs and the input from HCPs and PV experts
- AP was redefined as part of a wider LHS paradigm, based on the latest technical developments
- PCBRR was outlined in terms of data sources which could be used to support a personalized PV approach in the context of the proposed AP-LHS paradigm.

In conclusion, we argue that this new paradigm (and potentially the elaboration of the intermediate outcomes of this thesis, i.e. the identified BPs and UGs) could bring significant

benefits to the following aspects and therefore it should be actively investigated in terms of policy making:

- *Healthcare quality* would definitely be improved as the proposed adoption of LHS principles and technical measures could reduce the research gap and provide benefits regarding drug safety among other domains
- *Drug development* processes would be accelerated and their costs could be reduced as the availability of “real-world” data would significantly increase, facilitating the “in-silico” clinical trials rationale via observational health studies
- *Healthcare cost* effect is not easily estimated. However, given the huge cost of ADRs in today’s modus operandi, we argue that the investment of adopting new technologies and adapting operational processes should be beneficiary.

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