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Utility of social media and crowd-sourced data for pharmacovigilance: A scoping review protocol

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ABSTRACT

Introduction: Adverse events associated with medications are underreported in the current post-marketing surveillance systems. It is estimated that only 4% to 10% of adverse events identified between 1995 and 2000 were reported to the Canada Vigilance Program. This scoping review aims to assess the utility of social media and crowd-sourced data to detect and monitor adverse events related to health products, which include pharmaceuticals, medical devices, biologics, and natural health products.

Methods and analysis: This scoping review will be conducted according to the manual published by the Joanna Briggs Institute for scoping reviews. Literature searches were conducted in MEDLINE, EMBASE, and the Cochrane Library from inception to May 13, 2016. Additional sources included searches of study registries, conference abstracts, dissertations, as well as websites of international regulatory authorities (e.g., FDA, World Health Organization, European Medicines Agency). Search results will be supplemented by scanning the references of relevant reviews. We will include all publication types including published articles, editorials, websites, and book sections that describe use of social media and crowd-sourced data for surveillance of adverse events associated with health products, across all populations. Two reviewers will perform study selection and data abstraction independently, and discrepancies will be resolved through discussion. Data analysis will involve quantitative (e.g., frequencies) and qualitative (e.g., content analysis) methods.

Dissemination: The summary of results will be sent to Health Canada, who commissioned the review, and other relevant policy-makers involved with the Drug Safety and Effective Network. We will compile and circulate a 1-page policy brief and host a 1-day stakeholder meeting to discuss the implications, key messages, and finalize the knowledge translation strategy. Findings from this review will ultimately

inform the design and development of a data analytics platform for social media and crowd-sourced data for pharmacovigilance in Canada, and internationally.

Registration details: Not applicable

INTRODUCTION

Social media has gained unprecedented popularity worldwide. Currently, there are over 2.3 billion active social media users, and grows by an estimated 1 million new users every day.[1] Social media platforms such as Twitter, Tumblr and Facebook are increasingly being used to discuss and share health issues. Statistics Canada revealed that over 80% of Canadians were internet users as of 2009,[2] and almost 70% of these individuals were using the internet to search for medical or health-related information.[3] Social media and crowd-sourced data have been used to successfully extract information for surveillance of disease outbreaks,[4 5] health behaviour,[6 7] and patient views on health issues.[8]

The use of social media to exchange and discuss health information by the general public generates a large volume of unsolicited and real-time information. Health related social networks that focus specifically on issues related to health, such as DailyStrength and MedHelp, attract users daily to discuss their health-related experiences, including use of prescription drugs, health products, side effects and treatments. During the 2004-2005 flu season, social media listening by means of a Google 'click ad', which appeared on the search page when information-seekers typed influenza-specific key words into the Google search engine, closely approximated the incident of influenza cases.[9] It was revealed that the Google ad click-rate correlated more closely with retrospectively confirmed cases of influenza than the Physicians Sentinel Surveillance system for "influenza-like illness".[9] Similarly, during the Canadian listeriosis outbreak, online search trends related to listeriosis correlated closely with laboratory-confirmed cases determined retrospectively, and preceded official announcements of an epidemic.[10]

Given the observed predictive power of social media and crowd-sourced data as an information source for public health surveillance, a lot of interest has been generated about its use for surveillance of adverse events to health products, often referred to as pharmacovigilance.

Pharmacovigilance is defined as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'.[11] It includes drug

safety surveillance activities to monitor incidents of adverse effects in real-life conditions. Adverse reactions, in particular to drug use, are a significant cause of morbidity and mortality, and are the fourth most common cause of death in hospitalized patients.[12] Since many adverse events are not captured in randomised clinical trials, post-marketing surveillance of health and drug products is of paramount importance for drug and health technology industries and regulatory authorities, such as Health Canada, the US Food and Drug Administration (FDA), and European Medicines Agency (EMA). These governmental agencies require clinicians to report all suspected adverse events, but the voluntary nature of the reporting systems likely contributes to the under-reporting of adverse events.[13-15] In fact, it is estimated that between 1995 and 2000, only 4% to 10% of serious adverse events were reported to the Canada Vigilance Program, Health Canada's post-market surveillance program for suspected adverse events to health products marketed in Canada.[16] In response to the limitations in the current post-marketing surveillance systems, attention is being directed towards using social media and crowd-sourced data to detect unknown adverse events and to improve consumer safety.

This scoping review aims to assess the utility of social media and crowd-sourced data to monitor and detect adverse events related to health products. For the purpose of this review, health products include pharmaceuticals and drug products, medical devices, biologics, and natural health products. The specific research questions are: (1) What social listening and analytics platforms exist internationally to detect adverse events related to health products using social media and crowd-sourced data? What are their capabilities and characteristics? (2) What is the validity of user-generated data from social media for surveillance of adverse events to health products?

METHODS

Study Design

Our research objectives will be addressed using the scoping review methodology, which is a type of knowledge synthesis approach used to map the concepts underpinning a research area and the main

sources and types of evidence available.[17] This scoping review will be conducted in accordance to standard practices used by the Knowledge Synthesis Team within the Knowledge Translation Program of St Michael's Hospital.[18] Our approach will be informed by the methodological framework proposed by Arksey and O'Malley,[17] as well as the methodology manual published by the Joanna Briggs Institute for scoping reviews.[19] This review has been commissioned by the Health Products and Food Branch (HPFB) of Health Canada and funded by the Canadian Institutes of Health Research Drug Safety and Effectiveness Network with a 6-month timeline.

Protocol

Our protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P),[20] which was revised by the research team and members of Health Canada, and was disseminated through our program's Twitter account (@KTCanada) and newsletter to solicit additional feedback. The protocol will be posted on our institutional website.[18]

Eligibility criteria

The PICO (Population, Intervention, Comparator, Outcome, Study design)[21] eligibility criteria is as follows:

Population: Patients of all ages with an adverse event related to health products which includes pharmaceuticals and drug products, biologics, medical devices and natural health products.[22] Examples of pharmaceuticals and drug products include both prescription and non-prescription (over-the-counter) medicines, disinfectants and sanitizers with disinfectant claims. Biologics can include, but are not limited to: vaccines, insulin, serums, blood-derived products, hormones, growth factors and enzymes manufactured in bacterial, yeast or mammalian cell lines; and gene therapy and cell therapy products. Medical devices can include defibrillators, syringes, surgical lasers, hip implants, medical laboratory diagnostic instruments (including X-ray, ultrasound devices), contact lenses, and condoms. Natural health products can include vitamins and minerals, herbal remedies, homeopathic and traditional

medicines, probiotics, and other products like amino acids and essential fatty acids. Adverse events, such as addiction and overdose from prescription medical products are also eligible for inclusion. Adverse events related to programs of care, health services, organization of care, public health programs, health promotion programs, and health education programs were excluded.

Intervention: Any data analytics or social listening platforms that enable the extraction of user-generated and crowd-sourced data about adverse events to health products from social media. Social media technology is defined as a web-based application that allows for the creation and exchange of user-generated content. This includes, but is not limited to: websites, web pages, blogs, vlogs, social networks, Internet forums, chat rooms, wikis, and smartphone applications, where users have the ability to generate content (typically by providing posts and comments, often in an anonymous fashion or with limited identifying information) and are able to view/exchange content from and with others in an interactive digital environment.[23] Crowd-sourcing is the practice of obtaining needed services, ideas, or content by soliciting contributions from a large group of people and especially from the online community rather than from traditional employees or suppliers.[24] Social media listening and data analytics for public health surveillance related to non-communicable (e.g., disease prevalence) and communicable diseases (e.g., outbreak investigation) were excluded.

Comparators: Any comparator is relevant for inclusion (e.g., studies comparing one form of social media or crowd-sourced data to another or comparing social media with traditional reporting systems). In addition, studies without a comparator are eligible for inclusion.

Outcomes: There are two broad categories of outcomes that are of interest: (1) characteristics of social media listening and analytics platform (e.g., data sources, scope of surveillance, capabilities, data extraction, preprocessing data, annotation, text mining methods, computational frameworks, added value to existing surveillance capacities, technical skills required, infrastructure support to implement and sustain, privacy and security of the data); and, (2) validity of user-generated data through social

media and crowd-sourcing networks (e.g., relationship between health technologies and adverse events, algorithms or processes used to validate the data, and related results of the evaluation).

Study designs: All types of publications including published articles, articles in conference proceedings, editorials, websites, and chapters in textbooks are relevant.

Time periods: All periods of time and duration of follow-up are eligible.

Other: Given the 6-month timeline, only publications written in English will be considered for inclusion. If time allows, publications other languages may be considered.

Information sources and search strategy

Comprehensive literature search strategies were developed by an experienced librarian for the following electronic bibliographic databases: MEDLINE, EMBASE, and the Cochrane Library. The search strategy was peer-reviewed by another expert librarian using the PRESS (Peer Review of Electronic Search Strategies) checklist.[25] The final search strategy incorporated feedback from the peer review process and the complete search string for MEDLINE can be found in *Appendix A*. A trained library technician performed the final searches from inception to May 2016, exported the search results into Endnote and removed all duplicates.

A grey literature search was conducted according to the CADTH guide.[26] Specifically, we searched 59 sources and websites of approximately 119 relevant regulatory authorities for additional publications or pre-existing platforms of social media listening and data analytics. Examples of such social media listening and analytics platform include the MedWatcher Social created in collaboration with the US Food and Drug Administration and WEB-RADR for the European Union regulators.[27 28] See *Appendix B* for a full list of grey literature sources that were searched. Literature saturation will be ensured by searching the reference lists of relevant reviews.

Study selection process

To ensure high inter-rater reliability, a training exercise will be conducted prior to commencing the screening process. Using our predefined eligibility criteria, a standardized questionnaire for study selection will be developed and tested on a random sample of 50 titles and abstracts (i.e., level 1 screening) by all team members. The same training exercise will be repeated for screening of full-text articles (i.e., level 2 screening). Subsequently, pairs of reviewers will screen citations and full-text articles for inclusion, independently, for both level 1 and level 2 screening. Inter-rater discrepancies will be resolved by discussion or a third adjudicator. All levels of screening will be conducted using Synthesi.SR, the proprietary online software developed by the Knowledge Synthesis Team.[29]

Data items and data abstraction process

We will abstract data on characteristics of the articles (e.g., type of article or study, country of corresponding author), population characteristics (e.g., type of patients, type of adverse events, disease condition), intervention characteristics (e.g., type of social media or crowd-sourced data used), and outcomes (e.g., platform characteristics, data analytics used, validity of social media or crowd-sourced data). A standardized data abstraction will be developed *a priori* and revised, as needed, after the completion of a training exercise.

Prior to data abstraction, we will complete a training exercise of the data abstraction form on a random sample of 5 articles. Subsequently, all included studies will be abstracted by pairs of reviewers, independently. Data discrepancies will be resolved by discussion or the involvement of a third reviewer.

Risk of bias assessment or quality appraisal

Since this is a scoping review aiming to map all available evidence, we will not conduct any risk of bias assessment or quality appraisal of included studies. This approach is consistent with the methods manual published by the Joanna Briggs Institute,[19] as well as a database of scoping reviews on clinical topics.[30]

Synthesis of results

The synthesis will focus on providing a description of all social media and crowd-sourcing platforms that exist internationally, and the validity of data from these platforms when available. This will be achieved by summarizing the literature according to the types of participants, interventions, comparators, and outcomes identified. Quantitative analysis will be conducted using descriptive statistics (e.g., frequencies, measures of central tendency). As well, we will consider qualitative analysis (e.g., content analysis) for open-text data, as necessary. Two reviewers will conduct the initial categorization coding independently, using NVivo software,[31] and the results will be discussed by the team. These reviewers will subsequently identify, code, and chart relevant units of text from the articles using the categorization code. Discrepancies will be resolved through team discussion.

DISCUSSION

Implications

Findings from this scoping review will inform decision-makers of the types of social listening and analytics platforms that exist to extract user-generated data from social media for surveillance of adverse events to health products. This will inform Health Canada and other regulatory authorities internationally about the potential use of social media and crowd-sourced data for post-marketing surveillance.

Dissemination

The summary of results will be sent to Health Canada and other relevant policy-makers and researchers working with the Drug Safety and Effective Network in the form of a 1-page policy brief (link for an example). As well, a 1-day stakeholder meeting (i.e., consultation exercise)[17] will be held to discuss the implications of our scoping review, key messages, and to finalize the knowledge translation strategy. All relevant stakeholders will be invited to attend, as recommended by members from the Health Canada HPFB. This meeting will be essential to ensure extensive knowledge translation of our findings and to engage stakeholders and promote our research agenda. We will also present our results at an

international conference and publish in an open-access journal. Finally, team members will use their networks to encourage broad dissemination of results.

ETHICS APPROVAL

Since this is a scoping review, ethics approval is not required.

AUTHOR'S CONTRIBUTIONS

ACT obtained funding, conceptualized the research, and drafted the protocol. WZ helped write the protocol. EL and BP reviewed and edited the protocol. SES obtained funding, helped conceptualize the research, and edited the protocol.

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COMPETING INTERESTS

We have read and understood BMJ Open's policy on declaration of interests and declare that we have no competing interests.

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Appendix A. MEDLINE search strategy

Interface: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1. social media/
2. Social Networking/
3. blogging/
4. Crowdsourcing/
5. (social adj3 (media or medium* or network* or bookmark*)).tw.
6. (blog* or microblog*).tw.
7. ((patient or discussion or web or chat or internet or online) adj3 (forum* or fora or message board*)).tw.
8. (facebook or twitter or wiki or youtube or web 2* or instagram or foursquare or linkedin or pinterest or lifestream*).tw.
9. (crowdsourc* or crowd sourc*).tw.
10. or/1-9
11. product surveillance, postmarketing/ or adverse drug reaction reporting systems/ or pharmacovigilance/
12. exp "Drug-Related Side Effects and Adverse Reactions"/
13. (side effect* or (adverse adj3 (effect* or event* or reaction*))).tw.
14. (pharmacovigilance or ((postmarketing or post-marketing) adj3 surveillance)).tw.
15. Patient Safety/
16. ae.fs.
17. Pharmacoepidemiology/
18. Medication Errors/
19. Abnormalities, Drug-Induced/
20. ci.fs.
21. (drug* or medication* or pharmaceutical* or medicine* or biologics or vaccine* or herb* or vitamin*).tw.
22. ((medical or health) adj2 (device* or equipment* or instrument* or supply or supplies)).tw.
23. 21 or 22
24. (safe* or harm* or toxicity).tw.
25. 23 and 24
26. or/11-20,25
27. 10 and 26

Appendix B. Sources for Grey Literature Search

Adverse drug reporting / pharmacovigilance

- Australia - https://www.ebs.tga.gov.au/ebs/ADRS/ADRSRepo.nsf?OpenDatabase
- Canada - http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php AND http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php
- European database of ae - http://www.adrreports.eu/en/
- European pharmacovigilance database called EudraVigilance - http://eudravigilance.ema.europa.eu/
- UK Yellow care - https://yellowcard.mhra.gov.uk AND see http://webarchive.nationalarchives.gov.uk/20141205150130/http:/www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con408250.pdf
- US MedWatch - http://www.fda.gov/Safety/MedWatch/
- US Sentinel Initiative - http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm
- US FAERS - https://open.fda.gov/data/faers/
- Vigibase - http://www.who-umc.org/DynPage.aspx?id=98082&mn1=7347&mn2=7252&mn3=7322&mn4=7326

Associations

- AIIM - http://www.aiim.org
- American Health Information Management Association - http://www.ahima.org
- CHIMA - https://www.echima.ca
- CIHI – www.cihi.ca
- COACH - http://www.coachorg.com/en/index.asp
- The Institute of Electrical and Electronics Engineers, Incorporated - https://www.ieee.org/index.html
- HIME - https://www.efmi.org/index.php/workinggroups/hime-health-information-management-europe
- HIMSS - http://www.himss.eu
- IMS Institute - http://www.imshealth.com/en/thought-leadership/ims-institute
- IFHIMA - https://ifhima.org
- IMIA - http://www.imia-medinfo.org/new2/
- Medicine for Europe - http://www.medicinesforeurope.com
- UK Chip - http://www.ukchip.org

See also: http://www.healthinformaticsforum.com/health-informatics-associations-and-societies

Regulatory authority websites:

Asia and Pacific

World Health Organization	World Health Organization
Pan-American Health Organization	Pan-American Health Organization
WHO Regional Office for Europe	WHO Regional Office for Europe
WHO Regional Office for Africa	WHO Regional Office for Africa

WHO Regional Office for the Eastern Mediterranean	WHO Regional Office for the Eastern Mediterranean
WHO Regional Office for Southeast Asia	WHO Regional Office for Southeast Asia
WHO Regional Office for the Western Pacific	WHO Regional Office for the Western Pacific
Food and Agriculture Organizations of the United Nations	Food and Agriculture Organizations of the United Nations
Codex Alimentarius	Codex Alimentarius
World Trade Organization	World Trade Organization
Europe	
Belgium: Health, Food Chain Safety and Environment	Belgium: Health, Food Chain Safety and Environment
Belgium: Pharmaceutical Inspectorate	Belgium: Pharmaceutical Inspectorate
Croatia: Ministry of Health and Social Care	Croatia: Ministry of Health and Social Care
Danish Medicines Agency	Danish Medicines Agency
Denmark: Ministry of Food, Agriculture and Fisheries	Denmark: Ministry of Food, Agriculture and Fisheries
Denmark: Ministry of Health	Denmark: Ministry of Health
Denmark: Veterinary and Food Administration	Denmark: Veterinary and Food Administration
Estonia: Ministry of Social Affairs	Estonia: Ministry of Social Affairs
Estonia: State Agency of Medicines	Estonia: State Agency of Medicines
European Commission Consumer Affairs: Medical Devices	European Commission Consumer Affairs: Medical Devices
European Commission Directorate General for Health & Consumers	European Commission Directorate General for Health & Consumers
European Commission Directorate General: Health Notice to Applicants	European Commission Directorate General: Health Notice to Applicants
European Commission Directorate General: Medicinal Products for Veterinary Use	European Commission Directorate General: Medicinal Products for Veterinary Use
European Medicines Agency	European Medicines Agency (EMA)
Finland: Ministry of Social Affairs and Health	Finland: Ministry of Social Affairs and Health
Finnish Food Safety Authority Evira	Finnish Food Safety Authority Evira
Finnish Medicines Agency	Finnish Medicines Agency
France: National Agency for Veterinary Medicinal Products	France: National Agency for Veterinary Medicinal Products
Germany: Federal Institute for Drugs and Medical Devices	Germany: Federal Institute for Drugs and Medical Devices
Germany: Ministry of Health	Germany: Ministry of Health
Greece: Hellenic Food Authority	Greece: Hellenic Food Authority
Greece: Hellenic Ministry of Agriculture	Greece: Hellenic Ministry of Agriculture
Greece: National Organization for Medicines	Greece: National Organization for Medicines
Iceland: The Environment Agency	Iceland: The Environment Agency
Ireland: Agriculture and Food Development Authority	Ireland: Agriculture and Food Development Authority
Ireland: Department of Health and Children	Ireland: Department of Health and Children
Ireland: Food Safety Authority	Ireland: Food Safety Authority
Irish Medicines Board	Irish Medicines Board
Lithuania: Ministry of Health	Lithuania: Ministry of Health

Lithuania: State Medicines Control Agency	Lithuania: State Medicines Control Agency
Malta: Ministry of Health, Elderly and Community Care	Malta: Ministry of Health, Elderly and Community Care
Netherlands: Ministry of Health, Welfare and Sport	Netherlands: Ministry of Health, Welfare and Sport
Norway: Ministry of Agriculture and Food	Norway: Ministry of Agriculture and Food
Norway: Ministry of Health and Care Services	Norway: Ministry of Health and Care Services
Norway: Norwegian Board of Health Supervision	Norway: Norwegian Board of Health Supervision
Norway: Norwegian Medicines Agency	Norway: Norwegian Medicines Agency
Poland: Drug Institute	Poland: Drug Institute
Slovak Republic: Ministry of Agriculture and Rural Development	Slovak Republic: Ministry of Agriculture and Rural Development
Slovenia: Ministry of Agriculture, Forestry and Food	Slovenia: Ministry of Agriculture, Forestry and Food
Sweden: Medical Products Agency	Sweden: Medical Products Agency
Sweden: Ministry for Rural Affairs	Sweden: Ministry for Rural Affairs
Sweden: National Food Administration	Sweden: National Food Administration
Switzerland: Federal Office of Public Health	Switzerland: Federal Office of Public Health
Switzerland: Federal Veterinary Office	Switzerland: Federal Veterinary Office
UK: Department of Health	UK: Department of Health
UK: Food Standards Agency	UK: Food Standards Agency
UK: Health Protection Agency	UK: Health Protection Agency
UK: Medicines and Healthcare Products Regulatory Agency	UK: Medicines and Healthcare Products Regulatory Agency
UK: National Institute for Biological Standards and Control	UK: National Institute for Biological Standards and Control
UK: Veterinary Medicines Directorate	UK: Veterinary Medicines Directorate
Middle East	
Israel: Ministry of Health	Israel: Ministry of Health
Israel: Ministry of Industry, Trade and Labor	Israel: Ministry of Industry, Trade and Labor
Jordan: Ministry of Health	Jordan: Ministry of Health
Lebanon: Ministry of Public Health	Lebanon: Ministry of Public Health
Saudi Arabia: Ministry of Health	Saudi Arabia: Ministry of Health
United Arab Emirates: Ministry of Health	United Arab Emirates: Ministry of Health
United Arab Emirates: Federal Department of Pharmacies	United Arab Emirates: Federal Department of Pharmacies
Yemen: Ministry of Public Health & Population	Yemen: Ministry of Public Health & Population
Africa	
Botswana: Ministry of Health	Botswana: Ministry of Health
Egypt: Ministry of Agriculture and Land Reclamation	Egypt: Ministry of Agriculture and Land Reclamation
Ghana: Ministry of Health	Ghana: Ministry of Health
Ghana: Ministry of Food and Agriculture	Ghana: Ministry of Food and Agriculture
Kenya: Ministry of Health	Kenya: Ministry of Health
Maldives: Ministry of Health	Maldives: Ministry of Health
Mauritius: Ministry of Health & Quality of Life	Mauritius: Ministry of Health & Quality of Life
Mauritius: Ministry of Agro Industry and Food	Mauritius: Ministry of Agro Industry and Food

Security	Security
Namibia: Ministry of Health and Social Services	Namibia: Ministry of Health and Social Services
Namibia: Ministry of Fisheries and Marine Resources	Namibia: Ministry of Fisheries and Marine Resources
South Africa: Department of Health	South Africa: Department of Health
Swaziland: Ministry of Health and Social Welfare	Swaziland: Ministry of Health and Social Welfare
Tanzania: Ministry of Health	Tanzania: Ministry of Health
Uganda: Ministry of Health	Uganda: Ministry of Health
Zimbabwe: Ministry of Health and Child Welfare	Zimbabwe: Ministry of Health and Child Welfare
America	
Belize: Ministry of Health	Belize: Ministry of Health
Bolivia: Ministry of Health and Social Welfare	Bolivia: Ministry of Health and Social Welfare
Brazil: Fundacao Oswaldo Cruz	Brazil: Fundacao Oswaldo Cruz
Canada: Food Inspection Agency	Canada: Food Inspection Agency
Canada: Health Products and Food Branch	Canada: Health Products and Food Branch
Guyana: Ministry of Health	Guyana: Ministry of Health
Guyana: National Bureau of Standards	Guyana: National Bureau of Standards
Jamaica: Ministry of Health	Jamaica: Ministry of Health
Mexico: Federal Commission for the Protection Against Sanitary Risks	Mexico: Federal Commission for the Protection Against Sanitary Risks
Netherlands Antilles: Department of Public Health and Environmental Protection	Netherlands Antilles: Department of Public Health and Environmental Protection
St. Lucia: Ministry of Agriculture, Lands Forestry and Fisheries	St. Lucia: Ministry of Agriculture, Lands Forestry and Fisheries
Trinidad & Tobago: Bureau of Standards	Trinidad & Tobago: Bureau of Standards
Trinidad and Tobago: Ministry of Health	Trinidad and Tobago: Ministry of Health
Multinational	
World Health Organization	World Health Organization
Pan-American Health Organization	Pan-American Health Organization
WHO Regional Office for Europe	WHO Regional Office for Europe
WHO Regional Office for Africa	WHO Regional Office for Africa
WHO Regional Office for the Eastern Mediterranean	WHO Regional Office for the Eastern Mediterranean
WHO Regional Office for Southeast Asia	WHO Regional Office for Southeast Asia
WHO Regional Office for the Western Pacific	WHO Regional Office for the Western Pacific
Food and Agriculture Organizations of the United Nations	Food and Agriculture Organizations of the United Nations
Codex Alimentarius	Codex Alimentarius
World Trade Organization	World Trade Organization

Crowdsourcing – medical focus

- https://www.crowdflower.com/discovering-drug-side-effects-with-crowdsourcing/ - allow researchers to design and submit crowdsourcing tasks
- http://www.sermo.com - a global social crowdsourcing network for physicians and medical providers

- http://www.medhelp.org
- http://curetogether.com
- https://www.upwork.com
- https://fold.it/portal/
- https://www.mturk.com/mturk/welcome
- https://www.patientslikeme.com

Stanford links:

- http://crowdresearch.stanford.edu/w/index.php?title=Introducing_Crowd_Research_Initiative_and_Recap

Resources

- Relevant Work - used to save relevant articles, links and papers
- Forums - discussions about this project on external sites. Note that all official announcements and communications will occur via Slack and email.
- Resources - used to index all platforms and resources as we evolve
- Infrastructure and GettingStarted
- Archives - older meetings, slides and milestones
  http://voxpopuli.stanford.edu
- http://stanfordhci.github.io/twitchcrowdsourcing/
- https://github.com/crowdresearch/crowdsource-platform

Government drug regulators (this list is key, however, see the WHO list for all countries or EMA for Europe) and related research agencies

- Australia – Therapeutic Good Administration - http://www.tga.gov.au
- Canada data - http://open.canada.ca/en
- Canada ICES - http://www.ices.on.ca/About-ICES.aspx
- European Commission - http://ec.europa.eu/growth/index_en.htm and http://ec.europa.eu/health/human-use/advanced-therapies/index_en.htm
- European Medicines Agency –
- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp - see guideline and module
  - Full list of European country agencies: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp
- Finish Medicine Agency - http://www.fimea.fi/web/en/frontpage
- France - http://www.afssaps.fr
- Germany – Federal Institute for Drugs http://www.bfarm.de/EN/Home/home_node.html;jsessionid=7CCFCA856FC813AC19DD69E86C4742CB.1_cid322
- Health Canada - http://www.hc-sc.gc.ca/dhp-mps/index-eng.php
- NEHI - http://www.nehi.net
- Netherland Medicines Evaluation Board - http://english.cbg-meb.nl
- New Zealand - http://www.health.govt.nz
- PHAC - http://www.phac-aspc.gc.ca/index-eng.php
- StatsCan - http://www.statcan.gc.ca

- Sweden - https://lakemedelsverket.se/english/
- US data - https://www.data.gov
- US CDC - http://www.cdc.gov
- US IOM - http://www.nationalacademies.org/hmd/
- US FDA
    - (FEARS) – http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm083765.htm
- US NIH - https://www.nih.gov
- US NIMH - http://www.nimh.nih.gov/
- UK Medicine and Health products Regulator Agency - https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
- WHO – search site, publications section and WHOLIS database
    - http://www.who-umc.org/DynPage.aspx?id=98080&mn1=7347&mn2=7252&mn3=7322&mn4=7324
    - http://www.who.int/en/
    - http://www.who.int/library/databases/en/
    - **See List of Globally identified Websites of Medicines Regulatory Authorities -** http://www.who.int/medicines/areas/quality_safety/regulation_legislation/list_mra_websites_nov2012.pdf OR https://www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/global-regulatory-authority-websites

Pharma-related

- FDABLE - http://www.fdable.com/basic_query/aers
- EudraVigiance: http://eudravigilance.ema.europa.eu/highres.htm
- Social Media, Mobile, Wearable News & Views - http://www.scoop.it/t/pharmaguy-s-social-media-news-views/?tag=adverse+events
- Innovative medicine initiative: http://www.imi.europa.eu

Software

- Open PHACTS - https://www.openphacts.org and http://www.openphactsfoundation.org
- DebugIT - http://www.debugit.com.au
- Khresmoi - http://khresmoi.atosresearch.eu
- EHR4CR - http://www.ehr4cr.eu

Articles

Suggest to do 1) an author search on Clark Freifeld and 2) a web of science search of his publications for related articles.

- **Digital pharmacovigilance: The MedWatcher system for monitoring adverse events through automated processing of Internet social media and crowdsourcing (Thesis).**

Freifeld, Clark C., Ph.D., BOSTON UNIVERSITY, 2014, 148 pages; 3581025http://gradworks.umi.com/35/81/3581025.html

- **Freifeld CC, Chunara R, Mekaru SR, Chan EH, Kass-Hout T, et al. (2010) Participatory Epidemiology: Use of Mobile Phones for Community-Based Health Reporting. PLoS Med 7(12): e1000376. doi:10.1371/journal.pmed.1000376**
- **Freifeld CC, Brownstein JS, Menone CM *et al*. Digital drug safety surveillance: monitoring pharmaceutical products in Twitter. *Drug Safety* 2014;37:343–350.**

Guidance for Industry Internet/Social Media Platforms with Character Space Limitations— Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm401087.pdf

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- The Impact and Use of Social Media in Pharmacovigilance - https://www.sciformix.com/wp-content/uploads/Social_Media_in_PV_Whitepaper.pdf
- See report WEBAE project (Web Adverse Events) - http://www.imi.europa.eu/webfm_send/912

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Utility of social media and crowd-sourced data for pharmacovigilance: A scoping review protocol

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Utility of social media and crowd-sourced data for pharmacovigilance: A scoping review protocol

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ABSTRACT

Introduction: Adverse events associated with medications are underreported in post-marketing surveillance systems. A systematic review of published data from 37 studies worldwide (including Canada) found the median underreporting rate of adverse events to be 94% in spontaneous reporting systems. This scoping review aims to assess the utility of social media and crowd-sourced data to detect and monitor adverse events related to health products including pharmaceuticals, medical devices, biologics, and natural health products.

Methods and analysis: Our review conduct will follow the Joanna Briggs Institute scoping reviews methods manual. Literature searches were conducted in MEDLINE, EMBASE, and the Cochrane Library from inception to May 13, 2016. Additional sources included searches of study registries, conference abstracts, dissertations, as well as websites of international regulatory authorities (e.g., FDA, World Health Organization, European Medicines Agency). Search results will be supplemented by scanning the references of relevant reviews. We will include all publication types including published articles, editorials, websites, and book sections that describe use of social media and crowd-sourced data for surveillance of adverse events associated with health products. Two reviewers will perform study selection and data abstraction independently, and discrepancies will be resolved through discussion. Data analysis will involve quantitative (e.g., frequencies) and qualitative (e.g., content analysis) methods.

Dissemination: The summary of results will be sent to Health Canada, who commissioned the review, and other relevant policy-makers involved with the Drug Safety and Effective Network. We will compile and circulate a 1-page policy brief and host a 1-day stakeholder meeting to discuss the implications, key messages, and finalize the knowledge translation strategy. Findings from this review will ultimately inform the design and development of a data analytics platform for social media and crowd-sourced dat for pharmacovigilance in Canada, and internationally.

Registration details: Our protocol was registered prospectively with the Open Science Framework (https://osf.io/kv9hu/).

STRENGTHS AND LIMITATIONS

- *We will conduct a comprehensive literature search of multiple electronic databases and sources for difficult to locate and unpublished studies (or grey literature).*
- *Our scoping review will conform to the methodologically rigorous methods manual by the Joanna Briggs Institute.*
- *Numerous strategies will be used to disseminate our results widely.*
- *To increase the feasibility of our scoping review, we will limit to English and have one data abstractor and one verifier.*

INTRODUCTION

Social media has gained unprecedented popularity worldwide. Currently, there are over 2.3 billion active social media users, and grows by an estimated 1 million new users every day.[1] Social media platforms such as Twitter, Tumblr and Facebook are increasingly being used to discuss and share health issues. Statistics Canada revealed that over 80% of Canadians were internet users as of 2009,[2] and almost 70% of these individuals were using the internet to search for medical or health-related information.[3] Social media and crowd-sourced data have been used to successfully extract information for surveillance of disease outbreaks,[4 5] health behaviour,[6 7] and patient views on health issues.[8]

The use of social media to exchange and discuss health information by the general public generates a large volume of unsolicited and real-time information. Health related social networks, such as DailyStrength and MedHelp, attract users daily to discuss their health-related experiences, including use of prescription drugs, health products, side effects and treatments. During the 2004-2005 flu season, social media listening by means of a Google 'click ad', which appeared on the search page when information-seekers typed influenza-specific key words into the Google search engine, closely approximated the incident of influenza cases.[9] It was revealed that the Google ad click-rate correlated more closely with retrospectively confirmed cases of influenza than the Physicians Sentinel Surveillance system for "influenza-like illness".[9] Other researchers have also examined the use of social media for influenza outbreaks.[10-12] Similarly, during the Canadian listeriosis outbreak, online search trends related to listeriosis correlated closely with laboratory-confirmed cases determined retrospectively, and preceded official announcements of an epidemic.[13]

And more recently, researchers evaluated the types of information [14] including the prevalence of misinformation [15] posted on Twitter and the Sina Weibo Chinese microblog platform related to the 2014-2015 Ebola epidemic. Given the observed predictive power of social media and crowd-sourced

data as an information source for public health surveillance, a lot of interest has been generated about its use for surveillance of adverse events to health products, often referred to as pharmacovigilance. Pharmacovigilance is defined as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'.[16] It includes drug safety surveillance activities to monitor incidents of adverse effects in real-life conditions. Adverse events, in particular to drug use, are a significant cause of morbidity and mortality, and are the fourth most common cause of death in hospitalized patients.[17] Since many adverse events are not captured in randomised clinical trials, post-marketing surveillance of health and drug products is of paramount importance for drug and health technology industries and regulatory authorities, such as Health Canada, the US Food and Drug Administration (FDA), and European Medicines Agency (EMA). These governmental agencies require clinicians to report all suspected adverse events, but the voluntary nature of the reporting systems likely contributes to the under-reporting of adverse events.[18-20] A systematic review of published data from 37 studies worldwide (including Canada) found the median under-reporting rate of adverse events to be 94% in spontaneous reporting systems. In response to the limitations in the current post-marketing surveillance systems, attention is being directed towards using social media and crowd-sourced data to detect adverse events and to improve consumer safety. Reviews have been conducted assessing social media for pharmacovigilance, such as a systematic review including 51 studies [22] and a scoping review including 24 studies, [23] but this is a rapidly evolving field and an updated scoping review with a comprehensive grey literature search may provide more clarity to the field. As well, these previous reviews did not summarize pre-existing platforms that exist on this topic, which was requested by our knowledge user, Health Canada.

As such, we aim to assess the utility of social media and crowd-sourced data to monitor and detect adverse events related to health products. For the purpose of this review, health products include

pharmaceuticals and drug products, medical devices, biologics, and natural health products. The specific research questions are:

(1) What social listening and analytics platforms exist internationally to detect adverse events related to health products using social media and crowd-sourced data? What are their capabilities and characteristics?

(2) What is the validity and reliability of user-generated data from social media for surveillance of adverse events to health products?

METHODS

Study Design

Our research objectives will be addressed using the scoping review methodology, which is a type of knowledge synthesis approach used to map the concepts underpinning a research area and the main sources and types of evidence available.[24] This scoping review will be conducted in accordance to standard practices used by the Knowledge Synthesis Team within the Knowledge Translation Program of St Michael's Hospital.[25] Our approach will be informed by the methodological framework proposed by Arksey and O'Malley,[24] as well as the methodology manual published by the Joanna Briggs Institute for scoping reviews.[26] This review has been commissioned by the Health Products and Food Branch (HPFB) of Health Canada and funded by the Canadian Institutes of Health Research Drug Safety and Effectiveness Network with a 6-month timeline.

Protocol

Our protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P; see *Appendix A*),[27] which was revised by the research team and members of Health Canada, and was disseminated through our program's Twitter account (@KTCanada) and newsletter to solicit additional feedback. The final protocol was registered prospectively with the Open Science Framework on September 6, 2016 (https://osf.io/kv9hu/).

Eligibility criteria

The PICO (Population, Intervention, Comparator, Outcome, Study design)[28] eligibility criteria is as follows:

Population: Patients of any age with an adverse event related to health products including pharmaceuticals and drug products, biologics, medical devices and natural health products.[29] Examples of pharmaceuticals and drug products include both prescription and non-prescription (over-the-counter) medicines, disinfectants and sanitizers with disinfectant claims. Biologics can include, but are not limited to: vaccines, insulin, serums, blood-derived products, hormones, growth factors and enzymes manufactured in bacterial, yeast or mammalian cell lines; and gene therapy and cell therapy products. Medical devices can include defibrillators, syringes, surgical lasers, hip implants, medical laboratory diagnostic instruments (including X-ray, ultrasound devices), contact lenses, and condoms. Natural health products can include vitamins and minerals, herbal remedies, homeopathic and traditional medicines, probiotics, and other products like amino acids and essential fatty acids. Adverse events, such as addiction and overdose from prescription medical products are also eligible for inclusion. Adverse events related to programs of care, health services, organization of care, public health programs, health promotion programs, and health education programs were excluded.

Intervention: Any data analytics or social listening platforms that enable the extraction of user-generated and crowd-sourced data about adverse events to health products from social media. Social media technology is defined as a web-based application that allows for the creation and exchange of user-generated content. This includes, but is not limited to: websites, web pages, blogs, vlogs, social networks, Internet forums, chat rooms, wikis, and smartphone applications, where users have the ability to generate content (typically by providing posts and comments, often in an anonymous fashion or with limited identifying information) and are able to view/exchange content from and with others in an interactive digital environment.[30] Crowd-sourcing is the practice of obtaining needed services, ideas, or

content by soliciting contributions from a large group of people and especially from the online community rather than from traditional employees or suppliers.[31] Social media listening and data analytics for public health surveillance related to non-communicable (e.g., disease prevalence) and communicable diseases (e.g., outbreak investigation) were excluded.

Comparators: Any comparator is relevant for inclusion (e.g., studies comparing one form of social media or crowd-sourced data to another or comparing social media with traditional reporting systems). In addition, studies without a comparator are eligible for inclusion.

Outcomes: There are two broad categories of outcomes that are of interest: (1) characteristics of social media listening and analytics platform (e.g., data sources, scope of surveillance, capabilities, data extraction, preprocessing data, annotation, text mining methods, computational frameworks, added value to existing surveillance capacities, technical skills required, infrastructure support to implement and sustain, privacy and security of the data); and, (2) validity and reliability of user-generated data captured through social media and crowd-sourcing networks (e.g., relationship between medications and adverse events, algorithms or processes used to validate the data from social media, and related results of the evaluation).

Study designs: All types of publications including published articles, articles in conference proceedings, editorials, websites, and chapters in textbooks are relevant.

Time periods: All periods of time and duration of follow-up are eligible.

Other: Given the 6-month timeline, only publications written in English will be considered for inclusion. If time allows, publications other languages may be considered.

Information sources and search strategy

Comprehensive literature search strategies were developed by an experienced librarian for the following electronic bibliographic databases: MEDLINE, EMBASE, and the Cochrane Library. The search strategy was peer-reviewed by another expert librarian using the PRESS (Peer Review of Electronic Search

Strategies) checklist.[32] The final search strategy incorporated feedback from the peer review process and the complete search string for MEDLINE can be found in *Appendix B*. The full search terms for the other databases can be obtained by contacting the corresponding author. A trained library technician performed the final searches from inception to May 2016, exported the search results into Endnote and removed all duplicates.

A grey literature search was conducted according to the CADTH guide.[33] Specifically, we searched 59 sources and websites of approximately 119 relevant regulatory authorities for additional publications or pre-existing platforms of social media listening and data analytics. Examples of such social media listening and analytics platforms include the MedWatcher Social created in collaboration with the US Food and Drug Administration and WEB-RADR for the European Union regulators.[34 35] See *Appendix C* for a full list of grey literature sources that were searched. Literature saturation will be ensured by searching the reference lists of relevant reviews [22 23 36].

Study selection process

To ensure high inter-rater reliability, a training exercise will be conducted prior to commencing the screening process. Using our predefined eligibility criteria, a standardized questionnaire for study selection will be developed and tested on a random sample of 50 titles and abstracts (i.e., level 1 screening) by all team members. The same training exercise will be repeated for screening of full-text articles (i.e., level 2 screening). Subsequently, pairs of reviewers will screen citations and full-text articles for inclusion, independently, for both level 1 and level 2 screening. Inter-rater discrepancies will be resolved by discussion or a third adjudicator. All levels of screening will be conducted using Synthesi.SR, the proprietary online software developed by the Knowledge Synthesis Team.[37]

Data items and data abstraction process

We will abstract data on characteristics of the articles (e.g., type of article or study, country of corresponding author), population characteristics (e.g., type of patients, type of adverse events, disease

condition), intervention characteristics (e.g., type of social media or crowd-sourced data used), and outcomes (e.g., data analytics/listening platform characteristics, data analytics used, validity and reliability of social media or crowd-sourced data). A standardized data abstraction form will be developed *a priori* and revised, as needed, after the completion of a training exercise.

Prior to data abstraction, we will complete a training exercise of the data abstraction form on a random sample of 5 articles. Subsequently, all included studies will be abstracted by pairs of reviewers, independently, with conflicts resolved by a third reviewer. If a large number of studies is identified (>25), we will conduct data abstraction with one reviewer and one verifier.

Risk of bias assessment or quality appraisal

Since this is a scoping review aiming to map all available evidence, we will not conduct any risk of bias assessment or quality appraisal of included studies. This approach is consistent with the methods manual published by the Joanna Briggs Institute,[26] as well as a database of scoping reviews on clinical topics.[38]

Synthesis of results

The synthesis will focus on providing a description of all social media listening platforms that exist internationally, and the validity and reliability of data from these social listening platforms, when available. This will be achieved by summarizing the literature according to the types of participants, interventions, comparators, and outcomes identified. Quantitative analysis will be conducted using descriptive statistics (e.g., frequencies, measures of central tendency). As well, we will consider qualitative analysis (e.g., content analysis) for open-text data, as necessary. Two reviewers will conduct the initial categorization coding independently, using NVivo software,[39] and the results will be discussed by the team. These reviewers will subsequently identify, code, and chart relevant units of text from the articles using the categorization code. Discrepancies will be resolved through team discussion.

DISCUSSION

Implications

Findings from this scoping review will inform decision-makers of the types of social listening and analytics platforms that exist to extract user-generated data from social media for surveillance of adverse events to health products. This will inform Health Canada and other regulatory authorities internationally about the potential use of social media and crowd-sourced data for post-marketing surveillance.

Dissemination

The summary of results will be sent to Health Canada and other relevant policy-makers and researchers working with the Drug Safety and Effective Network in the form of a 1-page policy brief (link for an example). As well, a 1-day stakeholder meeting (i.e., consultation exercise)[24] will be held to discuss the implications of our scoping review, key messages, and to finalize the knowledge translation strategy. All relevant stakeholders will be invited to attend, as recommended by members from the Health Canada HPFB. This meeting will be essential to ensure extensive knowledge translation of our findings and to engage stakeholders and promote our research agenda. We will also present our results at an international conference and publish in an open-access journal. Finally, team members will use their networks to encourage broad dissemination of results.

ETHICS APPROVAL

Since this is a scoping review, ethics approval is not required.

AUTHOR'S CONTRIBUTIONS

ACT obtained funding, conceptualized the research, and drafted the protocol. WZ helped write the protocol. EL and BP reviewed and edited the protocol. SES obtained funding, helped conceptualize the research, and edited the protocol.

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COMPETING INTERESTS

We have read and understood BMJ Open's policy on declaration of interests and declare that we have no competing interests. The study funder had no input into the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

SUPPLEMENTARY FILES

Appendix A. PRISMA checklist

Appendix B. MEDLINE search strategy

Appendix C. Sources for Grey Literature Search

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Appendix A: PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	47-48
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-21
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	243-246
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	251-255
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	252
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	258-260
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	70-102
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	103-111

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	129-172
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	173-188
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	178 (Appendix B)
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	179-181
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	189-197
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	203-208
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	199-203
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	160-167
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	209-213
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	214-223
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☐	NA
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☐	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☐	NA
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	☐	☐	NA

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		reporting within studies)			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☐	NA

Appendix B. MEDLINE search strategy

Interface: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1. social media/
2. Social Networking/
3. blogging/
4. Crowdsourcing/
5. (social adj3 (media or medium* or network* or bookmark*)).tw.
6. (blog* or microblog*).tw.
7. ((patient or discussion or web or chat or internet or online) adj3 (forum* or fora or message board*)).tw.
8. (facebook or twitter or wiki or youtube or web 2* or instagram or foursquare or linkedin or pinterest or lifestream*).tw.
9. (crowdsourc* or crowd sourc*).tw.
10. or/1-9
11. product surveillance, postmarketing/ or adverse drug reaction reporting systems/ or pharmacovigilance/
12. exp "Drug-Related Side Effects and Adverse Reactions"/
13. (side effect* or (adverse adj3 (effect* or event* or reaction*))).tw.
14. (pharmacovigilance or ((postmarketing or post-marketing) adj3 surveillance)).tw.
15. Patient Safety/
16. ae.fs.
17. Pharmacoepidemiology/
18. Medication Errors/
19. Abnormalities, Drug-Induced/
20. ci.fs.
21. (drug* or medication* or pharmaceutical* or medicine* or biologics or vaccine* or herb* or vitamin*).tw.
22. ((medical or health) adj2 (device* or equipment* or instrument* or supply or supplies)).tw.
23. 21 or 22
24. (safe* or harm* or toxicity).tw.
25. 23 and 24
26. or/11-20,25
27. 10 and 26

Appendix C. Sources for Grey Literature Search

Adverse drug reporting / pharmacovigilance

- Australia - https://www.ebs.tga.gov.au/ebs/ADRS/ADRSRepo.nsf?OpenDatabase
- Canada - http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php AND http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php
- European database of ae - http://www.adrreports.eu/en/
- European pharmacovigilance database called EudraVigilance - http://eudravigilance.ema.europa.eu/
- UK Yellow care - https://yellowcard.mhra.gov.uk AND see http://webarchive.nationalarchives.gov.uk/20141205150130/http:/www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con408250.pdf
- US MedWatch - http://www.fda.gov/Safety/MedWatch/
- US Sentinel Initiative - http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm
- US FAERS - https://open.fda.gov/data/faers/
- Vigibase - http://www.who-umc.org/DynPage.aspx?id=98082&mn1=7347&mn2=7252&mn3=7322&mn4=7326

Associations

- AIIM - http://www.aiim.org
- American Health Information Management Association - http://www.ahima.org
- CHIMA - https://www.echima.ca
- CIHI – www.cihi.ca
- COACH - http://www.coachorg.com/en/index.asp
- The Institute of Electrical and Electronics Engineers, Incorporated - https://www.ieee.org/index.html
- HIME - https://www.efmi.org/index.php/workinggroups/hime-health-information-management-europe
- HIMSS - http://www.himss.eu
- IMS Institute - http://www.imshealth.com/en/thought-leadership/ims-institute
- IFHIMA - https://ifhima.org
- IMIA - http://www.imia-medinfo.org/new2/
- Medicine for Europe - http://www.medicinesforeurope.com
- UK Chip - http://www.ukchip.org

See also: http://www.healthinformaticsforum.com/health-informatics-associations-and-societies

Regulatory authority websites:

Asia and Pacific

World Health Organization	World Health Organization
Pan-American Health Organization	Pan-American Health Organization
WHO Regional Office for Europe	WHO Regional Office for Europe
WHO Regional Office for Africa	WHO Regional Office for Africa

WHO Regional Office for the Eastern Mediterranean	WHO Regional Office for the Eastern Mediterranean
WHO Regional Office for Southeast Asia	WHO Regional Office for Southeast Asia
WHO Regional Office for the Western Pacific	WHO Regional Office for the Western Pacific
Food and Agriculture Organizations of the United Nations	Food and Agriculture Organizations of the United Nations
Codex Alimentarius	Codex Alimentarius
World Trade Organization	World Trade Organization
Europe	
Belgium: Health, Food Chain Safety and Environment	Belgium: Health, Food Chain Safety and Environment
Belgium: Pharmaceutical Inspectorate	Belgium: Pharmaceutical Inspectorate
Croatia: Ministry of Health and Social Care	Croatia: Ministry of Health and Social Care
Danish Medicines Agency	Danish Medicines Agency
Denmark: Ministry of Food, Agriculture and Fisheries	Denmark: Ministry of Food, Agriculture and Fisheries
Denmark: Ministry of Health	Denmark: Ministry of Health
Denmark: Veterinary and Food Administration	Denmark: Veterinary and Food Administration
Estonia: Ministry of Social Affairs	Estonia: Ministry of Social Affairs
Estonia: State Agency of Medicines	Estonia: State Agency of Medicines
European Commission Consumer Affairs: Medical Devices	European Commission Consumer Affairs: Medical Devices
European Commission Directorate General for Health & Consumers	European Commission Directorate General for Health & Consumers
European Commission Directorate General: Health Notice to Applicants	European Commission Directorate General: Health Notice to Applicants
European Commission Directorate General: Medicinal Products for Veterinary Use	European Commission Directorate General: Medicinal Products for Veterinary Use
European Medicines Agency	European Medicines Agency (EMA)
Finland: Ministry of Social Affairs and Health	Finland: Ministry of Social Affairs and Health
Finnish Food Safety Authority Evira	Finnish Food Safety Authority Evira
Finnish Medicines Agency	Finnish Medicines Agency
France: National Agency for Veterinary Medicinal Products	France: National Agency for Veterinary Medicinal Products
Germany: Federal Institute for Drugs and Medical Devices	Germany: Federal Institute for Drugs and Medical Devices
Germany: Ministry of Health	Germany: Ministry of Health
Greece: Hellenic Food Authority	Greece: Hellenic Food Authority
Greece: Hellenic Ministry of Agriculture	Greece: Hellenic Ministry of Agriculture
Greece: National Organization for Medicines	Greece: National Organization for Medicines
Iceland: The Environment Agency	Iceland: The Environment Agency
Ireland: Agriculture and Food Development Authority	Ireland: Agriculture and Food Development Authority
Ireland: Department of Health and Children	Ireland: Department of Health and Children
Ireland: Food Safety Authority	Ireland: Food Safety Authority
Irish Medicines Board	Irish Medicines Board
Lithuania: Ministry of Health	Lithuania: Ministry of Health

Lithuania: State Medicines Control Agency	Lithuania: State Medicines Control Agency
Malta: Ministry of Health, Elderly and Community Care	Malta: Ministry of Health, Elderly and Community Care
Netherlands: Ministry of Health, Welfare and Sport	Netherlands: Ministry of Health, Welfare and Sport
Norway: Ministry of Agriculture and Food	Norway: Ministry of Agriculture and Food
Norway: Ministry of Health and Care Services	Norway: Ministry of Health and Care Services
Norway: Norwegian Board of Health Supervision	Norway: Norwegian Board of Health Supervision
Norway: Norwegian Medicines Agency	Norway: Norwegian Medicines Agency
Poland: Drug Institute	Poland: Drug Institute
Slovak Republic: Ministry of Agriculture and Rural Development	Slovak Republic: Ministry of Agriculture and Rural Development
Slovenia: Ministry of Agriculture, Forestry and Food	Slovenia: Ministry of Agriculture, Forestry and Food
Sweden: Medical Products Agency	Sweden: Medical Products Agency
Sweden: Ministry for Rural Affairs	Sweden: Ministry for Rural Affairs
Sweden: National Food Administration	Sweden: National Food Administration
Switzerland: Federal Office of Public Health	Switzerland: Federal Office of Public Health
Switzerland: Federal Veterinary Office	Switzerland: Federal Veterinary Office
UK: Department of Health	UK: Department of Health
UK: Food Standards Agency	UK: Food Standards Agency
UK: Health Protection Agency	UK: Health Protection Agency
UK: Medicines and Healthcare Products Regulatory Agency	UK: Medicines and Healthcare Products Regulatory Agency
UK: National Institute for Biological Standards and Control	UK: National Institute for Biological Standards and Control
UK: Veterinary Medicines Directorate	UK: Veterinary Medicines Directorate
Middle East	
Israel: Ministry of Health	Israel: Ministry of Health
Israel: Ministry of Industry, Trade and Labor	Israel: Ministry of Industry, Trade and Labor
Jordan: Ministry of Health	Jordan: Ministry of Health
Lebanon: Ministry of Public Health	Lebanon: Ministry of Public Health
Saudi Arabia: Ministry of Health	Saudi Arabia: Ministry of Health
United Arab Emirates: Ministry of Health	United Arab Emirates: Ministry of Health
United Arab Emirates: Federal Department of Pharmacies	United Arab Emirates: Federal Department of Pharmacies
Yemen: Ministry of Public Health & Population	Yemen: Ministry of Public Health & Population
Africa	
Botswana: Ministry of Health	Botswana: Ministry of Health
Egypt: Ministry of Agriculture and Land Reclamation	Egypt: Ministry of Agriculture and Land Reclamation
Ghana: Ministry of Health	Ghana: Ministry of Health
Ghana: Ministry of Food and Agriculture	Ghana: Ministry of Food and Agriculture
Kenya: Ministry of Health	Kenya: Ministry of Health
Maldives: Ministry of Health	Maldives: Ministry of Health
Mauritius: Ministry of Health & Quality of Life	Mauritius: Ministry of Health & Quality of Life
Mauritius: Ministry of Agro Industry and Food	Mauritius: Ministry of Agro Industry and Food

Security	Security
Namibia: Ministry of Health and Social Services	Namibia: Ministry of Health and Social Services
Namibia: Ministry of Fisheries and Marine Resources	Namibia: Ministry of Fisheries and Marine Resources
South Africa: Department of Health	South Africa: Department of Health
Swaziland: Ministry of Health and Social Welfare	Swaziland: Ministry of Health and Social Welfare
Tanzania: Ministry of Health	Tanzania: Ministry of Health
Uganda: Ministry of Health	Uganda: Ministry of Health
Zimbabwe: Ministry of Health and Child Welfare	Zimbabwe: Ministry of Health and Child Welfare
America	
Belize: Ministry of Health	Belize: Ministry of Health
Bolivia: Ministry of Health and Social Welfare	Bolivia: Ministry of Health and Social Welfare
Brazil: Fundacao Oswaldo Cruz	Brazil: Fundacao Oswaldo Cruz
Canada: Food Inspection Agency	Canada: Food Inspection Agency
Canada: Health Products and Food Branch	Canada: Health Products and Food Branch
Guyana: Ministry of Health	Guyana: Ministry of Health
Guyana: National Bureau of Standards	Guyana: National Bureau of Standards
Jamaica: Ministry of Health	Jamaica: Ministry of Health
Mexico: Federal Commission for the Protection Against Sanitary Risks	Mexico: Federal Commission for the Protection Against Sanitary Risks
Netherlands Antilles: Department of Public Health and Environmental Protection	Netherlands Antilles: Department of Public Health and Environmental Protection
St. Lucia: Ministry of Agriculture, Lands Forestry and Fisheries	St. Lucia: Ministry of Agriculture, Lands Forestry and Fisheries
Trinidad & Tobago: Bureau of Standards	Trinidad & Tobago: Bureau of Standards
Trinidad and Tobago: Ministry of Health	Trinidad and Tobago: Ministry of Health
Multinational	
World Health Organization	World Health Organization
Pan-American Health Organization	Pan-American Health Organization
WHO Regional Office for Europe	WHO Regional Office for Europe
WHO Regional Office for Africa	WHO Regional Office for Africa
WHO Regional Office for the Eastern Mediterranean	WHO Regional Office for the Eastern Mediterranean
WHO Regional Office for Southeast Asia	WHO Regional Office for Southeast Asia
WHO Regional Office for the Western Pacific	WHO Regional Office for the Western Pacific
Food and Agriculture Organizations of the United Nations	Food and Agriculture Organizations of the United Nations
Codex Alimentarius	Codex Alimentarius
World Trade Organization	World Trade Organization

Crowdsourcing – medical focus

- https://www.crowdflower.com/discovering-drug-side-effects-with-crowdsourcing/ - allow researchers to design and submit crowdsourcing tasks
- http://www.sermo.com - a global social crowdsourcing network for physicians and medical providers

- http://www.medhelp.org
- http://curetogether.com
- https://www.upwork.com
- https://fold.it/portal/
- https://www.mturk.com/mturk/welcome
- https://www.patientslikeme.com

Stanford links:

- http://crowdresearch.stanford.edu/w/index.php?title=Introducing_Crowd_Research_Initiative_and_Recap

Resources

- Relevant Work - used to save relevant articles, links and papers
- Forums - discussions about this project on external sites. Note that all official announcements and communications will occur via Slack and email.
- Resources - used to index all platforms and resources as we evolve
- Infrastructure and GettingStarted
- Archives - older meetings, slides and milestones
  http://voxpopuli.stanford.edu
- http://stanfordhci.github.io/twitchcrowdsourcing/
- https://github.com/crowdresearch/crowdsource-platform

Government drug regulators (this list is key, however, see the WHO list for all countries or EMA for Europe) and related research agencies

- Australia – Therapeutic Good Administration - http://www.tga.gov.au
- Canada data - http://open.canada.ca/en
- Canada ICES - http://www.ices.on.ca/About-ICES.aspx
- European Commission - http://ec.europa.eu/growth/index_en.htm and http://ec.europa.eu/health/human-use/advanced-therapies/index_en.htm
- European Medicines Agency –
- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp - see guideline and module
  - Full list of European country agencies: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp
- Finish Medicine Agency - http://www.fimea.fi/web/en/frontpage
- France - http://www.afssaps.fr
- Germany – Federal Institute for Drugs http://www.bfarm.de/EN/Home/home_node.html;jsessionid=7CCFCA856FC813AC19DD69E86C4742CB.1_cid322
- Health Canada - http://www.hc-sc.gc.ca/dhp-mps/index-eng.php
- NEHI - http://www.nehi.net
- Netherland Medicines Evaluation Board - http://english.cbg-meb.nl
- New Zealand - http://www.health.govt.nz
- PHAC - http://www.phac-aspc.gc.ca/index-eng.php
- StatsCan - http://www.statcan.gc.ca

- Sweden - https://lakemedelsverket.se/english/
- US data - https://www.data.gov
- US CDC - http://www.cdc.gov
- US IOM - http://www.nationalacademies.org/hmd/
- US FDA
    - (FEARS) – http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm083765.htm
- US NIH - https://www.nih.gov
- US NIMH - http://www.nimh.nih.gov/
- UK Medicine and Health products Regulator Agency - https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
- WHO – search site, publications section and WHOLIS database
    - http://www.who-umc.org/DynPage.aspx?id=98080&mn1=7347&mn2=7252&mn3=7322&mn4=7324
    - http://www.who.int/en/
    - http://www.who.int/library/databases/en/
    - **See List of Globally identified Websites of Medicines Regulatory Authorities -** http://www.who.int/medicines/areas/quality_safety/regulation_legislation/list_mra_websites_nov2012.pdf OR https://www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/global-regulatory-authority-websites

Pharma-related

- FDABLE - http://www.fdable.com/basic_query/aers
- EudraVigiance: http://eudravigilance.ema.europa.eu/highres.htm
- Social Media, Mobile, Wearable News & Views - http://www.scoop.it/t/pharmaguy-s-social-media-news-views/?tag=adverse+events
- Innovative medicine initiative: http://www.imi.europa.eu

Software

- Open PHACTS - https://www.openphacts.org and http://www.openphactsfoundation.org
- DebugIT - http://www.debugit.com.au
- Khresmoi - http://khresmoi.atosresearch.eu
- EHR4CR - http://www.ehr4cr.eu

Articles

Suggest to do 1) an author search on Clark Freifeld and 2) a web of science search of his publications for related articles.

- **Digital pharmacovigilance: The MedWatcher system for monitoring adverse events through automated processing of Internet social media and crowdsourcing (Thesis).**

Freifeld, Clark C., Ph.D., BOSTON UNIVERSITY, 2014, 148 pages; 3581025http://gradworks.umi.com/35/81/3581025.html

- **Freifeld CC, Chunara R, Mekaru SR, Chan EH, Kass-Hout T, et al. (2010) Participatory Epidemiology: Use of Mobile Phones for Community-Based Health Reporting. PLoS Med 7(12): e1000376. doi:10.1371/journal.pmed.1000376**
- **Freifeld CC, Brownstein JS, Menone CM *et al*. Digital drug safety surveillance: monitoring pharmaceutical products in Twitter. *Drug Safety* 2014;37:343–350.**

Guidance for Industry Internet/Social Media Platforms with Character Space Limitations— Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm401087.pdf

- Inman WH: Attitudes to adverse drug-reaction reporting. Br J Clin Pharmacol 1996; 41:433-435
- Lardon J, Abdellaoui R, Bellet F, Asfari H, Souvignet J, Texier N, Jaulent MC, Beyens MN, Burgun A, Bousquet C. Adverse Drug Reaction Identification and Extraction in Social Media: A Scoping Review J Med Internet Res 2015;17(7):e171. http://www.jmir.org/2015/7/e171/
- Lopez- Gonzalez E, Herdeiro MT, Figueiras A: Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf 2009; 32:19-31; Hugman B. The fatal love of forms. Drug Saf 2011; 34 (8): 705-707.
- R. Edwards and M. Lindquist: Social Media and Networks in Pharmacovigilance. Boon or Bane? Drug Saf 2011; 34 (4): 267-271
- Manhattan Research 2011. Cybercitizen Health Europe v10.0. Manhattan Research 2009. Navigating the European eHealth Landscape.
- Sai Moturu and Huan Liu. "Quantifying the Trustworthiness of Social Media Content", Journal of Distributed and Parallel Databases, Springer, Volume 29, January 4, 2011. DOI: 10.1007/s10619-010-7077-0. Geoffrey Barbier, and Huan Liu. Information Provenance in Social Media. SBP 2011: 276-283. Springer-Verlag Berlin, Heidelberg, ISBN: 978-3-642-19655-3
- The Impact and Use of Social Media in Pharmacovigilance - https://www.sciformix.com/wp-content/uploads/Social_Media_in_PV_Whitepaper.pdf
- See report WEBAE project (Web Adverse Events) - http://www.imi.europa.eu/webfm_send/912