

Involvement Level of Electronic Records in Studies Considering Sex Differences in Adverse
Drug Reactions: A Scoping Review

by

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A Project Submitted in Partial Fulfillment
of the Requirements for the Degree of

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Supervisory Committee

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Abstract

Objective

The purpose of this study is to evaluate “level of involvement” of electronic records and their tools with witnessed sex differences in adverse drug reactions, by reviewing scope of current relevant literature.

Methods

We conducted a scoping review of literature published from 1990 to Sep 2016 on studies that involved electronic records, and as part of their results, indicated “sex differences in adverse drug reactions”.

Next, we analyzed current level of usage of electronic records according to gender patterns of ADRs, and also pictured unused potentials of them in preventing adverse drug reactions considering patterns in sex differences.

Results

From 9829 located articles, 46 met inclusion/exclusion criteria. Electronic records in these studies have mostly been used as a data resource either for obtaining general health data about study subjects or at their best, as data repositories of adverse drug reactions’ reports. Despite presenting a gender difference in ADRs with female/male dominance ratio of 32/8 (with 6 studies having a mixed gender results), we couldn’t locate studies suggesting a preventing role for electronic records in adverse drug reactions.

Conclusion

Electronic records are holding huge amounts of aggregated data, and are playing a progressively major role in multiple aspects of healthcare management, including medication prescription.

Concealed embedded patterns in this data should be exposed in forthcoming studies and considered in implementing decision support systems. This is in fact part of the efferent side of a learning healthcare system, in which the analyzed and interpreted data is fed back into the system to deliver tailored messages to decision makers and eventually make a start to change the practice; in this case adding preventive elements at the point of medication prescription, in order to foresee and decrease adverse drug reactions.

Table of Contents

Supervisory Committee.....	2
Acknowledgments.....	3
Abstract.....	4
Objective.....	4
Methods.....	4
Results.....	4
Conclusion.....	5
Table of Contents.....	6
List of Tables.....	7
List of Figures.....	7
Acronyms.....	7
Project Organization.....	8
Chapter 1: Introduction.....	9
Background and Rationale.....	9
Research Aim.....	12
Ethics.....	12
Deliverables.....	13
Chapter 2: Methodological Framework.....	14
Stage 1: Research Questions.....	14
Stage 2: Article Identification.....	15
Stage 3: Article Selection.....	16
Stage 4: Data Charting.....	18
Stage 5: Results Collection, Summarization, and Report.....	20
Chapter 3: Discussion.....	30
Chapter 4: Conclusion.....	33
Bibliography.....	35
Appendix.....	42

List of Tables

Table 1- Study Selection Statistics.....	16
Table 2- General and Specific Categories of Studies.....	20
Table 3- Type and Functions of "Electronic Records" in Studies.....	27

List of Figures

Figure 1- Study Selection Flow Diagram.....	17
Figure 2- Studies by Outcome and Adverse Event.....	22
Figure 3- Studies by Outcome and Electronic Record.....	23
Figure 4- Studies by Location and Electronic Record.....	24
Figure 5- Studies by Year and Location.....	25

Acronyms

ADE: Adverse Drug Event
ADR: Adverse Drug Reaction
AE: Adverse Event
AERS: Adverse Event Reporting System
ALS: Automatic Laboratory Signals
CDSS: Clinical Decision Support System
CMR: Computerized Medical Record
CPOE: Computerized Physician Order Entry
CPR: Computerized Patient Record
CR: Clinical Record
DILI: Drug-Induced Liver Injury
ECR: Electronic Clinical Record

EES: Electronic Expert Support
EHR: Electronic Health Record
EPR: Electronic Patient Record
EPS: Electronic Prescribing System
EPSE: Extra-Pyramidal Side Effects
ER: Electronic record
GP: General Practice
MI: Myocardial Infarction
PMR: Patient Medical Record
SE: Side Effect
SJS: Stevens-Johnson Syndrome
TEN: Toxic Epidermal Necrolysis
UGIB: Upper Gastrointestinal Bleeding

Project Organization

This project has 4 chapters and 1 appendix:

- Chapter 1: Provides research background, aim, ethics and deliverables;
- Chapter 2: Provides methodological framework of the study;
- Chapter 3: Provides comprehensive discussion;
- Chapter 4: Provides conclusion, strengths, and limitation.
- Appendix 1: Ethics waiver emails.

Chapter 1: Introduction

Background and Rationale

According to World Health Organization (WHO) definition, adverse drug reaction (ADR) is “a response to a medicinal product which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy”. By this definition, ADRs occur at “normal” therapeutic doses and do not include medication errors (Ficheur et al., 2014).

As well, adverse drug events (ADE) have been stated as “injury resulting from administration of a medication, including errors in administration” (Lazarou, 1998, as cited in Yu, 2016), which significantly elongate stay, and increase both financial burden and morbidity-mortality risk for hospitalized patients (Classen, 1997, as cited in Yu, 2016).

Yu (2016), concludes that there is increasing evidence of sex differences in ADEs, which may be due to differences in pharmacokinetics and pharmacodynamics (Anderson, 2008, & Whitley, 2009 as cited in Yu, 2016), immunology (Rademaker, 2001, & Tuchinda, 2014, as cited in Yu, 2016), and genetics (Wilke, 2007, & Tharpe, 2011, as cited in Yu, 2016). These sex differences in drug-event combinations for specific drugs, can have preferences either for females (332 out of 736 total ADE signals), or males (404 out of 736 total ADE signals). This review also suggests that identifying these sex differences in ADEs can decrease its occurrence to patients and help for developing personalized medicine, as well as to recommend event reporting (AER) systems (Harpaz, 2012, as cited in Yu, 2016), electronic health records (EHRs) (Harpaz, 2012 & Zopf, 2009, as cited in Yu, 2016), and social media data (Sarker, 2015, as cited in Yu, 2016) as diverse sources for detecting adverse drug events.

In a study (Zopf et al., 2009), based on intensive prospective multicenter drug surveillance, drug

risk was stratified by gender after adjustment by age, number of prescriptions and class of drugs, and the results showed that anti-bacterial and anti-inflammatory medications are associated with significantly more ADRs in women than men, and can be considered high-risk therapeutic agents in females.

Adverse effects that occur in nonhospital settings may lead to emergency department visits and hospital admissions. The mean cost of an emergency department visit without hospital admission has been estimated to range from \$549 to \$704 per ADE, whereas the estimated mean cost of treating an ADE resulting in hospital admission has been estimated to range from \$5118 to \$11789 (in 2014 US currency) (Rodríguez-Monguió, 2003, as cited in Eguale, 2016). In 2004 by analyzing data of 18820 patients, the projected yearly costs for ADRs leading to hospital admissions were 5466m in total (Pirmohamed, 2004, as cited in Iqbal, 2015). Another study in USA collecting data from 1999 till 2006, has reported 2341 related deaths. From 0.08 to 0.12 per 100000, annual mortality has been significantly increasing with a rate of about 0.0058 per year (Shepherd, 2012, as cited in Iqbal, 2015).

Considering an association between a certain gender and specific medications, it's quite reasonable to include gender as a determinant factor while prescribing those specific medications to the higher-risk gender, and implementing this reasoning in electronic prescribing and decision support systems.

Dickinson (2004) has provided an HL7-developed “standardized functional specification for EHR systems (EHR-S)” in three sections of “Direct Care”, “Supportive”, and “Information Infrastructure” to describe more than 60 functions, yet the “sex” content has only been included in two “Direct Care” (DC) functions:

- DC.1.1.2 > Manage patient demographics > “... key demographic information such as

date of birth, sex, and other information is stored and maintained for reporting purposes and for the provision of care.”; and

- DC.2.5.1 > Present alerts for preventive services and wellness > “...age and sex appropriate screening exams, such as PAP smears...”.

A shorter version; HL7 list of EHR functions ("Understanding Features & Functions of an EHR", 2017) consists of 51 basic EHR roles that a number of them relate immediately or eventually to adverse events including ADRs.

- “Manage patient demographics”: Captures and maintains demographic data;
- “Patient specific dosing and warnings”: This function considers patient-specific conditions and characteristics in the course of ordering medications to recognize and present proper dosage recommendations;
- “Manage results”: This task enables the authorized clinical personnel, to review, filter, and compare historical and current test results. This is the case, when ADRs are showing up as abnormal laboratory values, signals, or alerts; and
- “Support for drug interaction checking”: This function detects drug interaction alerts at the spot of medication prescribing. Investigating situations in which ADRs happen, one could notice the concurrence and synergism of drugs’ effects, turning their “additive actions” into “adverse reactions”.

ADRs are a significant public health obstacle, responsible for up to 5% of hospital admissions, 28% of emergency ward referrals, and 5% of hospitals mortality (Liu et al., 2013). Although the majority of ADRs initiating during prescription stage are possibly avoidable (Bates et al., 1995), not all patient’s key characteristics that can support preventing ADRs in this stage, have been noticed and used to their deserved function; one of them, surprisingly basic, the patient’s “sex”.

My interest in this topic originated from watching a TED talk, which pointed out the dangerous side effects of medicine to affect women more than men. This notion brought up a number of queries about its accuracy and reliability, documents for and against it, the way of handling it in workaday healthcare domain, and future approach to it.

Looking at this extended line of inquiry, from a health information point of view, this study has focused on finding the footprints of this outcome (i.e. sex differences in adverse drug reactions) in research studies that used “electronic records” as an implement widely used for documenting, sharing and streamlining patients’ information, as well as providing tools for diagnosis, treatment and decision making.

Studies, which have brought “sex differences in ADRs” and “EHR functionalities” to an intersection, have carefully analyzed and provided new borders for terms like “used in man” and “normal therapeutic doses”, which have been mentioned in WHO’s definition of ADR. The resultant clear-cut horizons are essential in envisioning electronic records’ unused potentials, in pharmacosurveillance and drug safety in the future. This project tends to estimate the scope of such studies.

Research Aim

The purpose of this study is to evaluate “level of involvement” of electronic records with “sex differences” in “adverse drug reactions”, by reviewing the scope of relevant published literature.

Ethics

On December 12th, 2016, an ethics approval request email was sent to “Human Research Ethics Facilitator”. HREF and HREB Chair granted exemption status to this study, and HREB waiver was received on Dec 14th, 2016; “... *research ethics approval is not required*” (Appendix 1).

Deliverables

This project has two deliverables:

- 1) A project report, submitted to the supervisory committee; and
- 2) A PowerPoint presentation, presented in oral exam session.

Chapter 2: Methodological Framework

To find out the extent to which electronic records are performing according to sex differences in adverse drug reactions (ADRs), we thought of two different approaches:

- 1) Direct approach: Getting access to as many as possible electronic records and investigate how this concept has been functionalized in their context; or
- 2) Indirect approach: Exploring studies in which electronic records have played any role, leading to results that address sex differences in ADRs, reasoning that the usage shown for electronic records in published studies is a reflection of factual usage of them.

Due to boundaries in former approach concerning patients' data security, privacy, and confidentiality, this study prefers the latter, and depicts this role of electronic records, through carrying out a scoping review in published literature using Arksey and O'Malley methodological framework (Arksey & O'Malley, 2005) adopting five stages as followings:

- 1) Identifying research question;
- 2) Identifying pertinent studies;
- 3) Selecting articles;
- 4) Charting data; and
- 5) Collecting, summarizing, and reporting results

Stage 1: Research Questions

To bring the main three wings of this study (i.e. electronic records, sex differences, adverse drug reactions) to the crossroad of accomplishing objective of study, and grounded on an initial assessment of the existing literature, following research questions are addressed:

- 1) Is there published evidence of sex differences in ADRs?

- 2) Is there a difference between genders in ADRs?
- 3) What is the current conjunction of electronic records with sex differences in ADRs?
- 4) What are the unemployed potentials of electronic records in dealing with sex difference in ADRs?
- 5) Why should electronic records be used to their full capacities to decrease ADRs?

Stage 2: Article Identification

Scarcity of publications that included both EHR and “sex differences in ADRs” was one particular characteristic of gathering data for this scoping review. To overcome this obstacle, we looked for relevant studies in very preliminary stages of project to estimate the abundance of related studies and assure attaining sufficient number of publications, even before officially starting data collection. Mendeley Desktop 1.17.9 was used to its best capability for part of the articles search process and duplication removal.

These existing publications were searched in following sources:

- 1) Databases (Academic Search Complete, Applied Science and Technology Index, CINAHL, Google Scholar, IEEE, Ovid Medline, PubMed, Web of Science);
- 2) Grey literature (CIHI);
- 3) Mendeley suggests; and
- 4) Random 10% reference lists.

Boolean Search Terms:

- 1) (“adverse reaction?” OR “adverse effect?” OR “side effect?”) AND (drug? OR medication?);
- 2) ((female? OR wom?n) OR (male? OR m?n) OR (sex* OR gender?));
- 3) data OR information; and

- 4) “electronic health record” OR EHR.

MeSH (Medical Subject Headings) Terms:

- 1) (Sex Factors);
- 2) (Drug Hypersensitivity) OR (“Drug-Related Side Effects and Adverse Reactions”) OR (Adverse Drug Reaction Reporting Systems);
- 3) (Medical Records Systems, Computerized) OR (Medical Informatics); and
- 4) (Precision Medicine).

Stage 3: Article Selection:

For selecting eligible articles among studies found by search engines we set our inclusion/exclusion criteria as following:

Inclusion Criteria:

- 1) Utilizing an electronic record as part of the study methodology;
- 2) Evaluating adverse drug reactions as part of results; and
- 3) Providing sex-comparisons in ADRs results.

Exclusion Criteria:

- 1) Non-human studies;
- 2) Non-English language;
- 3) Before Jan 1990 and after September 2016; and
- 4) Case report, thesis/dissertation, Book.

We also decided to include those articles, which covered our main topics, even with different terminologies, because of following reasons:

- 1) When applicable, keywords were entered as MeSH terms, thus results included all terms under that subject heading.

- 2) Terms such as electronic health records vs. electronic medical records, adverse drug reactions vs. adverse drug events, and women vs. females were often used equivalently for research intentions.
- 3) The electronic record's roles in studies were compatible or comparable with our study's objectives, in terms of potentially being able to take part in decision support stage.
- 4) Binding to our very exact chosen keywords led to extremely low, if any number of articles for further analysis.
- 5) Last but not least, all studies retrieved through this strategy were examined cautiously to make sure they satisfy our outlined inclusion/exclusion criteria.

Table 1 and figure 1 represent study selection statistics and flow diagram respectively.

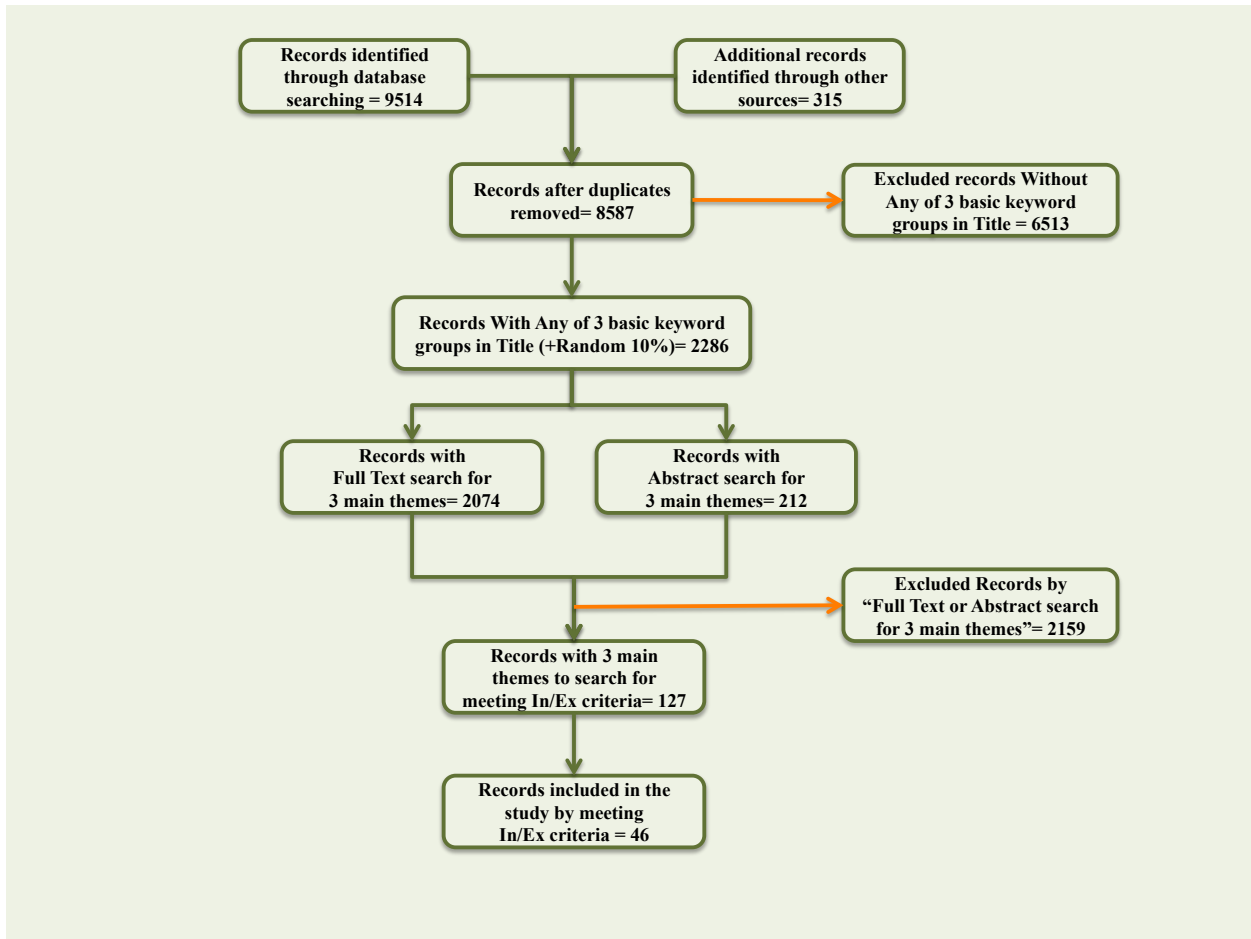
Table 1- Study Selection Statistics

# of studies	ASC	ASTI	CIHI [§]	CINAHL	IEEE	Google	Medline	Mendeley Suggests [§]	PubMed	WoS	Random 10% ref. [§]	Total
Through database search	1505	34	56	422	150	943	4195	47	23	2242	212	9829
After duplication removal	1316	24	56	280	29	837	4142	46	22	1623	212	8587
Including EHR-related keywords in their title <i>(searched for ALL 3 theme keywords in their full text)</i>	18	0	0	0	4	216	169	0	0	1	*	408
<i>(remaining from last phase)</i> Including ADR-related keywords in their title <i>(searched for ALL 3 theme keywords in their full text)</i>	36	1	2	13	13	30	851	13	4	172		1135
<i>(remaining from last phase)</i> Including Sex-related keywords in their title <i>(searched for "electronic" keywords in their full text)</i>	53	0	1	23	0	14	111	0	16	313		531
<i>(remaining from last phase)</i> Containing none of the keyword groups in their title <i>(no further search)</i>	1209	23	53	244	12	577	3011	33	2	1137		6513

*: Abstracts were searched for eligibility

§: Other (non-database) sources

Figure 1- Study Selection Flow Diagram



Stage 4: Data Charting

“Charting” (Ritchie & Spencer, 1994, as cited in Arksey & O'Malley, 2005) is a technique to synthesize and interpret qualitative data by filtering, charting, and classifying material due to key topics and themes, correspondent to “data extraction” is systematic review.

We chose a “descriptive-analytical” method to narrate (Pawson, 2002, as cited in Arksey & O'Malley, 2005) a broader view of the study and besides collecting standard information on each study, record information about process of each study, so that results are scrutinized and more plausible.

We used Microsoft Excel for Mac 2011, and NVivo for Mac 11.4.0 to chart data according to its category, and collated and summarized findings into two main groups (Arksey & O'Malley, 2005):

- 1) General information “about” the article.
- 2) Specific information “from” the article, such as study settings, type of electronic record, and outcomes.

Main areas of information charted are as following:

- General categories (first author, publication year, timespan, location, study setting, study type);
- Objective;
- Methodology;
- Electronic record type and role;
- Outcome (i.e. females, males, or a mixed combination dominance in adverse events);
- Adverse event (type, incidence);
- Biases and limitations; and
- Future research.

Our intention was to keep all 46 studies that covered our three main themes (i.e. electronic record, sex differences, ADR), even though not all of them could provide enough information to fulfill all charting areas (aforementioned in stage 4). Therefore, any possible occasional disparity between the aggregated results of categories and total number of articles (46), is a result of lack of information in relevant category of article and could be justified by citing; “data are not always presented in the most accessible of formats” (Badger, 2000, as cited in Arksey & O'Malley, 2005).

Stage 5: Results Collection, Summarization, and Report

As described by Arksey & O'Malley (2005), scoping reviews tend to present all material reviewed about a topic despite of size of material, in contrast to systematic reviews that include only a small percentage of studies in the final report and leave behind a hidden portion of information to the public.

Our search revealed 46 articles of which we charted information in 19 domains. Subsequently we reported prominent categories of charted data and noticeable associations among these categories in two parts; A and B:

A: First part is merely basic numerical reporting of data and comparisons among categories.

Tables and charts provided in this part posterize general information “about” the article, and part of the specific information “from” article such as but not limited to objective, setting, and ADR type. In second part (B), we organize studies due to different types of electronic records used in the study to further discuss potentials of electronic records in impacting ADRs as a tool of “decision making”.

Following general approach of performing a scoping review (Arksey & O'Malley, 2005), this study neither aims to justify “weight” of evidence provided in the articles, nor attempts to evaluate quality of studies, therefore it cannot ascertain the reader of strength and generalizability of studies’ outcomes.

Table 2 shows studies’ general and specific categories and five diagrams showing association between five pairs of categories.

Table 2- General and Specific Categories of Studies

First Author	Year	Location ¹	Setting	Timespan (months)	Population (patient, record)	AE Outcome (Dominance)	AE Type	AE Incidence (%)	Type R-P ¹²	Type E-O-CCC ¹³	Electronic Record
Akbarov	2015	UK	Hospital & GP	–	205519	Mixed	Medication Hazard	5.54- 7.65	P	Cross-Sec.	EHR
Boland	2015	USA	Clinic, Center	3	70050	Female	ADE (vaccine)	1.76	P	Cohort	EHR
Budnitz	2006	USA	Hospital	24	701547	Female	ADE	2.5- 6.7	P	Observ.	CR ⁹
Chen	2015	USA	Clinic, Center	156	1903	Female	Cosmetic side effects	5.8	R	Observ.	EMR
Classen	1991	USA	Hospital	18	36653	Female	ADE	2	P	Observ.	CMR ⁵
Coloma	2011	DNK ITA NLD UK	A- A- D	144	19647445	Male	Upper gastro-intestinal bleeding	0.03- 0.1	R	Observ.	EHR
Coloma	2013	DNK, ITA, NLD	A- A- D	168	4034232	Male	Acute myocardial infarction	47.6	P	Observ.	EHR
Davis	2015	USA	A- A- D	136	726	Female	Stevens-Johnson Synd. & Toxic Epidermal Necrolysis	14.1	R	Observ.	PMR ⁷
Egualde	2008	CAN	Clinic, Center	4	620	Female	Treatment change orders	21.9	P	Case-Cont.	EPS ⁶
Egualde	2016	CAN	Clinic, Center	60	46021	Female	ADE	0.2	P	Cohort	EHR
Evans	2005	USA	Hospital	120	4291	Female	ADE	N/A	R	Observ.	EMR
Fattinger	2000	CHE	Ward, Department	36	4331	Female	ADR	11	P	Cohort	Database
Ficheur	2014	FRA	Hospital	9	3444	Female	ADE (hyperkalemia)	1.66	R	Observ.	EMR
Genco	2016-2015	USA	Ward, Department	5	2144	Female	Drug alert	38.5	R	Observ.	EHR
González	2011	ESP	Clinic, Center	12	126838	Female	ADR	0.28- 0.43	R	Observ.	EMR
González	2012	ESP	Hospital	6	15534	Female	Allergy alert	12.7	P	Cross-Sec.	EHR
Haerian	2012	USA	Hospital	72	199920	Male	AE	0.34- 0.39	R	Observ.	EHR
Honigman	2001	USA	Hospital	12	15665	Female	ADE	5.52	R	Observ.	EMR
Hug	2010	USA	Hospital	20	1200	Female	ADE	11.75	R	Cohort	CPOE
Iqbal	2015	UK	A- A- D	84	12789	Mixed	Extra-pyramidal side effects	N/A	P	Observ.	EHR
Kidon	2004	SGP	Ward, Department	5	8437	Male	ADR	2.6	R	Case-Cont.	EMR
Kim	2012	KOR	Hospital	12	12483	Female	Hypersensitivity reactions	2.1	R	Observ.	EMR
Kirkendall	2016	USA	Clinic, Center	48	55770	Male	ADE	1	P	Cohort	EHR

First Author	Year	Location ¹	Setting	Timespan (months)	Population (patient, record)	AE Outcome (Dominance)	AE Type	AE Incidence (%)	Type R-P ¹²	Type E-O-CCC ¹³	Electronic Record
Lal	2009	USA	Clinic, Center	19	36	Female	Hypersensitivity reactions	8-45	R	Observ.	EMR
Levy	1999	ISR	Ward, Department	2	199	Female	ADR	32	P	Observ.	ADR detector
Li	2014	USA	Hospital	84	264155	Male	ADR signal	1.4-2.4	R	Case-Cont.	EHR
Macy	2015	USA	A- A- D	36	820124	Mixed	ADR & drug allergy	0.0007-0.002	R	Cohort	EHR
Moore	2009	USA	Hospital	5	456	Mixed	ADE alert triggers	N/A	P	Observ.	EMR
Moskow	2015	USA	A- A- D	12	319051	Female	Drug allergy	9.1	R	Observ.	EHR
Paisansinsup	2013	USA	A- A- D	90	1268	Female	ADR	1.4-2.6	R	Observ.	EHR
Park	2008	KOR	Hospital	10	75996	Mixed	Hypersensitivity reactions	0.05- 1	P	Observ.	EMR
Raimbault	2013	FRA	Ward, Department	6	241	Female	ADR	1.05	P	Observ.	CPOE
Ramirez	2010	ESP	Hospital	12	54525	Male	ALS ¹⁴ signal	0.2	P	Observ.	EMR
Ringqvist	2015	DNK	A- A- D ²	54	73	Female	ADR report	N/A	R	Cohort	ER ³ -Hospital
Roitmann	2014	DNK	Clinic, Center	156	2347	Male	AE	N/A	R	Cohort	EMR
Ryu	2015	KOR	Hospital	27	1335	Female	ADR	47.6	P	Observ.	EMR
Shin	2013	USA	A- A- D	80	1053979	Female	Drug induces liver injury	0.03	R	Cohort	EMR
Tabali	2012	DEU	A- A- D	66	88431	Female	ADR	0.44	P	Observ.	EMR
Tomlin	2012	NZL	Clinic, Center	72	338931	Female	AE	7.4	R	Observ.	ECR ⁸
Tora	2014	SWE	A- A- D	3	180059	Mixed	Drug-related problems	223.7 (<i>alerts</i>)	P	Observ.	EES ¹⁰
Trifiro	2009	NLD	Hospital	3	276	Female	Upper gastro-intestinal bleeding	N/A	R	Observ.	EHR
Trinkley	2016	USA	Clinic, Center	10	701	Female	ADE	9.6	P	Observ.	EHR
Tsang	2010	UK	A- A- D	12	69682	Female	ADE	0.2	R	Cohort	EPR ¹¹
Yildirim	2015	TUR	A- A- D	99	6531	Female	ADE	N/A	R	Observ.	AERS ⁴ database
Zhou	2016	USA	A- A- D	288	1766328	Female	Drug allergy	35.5	R	Observ.	EHR
Zuzana	2012	NLD	Clinic, Center	1	843	Female	ADR	42	R	Observ.	EMR

1) ISO ALPHA-3-Code; 2) Administrative, Authority, Database; 3) Electronic Record; 4) Adverse Event Reporting System; 5) Computerized Medical Record; 6) Electronic Prescribing System; 7) Patient Medical Record; 8) Electronic Clinical Record; 9) Clinical Record; 10) Electronic Expert Support; 11) Electronic Patient Record; 12) Retrospective, Prospective; 13) Experimental, Observational, Case-Control, Cohort, Cross-Sectional; 14) Automatic Laboratory Signal.

Figure 3- Studies by Outcome and Electronic Record



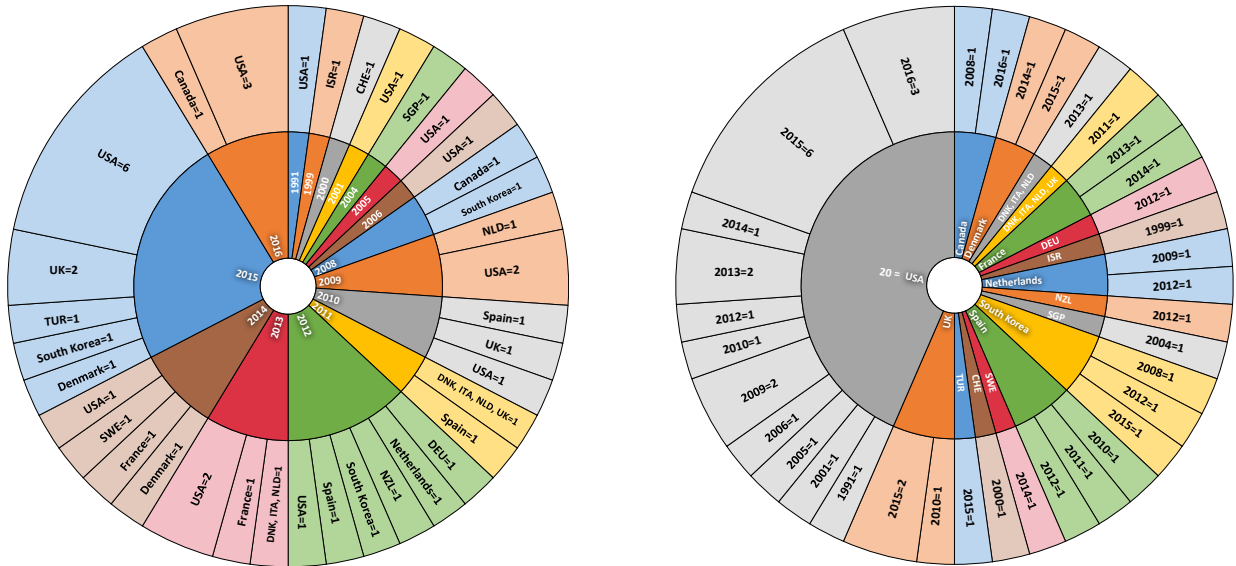
Figure 3 shows types and times of using different “Electronic Records”, in studies according to their outcomes in sex-dominance.

Fourteen variable terms have been used to refer to “Electronic Records”.

According to the number of studies (46), “EHR” has been used mostly (n=17, 37%); followed by “EMR” (n=16, 34.8%); “CPOE” (n=2, 4.3%); and the remaining 11 terms (see acronyms for definition), each being used once (2.2%).

Noticeably, articles with “female dominance” outcomes have used the majority of different terminologies of “Electronic Records” (13 of 14).

Figure 5- Studies by Year and Location



The dual reciprocal diagrams in figure 5 illustrate the first article to be published in 1991 in USA and number of articles in each year.

According to number of publications (46), during the first decade from 1991 till 2000 there are 3 published articles (6.5%); second decade from 2001 till 2010 has contributed 12 articles (26.1%); and 31 articles belong to the era between 2011 till 2016 (67.4%).

Noticeably, majority of articles have been published during 2015 (n=11, 23.9%), and USA has published the largest number of articles (n=20, 43.5%), covering from 1991 till 2016.

According to the type, 26 studies (56.5%) followed a retrospective approach, and 20 studies (43.5%) a prospective approach. All studies had an observational research strategy, with 3 studies (6.5%) being case-control, 8 studies (17.4%) cohort, and 2 studied (4.3%) cross-sectional.

B: In second part of reporting results, tabulated in table 3, we define “electronic record” as unit of analysis, highlighting its diversity in type and describing either its factual or its prospective role in each study. The role has been classified as close as possible to 4 basic functions ("Understanding Features & Functions of an EHR", 2017) aforementioned in background section of this scoping review:

- “Manage patient demographics”: Captures and maintains demographic data;
- “Patient specific dosing and warnings”: Considers patient-specific conditions and characteristics when ordering medications for proper dosage recommendations;
- “Manage results”: Ability to review, filter, and compare the historical and current test results, detecting abnormal laboratory values, signals, or alerts; and
- “Support for drug interaction checking”: To detect drug interaction alerts during prescription and to notice the concurrence and synergism among drugs, turning the “additive actions” into “adverse reactions”.

We also supplemented a fifth category to track referrals of articles to post-discharge strategies interpreted as pharmacosurveillance or treatment outcomes. In forming table 3, the first 2 functionalities have been collapsed into one category.

Noteworthy to emphasize that functions of electronic records in table 3 are taken by their description in studies according to their connection to adverse drug reactions, and we refrain to substitute this referred role as a whole introduction of the electronic record that has been used in setting of relevant study.

Table 3- Type and Functions of "Electronic Records" in Studies

Study	ER Type	Fs: Patient demographics & specific dosing and warnings	F: Manage results	F: Support for drug interaction checking	F: Post-discharge strategies
Akbarov (2015)	EHR	✓			✓
Boland (2015)	EHR	✓			
Budnitz (2006)	Clinical Record	✓	✓		
Chen (2015)	EMR	✓			
Classen (1991)	Computerized Medical Record	✓	✓		
Coloma (2011)	EHR	✓	✓		
Coloma (2013)	EHR				✓
Davis (2015)	Patient Medical Record	✓			
Egualde (2008)	Electronic Prescribing System			✓	✓
Egualde (2016)	EHR				✓
Evans (2005)	EMR	✓			
Fattinger (2000)	Database with electronic interface to CPR	✓	✓		
Ficheur (2014)	EMR	✓			
Genco (2016-2015)	EHR	✓		✓	
González (2011)	EMR				✓
González (2012)	EHR	✓			
Haerian (2012)	EHR		✓		
Honigman (2001)	EMR	✓	✓		
Hug (2010)	CPOE		✓	✓	
Iqbal (2015)	EHR		✓		
Kidon (2004)	EMR	✓			
Kim (2012)	EMR		✓		
Kirkendall (2016)	EHR	✓	✓		
Lal (2009)	EMR	✓			
Levy (1999)	ADR detector		✓		
Li (2014)	EHR	✓	✓		
Macy (2015)	EHR	✓			
Moore (2009)	EMR		✓		
Moskow (2015)	EHR	✓			
Paisansinsup (2013)	EHR	✓	✓		
Park (2008)	EMR				✓
Raimbault (2013)	CPOE			✓	
Ramirez (2010)	EMR		✓		
Ringqvist (2015)	Electronic Record	✓			✓
Roitmann (2014)	EMR	✓			
Ryu (2015)	EMR	✓			
Shin (2013)	EMR	✓	✓		
Tabali (2012)	EMR	✓			
Tomlin (2012)	Electronic Clinical Record	✓	✓		

Study	ER Type	Fs: Patient demographics & specific dosing and warnings	F: Manage results	F: Support for drug interaction checking	F: Post-discharge strategies
Tora (2014)	Electronic Expert Support	✓	✓	✓	
Trifiro (2009)	EHR				✓
Trinkley (2016)	EHR	✓		✓	
Tsang (2010)	Electronic Patient Record	✓			
Yildirim (2015)	Adverse Event Reporting System Database	✓			
Zhou (2016)	EHR	✓			
Zuzana (2012)	EMR	✓			

From 46 studied analyzed, 32 studies (69.6%) have focused on or pointed out “patient specific dosing and warnings” function of electronic records; 18 studies (39.1%) have focused on or pointed out “manage results” function of electronic records; 6 studies (13%) have focused on or pointed out “support for drug interaction checking” function of electronic records; and 8 studies (17.4%) have focused on or pointed out “post-discharge strategies”.

Chapter 3: Discussion

To describe the significance of findings in previous chapter we follow same approach in the “results” section, taking findings into consideration in both general categories and “Electronic Records” category in particular.

The majority of articles are showing female dominance in ADRs, which is in accordance with part of the previous knowledge about sex differences in ADRs (Zopf et al., 2009; Yu et al., 2016; Behr et al., 2013), as opposed to other studies (D’Incau et al., 2014). However the number of articles showing either male or mixed results, emphasizes a need to distinguish between different classes of drugs and their distinctive chance of creating adverse reactions in each sex.

Despite all evidence about sex differences in ADRs, very few articles in this study, have taken specific consideration into this part of their results. These studies have generally highlighted the association between demographics and ADRs (Yildirim, 2015); suggested clarifying possible interactions between side effects and vulnerability factors (Ringqvist et al., 2015); paid specific attention to sex dimorphism of immunogenic effect of immunosuppressive agents (Zelinkova et al., 2012); or suggested increasing selectivity, accuracy, and specificity of drug alerts or their triggers (Genco, 2016;2015; Moore, 2009); yet hardly any of them has recommended further research about the additional roles that electronic records can factually take in, using demographic data including patient’s sex, to foresee and prevent adverse events.

The usage of 24 variable terms to describe “Adverse Effect” and 14 variable terms to describe “Electronic records” brings up a concern about their commonalities and differences. Surely these terms have been chosen according to policy and infrastructure of their settings as well as the population whom they serve, but at the same time they produce some ambiguities for research

purposes and global shareholders. This really becomes a matter of concern when terms such as “recorded ADRs” are equated with “reported ADRs”, which come actually from two distinct categories; the latter describing an “action” rather than an “event” and threatened by risks of under-reporting and memory bias.

Tendency and efforts made towards a more steady terminology especially in publications (with a particular importance in the context of one single publication), not only assists researchers in their investigations, but also brings health informatics participants to a more robust stage to define components of healthcare systems and avoid overlapping or gaps in designing the structure of essential tools like electronic records.

Describing functions of electronic records in these studies deserves attention to a number of concerns. First, electronic records are of various forms, so it’s not unexpected for them to carry different functionalities. Second, they have been described towards and up to the objective and methodology of their own study, not necessarily providing a full description of the electronic record. Third, we related mentioned functionalities described in the article to the closest functional category provided by HL7 system, yet there is still a chance that these two prototypes don’t completely match.

After all, more than two-thirds of articles have used electronic records for extracting “patient demographics” while working on “patient specific dosing and warnings” according to the objective of study, which is just one very basic task of electronic records without granting a specific role to “demographic” characteristics (e.g. sex) at the point of “dosing and warning”.

Studies that have used the “manage results” function of electronic records have mostly used abnormal laboratory results, and to a fewer extent, the general condition of the patient (e.g. movement) as a surrogate to ADRs. Studies using “support for drug interaction checking” have

highlighted that aspect of drug interactions that ultimately converts into adverse drug reaction of each or all prescribed drugs. Again, in none of these two functions, patient's sex has been noticed as a determinant factor.

According to "post-discharge strategies" and our extended interpretation regarding to pharmacovigilance, a number of studies have provided suggestions or evidence of improved functionalities for electronic records, such as González (2011) suggesting that integrating data in EMRs and pharmacovigilance systems can improve the global knowledge of this subject; Ramirez (2010) developing a pharmacovigilance system from laboratory signals; Tomlin (2012) detecting drug-safety signals from patient switching medicines; and many more. However in none of this pharmacovigilance improvements or suggestions, patient's sex has been included as part of data to perform the program.

Chapter 4: Conclusion

Studies accomplished using the wealth of aggregated data in electronic records have already exposed patterns by revealing different categories in data and the associations across these categories, yet still have more concealed embedded patterns to be disclosed by data mining strategies and researches. For taking best advantage of this growing discovered knowledge, the outcomes need to be fed back to the practical part of healthcare structure, through the efferent part of a “learning healthcare system” (LHS). This enables up-to-date, analyzed, and interpreted data to be inserted back into LHS cycle, which provides tailored messages to decision makers and now this fresh prospect has the ability to start a change in planning and practice.

Exploiting this thriving affluent evidence about sex differences in ADRs and feeding back the message brought up by this information to the design of electronic records particularly at the point of medication prescription in EHRs is a decent example of this process.

Potential forthcoming researchers, stakeholders, or vendors will be able to compare the current functionality of their electronic records to overall potentials of these tools, and improve capacities of their upgrading electronic records, correspondent to the needs of their healthcare systems and pharmacovigilance programs, hence by extension to prevent ADRs.

This project report tends to shape the platform from where the achievements and potentials of electronic records in adjusting ADRs could nurture, so that the outcomes could finally be used in deepening electronic records’ role in minimizing or preventing ADRs in the future, diminishing morbidity, mortality, and resource and financial burdens on healthcare systems.

Since access to EHR prototypes is more feasible to certain groups of professionals, and majority of researches should resort to indirect methods to investigate EHR functionalities, the existence

of studies directly examining different roles of EHRs, seems a research gap in literature. Hereby following recommendations in articles by Iqbal (2015), we wish to emphasize on the “research support” function of EHRs, which is to provide de-identified version of this rich and valuable repository of information as an accessible research source and data mining milieu to the scholar society.

To the knowledge of the author and as strength of the study, this is the first scoping review carried out combining three subjects of electronic records, sex-differences, and adverse drug reactions. This project adds to the knowledge body of electronic records’ functionalities, illustrating their current role, and proposing their full potentials in incorporating patients’ demographics including patients’ sex, in decision support systems.

One major limitation of this study that merits discussion, occurred because of inaccessibility to electronic records, making us unable to directly examine their way of interpreting and using patient’s sex data according to adverse drug reactions. We were rather constrained to inch our way forward and evaluate this capacity by investigating through studies which included the main three themes; an approach similar to calculating the length of an object by measuring its shadow; yet one cannot tell if there is a problem if one doesn’t measure it.

This shortcoming doesn’t necessarily disable the study but proves out the necessity of sharing secure and confidential data among researchers and intellectual parties.

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Appendix

Ethics Waiver

From: Kenna Miskelly - Human Research Ethics Facilitator

Sent: Wednesday, December 14, 2016 11:09:04 AM

To: Homa Movahedi

Cc: Bergen Butterfield - Human Research Ethics Liaison

Subject: Re: Ethics for Scoping Review - Movahedi

Dear Homa Movahedi,

Thank you for this information. It was reviewed by the HREB Chair and I.

Given that there are no participants for this study, and data collection will only involve document review from publicly available sources, research ethics approval is not required.

When we write these emails we also include the following caveats: This decision does not release the researchers from any other applicable legal obligations, ethical oversight, or conforming to professional or occupational codes of ethics where applicable, such as obtaining data sharing agreements when necessary, etc.

Please note that this decision has been made without precedent and cannot be applied to other, seemingly similar, situations.

Please contact me if you have any questions or concerns.

Kind regards,

Kenna

Kenna Miskelly, B.Sc., M.A.

Human Research Ethics Facilitator | Office of Research Services | University of Victoria | Room B233, Michael Williams Building (MWB)

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We are in the Michael Williams Building (MWB) on Ring Road <http://www.uvic.ca/buildings/ssb.html>

Our Website, forms, and guidelines are located

on: <http://www.uvic.ca/research/conduct/home/regapproval/humanethics/>

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From: Homa Movahedi

Sent: December 12, 2016 4:59 PM

To: Kenna Miskelly - Human Research Ethics Facilitator

Subject: Re: Ethics for Scoping Review - Movahedi

Dear Kenna Miskelly

Thank you for your reply and informative conversation over the phone.

Here is a brief explanation about my project:

1. My project is a "Scoping Review" and is focusing on "adverse drug reactions" and how "electronic health records" (EHRs) include this concept in their functionality.
2. The project is interested on the current evidence in the literature body and **NOT** the personal data of any kind in EHRs used by health authorities.
3. So far I have gathered a couple thousands of articles from 4-5 databases found via UVic Library, plus grey literature from CIHI publications, which are accessible to public. I might add some open publications from NHI or other health organizations to my literature pool.
4. No direct or indirect individual contact is going to be made to any health authority for accessing information or data of any kind.
5. The scoping review process will downsize these thousands articles to less than 100, extract and categorize the objectives, and provide a scope of the current knowledge in the literature on this subject.

I appreciate your guidance about the required steps to an "ethics approval" for my scoping review, and also a record of these steps to be documented in my final report.

Please let me know if you need a more detailed proposal of my scoping review or further information about it.

Looking forward to your advice.

Best Regards

Homa Movahedi