Artificial Intelligence as a Medical Device (AIaMD) Adverse Event Reporting in Regulatory Databases: A systematic review protocol

Aditya U Kale, Riya Dattani, Ashley Tabansi, Henry David Jeffry Hogg, Russell Pearson, Ben Glocker, Su Golder, Justin Waring, Xiaoxuan Liu, David J Moore, Alastair K Denniston

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Abstract

Background: Adverse event (AE) reporting is a key feedback signal for detection of safety issues relating to healthcare products. The reporting of adverse events for medical devices is a longstanding area of concern, with suboptimal reporting due to a range of factors including a failure to recognise the association of AEs with medical devices, lack of knowledge of how to report AEs and a general culture of non-reporting. The introduction of Artificial Intelligence as a Medical Device (AIaMD) requires a robust safety monitoring environment that recognises both generic risks of a medical device, and some of the increasingly recognised risks of AI health technologies (such as algorithmic bias). There is an urgent need to understand the limitations of current AE reporting systems, and explore potential mechanisms for how AEs could be detected, attributed and reported with a view to improving early detection of safety signals.

Objective: This systematic review aims to search for existing adverse event reports for AIaMD, extract event data, and analyse the reported events to yield insights into their frequency and severity, whilst characterising the events using existing regulatory guidance.

Methods: Publicly accessible adverse event databases will be searched to identify adverse event reports for AIaMD. Scoping searches have identified three regulatory territories for which public access to AE reports is provided: USA, UK, and Australia. Data extraction will be conducted using a data extraction tool designed for this review and will be done independently by two reviewers. Descriptive analysis will be conducted to identify the types of AEs being reported, and their frequency, for different types of AIaMD. AEs will be analysed and characterised according to existing regulatory guidance.

Results: Scoping searches are being conducted and data extraction and synthesis will commence in August 2023, with planned completion by the end of 2023. The review has been registered on the Open Science Framework (https://osf.io/n2wrt/).

Conclusions: To our knowledge, this will be the first systematic review of three different regulatory sources reporting AEs associated with AIaMD. The review aims to outline the characteristics and frequency of adverse events reported for AIaMD, and

help regulators and policy-makers to continue developing robust safety monitoring processes.

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Abstract

Background

The reporting of adverse events (AEs) from medical devices is a longstanding area of concern, with suboptimal reporting due to a range of factors including a failure to recognise the association of AEs with medical devices, lack of knowledge of how to report AEs and a general culture of non-reporting. The introduction of Artificial Intelligence as a Medical Device (AIaMD) requires a robust safety monitoring environment that recognises both generic risks of a medical device, and some of the increasingly recognised risks of AIaMD (such as algorithmic bias). There is an urgent need to understand the limitations of current AE reporting systems and explore potential mechanisms for how AEs could be detected, attributed and reported with a view to improving early detection of safety signals. The systematic review outlined in this protocol aims to yield insights into the frequency and severity of AEs, whilst characterising the events using existing regulatory guidance.

Methods

Publicly accessible adverse event databases will be searched to identify adverse event reports for AIaMD. Scoping searches have identified three regulatory territories for which public access to AE reports is provided: USA, UK, and Australia. AEs will be included for analysis if an AI medical device was involved. Software as a medical device without AI is not within the scope of this review. Data extraction will be conducted using a data extraction tool designed for this review and will be done independently by two reviewers. Descriptive analysis will be conducted to identify the types of AEs being reported, and their frequency, for different types of AIaMD. AEs will be analysed and characterised according to existing regulatory guidance.

Results

Scoping searches are being conducted with screening to begin in April 2024. Data extraction and synthesis will commence in May 2024, with planned completion by August of 2024. The review will highlight the types of adverse events being reported for different types of AI medical devices, and where the gaps are. It is anticipated that there will be particularly low rates of reporting for indirect harms associated with AIaMD.

Discussion

To our knowledge, this will be the first systematic review of three different regulatory sources reporting AEs associated with AIaMD. The review will focus on real world evidence which brings

certain limitations, compounded by the opacity of regulatory databases generally. The review will outline the characteristics and frequency of adverse events reported for AIaMD and help regulators and policy-makers to continue developing robust safety monitoring processes.

Study registration

The review has been registered on the Open Science Framework: Kale A, Denniston A, Moore D, Liu X, Hogg J, Glocker B, et al. Artificial Intelligence as a Medical Device (AIaMD) Adverse Event Reporting in Regulatory Databases: A systematic review protocol 2023. osf.io/n2wrt.

Background

Patient safety has been defined as one of the six key indicators of healthcare quality by the Institute of Medicine (IOM).[1] In a landmark report published in 2001, the IOM identified that approximately 100,000 adverse events (AEs) resulted in patient death each year in the USA, with sources suggesting that medical error is third on the list of leading causes of death.[2,3] In the UK's National Health Service (NHS), it is estimated that 8-12% of hospital admissions may involve an AE resulting in harm to the patient.[4,5]

Whereas administration errors and AEs have been extensively explored in the context of medication, there has been much less attention given to similar issues in the context of medical devices.[6] Suboptimal reporting exists due to a range of factors such as failure to recognise the associated of AEs with medical devices, lack of knowledge of how to report AEs, as well as a common culture of not reporting events.[7] Evidence shows that a significant proportion of adverse events in hospitals (including drug and device AEs) are indeed preventable, and that transparency of AE reporting to generate insights into device safety issues is essential.[8–10]

Artificial Intelligence (AI) as a Medical Device (AIaMD) is an important new tool for improving healthcare, most notably in the areas of diagnosis, screening, prognosis and clinical decision support systems. There is however an increasingly recognised performance gap between the initial proof-of-concept studies, and what may be observed in the more challenging deployment in the real world where there is greater diversity of setting and population, and much less control of external factors.[11–13] An important factor in wider adoption of AIaMD will be to have adequate systems of safety signal detection, attribution and reporting that are transparent and can be trusted by health systems and the patients and public they serve. One key component of existing safety systems is AE reporting. An AE is defined as *"An unfavourable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it."*[14,15] It is important to note that definitions of adverse events are often centred around the use of medicines rather than medical devices. For the purposes of this review, relevant regulatory guidance such as that from the IMDRF will be used to guide classification of adverse events.[16]

AE reports can be submitted by different stakeholders including device manufacturers, clinical staff or patients and members of the public. The AE reporting processes vary by country, however in general each regulatory body has an adverse event or safety notice database, of which some are

publicly available and searchable. There are currently no specific AIaMD AE reporting processes and therefore existing processes for medical devices are currently used.

Guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) was recently released, aiming to aid manufacturers in understanding what events should be reported.[17] There still remains an urgent need to develop robust safety monitoring processes to ensure that patients, professionals, health systems and regulators can have confidence that AIaMDs are safe for patients. AE reporting is an important component of safety monitoring and aims to ensure that any AIaMD that is found to be unsafe after reaching market is swiftly detected and either corrected or removed.

Purpose

Adverse event reporting is a cornerstone of safety monitoring in medical devices and other healthcare products and will be a key component of the safe introduction of AIaMD. There are concerns however that current AE reporting systems are inadequate with many AEs remaining hidden. Even when AEs are reported, the details are not publicly available, leading to a lack of transparency, and reducing the opportunity for these and other health systems to learn and act early. Even for regulatory territories with stronger AE infrastructure (openly accessible dedicated AE databases), it is unclear how well AEs are reported and recorded within those databases. The systematic review described in this protocol aims to identify reported adverse events and data relating to frequency and severity for different types of AIaMD.

The secondary aims of the review described in this protocol are 1) to compare the number of AEs reported for different AIaMD risk classes, 2) to compare AE reporting across three jurisdictions with publicly available AE databases, and 3) to identify the level of clinical evidence available for devices with reported AEs.

Methods and analysis

Reporting of protocol and systematic review

The reporting of this protocol follows the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[18] Reporting of the subsequent review will adhere to the PRISMA reporting guideline for systematic reviews,[19] and the PRISMA-AI guideline (if available as this is still in development).[20]

Systematic review registration

This systematic review has been registered on the Open Science Framework[21]

Information sources

The search strategy for this review has been designed to identify reported AIaMD adverse events. We have identified searchable AE databases through scoping searches across three different jurisdictions. These include:

1. The Manufacturer and User Facility Device Experience (MAUDE), available from the US Food and Drug Administration (FDA), USA.[22]
    a. MAUDE contains reported adverse events associated with FDA approved medical devices. AEs can be reported by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters (e.g. health professionals, patients and consumers).[23]
2. The Database of Adverse Event Notifications (DAEN), available from the Therapeutic Goods Administration (TGA), Australia.[24]
    a. DAEN, similar to MAUDE, contains adverse event data for medicines and medical devices approved for use by the TGA.
3. Field Safety Notices (FSNs) website, available from the Medicines and Healthcare Products Regulatory Agency (MHRA), UK.[25]
    a. FSNs describe corrective actions taken by device manufacturers in response to an identified safety issue. These notices are not reported adverse events, however they can contain relevant device safety data that can be extracted. Field safety notices may be disclosed by manufacturers in response to adverse events.

Scoping searches have demonstrated that there are relatively fewer information sources for medical device AEs compared to AEs associated with medicines. The three databases above have been

identified as being searchable to yield details regarding safety events. In addition to the AE/FSN databases, each of the three regulatory bodies outlined above will be searched to identify any product recalls for AIaMDs.

Search strategy

We have undertaken an initial feasibility assessment of searching AE databases. Given that each database is unique to its own regulatory body, different search strategies are required. Search strategies cannot be transferred between AE databases due to inconsistencies in terminology, device names and search capabilities. It is important to note that the common thread in the search strategies is searching for AIaMDs for which AEs have been reported. The following search strategies are specific to each database listed below:

- MAUDE (provided by the FDA)
    - This database will be searched using the openFDA application programming interface (API). The openFDA was set up by the first Chief Health Information Officer in March 2013, and enables public access to relevant data including drug and medical device adverse events.
    - The API can be searched to request several data points. This approach has been employed in previous studies to identify adverse events for both drugs and devices. [26,27]
    - The database will be searched to find adverse events reported for Artificial Intelligence/Machine Learning (AI/ML) enabled devices listed on the FDA website. [28]
- DAEN (provided by the TGA)
    - The DAEN website allows for searches of medical device AEs. Due to a lack of AI or ML specific search terminology, it is not possible to search the database using these terms. However, the word “software” is indexed and will be used to search for relevant events. Events specific to AIaMDs will be identified through manual screening.
- FSNs website (provided by the MHRA)
    - The MHRA FSNs website has an in-built search function, and the database will be searched using a similar approach to the search of DAEN. As above, following identification of software related FSNs, manual screening will be undertaken to identify AIaMD related FSNs.

For devices where events are identified in one of the three information sources, online web searches will be used to identify the device manufacturer website. Where available, details for clinical evaluations will be identified from the device manufacturer's website. Data will be extracted for analysis including the type of study, sample size, reported demographics, and whether or not any adverse events were identified and reported. Further information regarding the extracted data is listed below, and a PRISMA flow diagram is shown in figure 1 to be populated during the review process.

Selection criteria

Intervention:

All regulatory approved AIaMDs will be included in this systematic review. Two reviewers will independently screen identified adverse event reports to ensure that the medical device in question is an AI medical device.

Types of documentation:

The following documentation will be reviewed to ensure appropriate selection of medical devices.

- MAUDE (provided by FDA)
    - The full AIaMD AE/incident report will be downloaded and cross-referenced with the FDA summary document. The summary documents include details regarding evidence submitted for approval and the date of regulatory approval. This documentation often includes the intended use and type of the AIaMD.
- DAEN (provided by TGA)
    - The full AE report will be downloaded and assessed to ensure that the medical device in question is AIaMD. This will be cross-referenced with online sources where required, such as the device manufacturer's website.
- FSNs (provided by MHRA)
    - The full FSN will be downloaded and assessed to ensure the medical device is AIaMD. As with the Australian database (DAEN), devices will be cross-referenced with online sources as required.

Selection process

Once AIaMDs are identified through searches, the adverse event reports, or field safety notices will be screened to ensure that the medical device is AI/ML enabled. Cross-referencing using online

sources, and available regulatory documents will be undertaken. Where required, manufacturers will be contacted for additional details. This will be undertaken independently by two reviewers. The main inclusion criterion is that the AE report concerns an AIaMD. The exclusion criteria are as follows:

- AE reports for AI health technologies that are not medical devices
- AE reports for software as a medical device with no use of AI

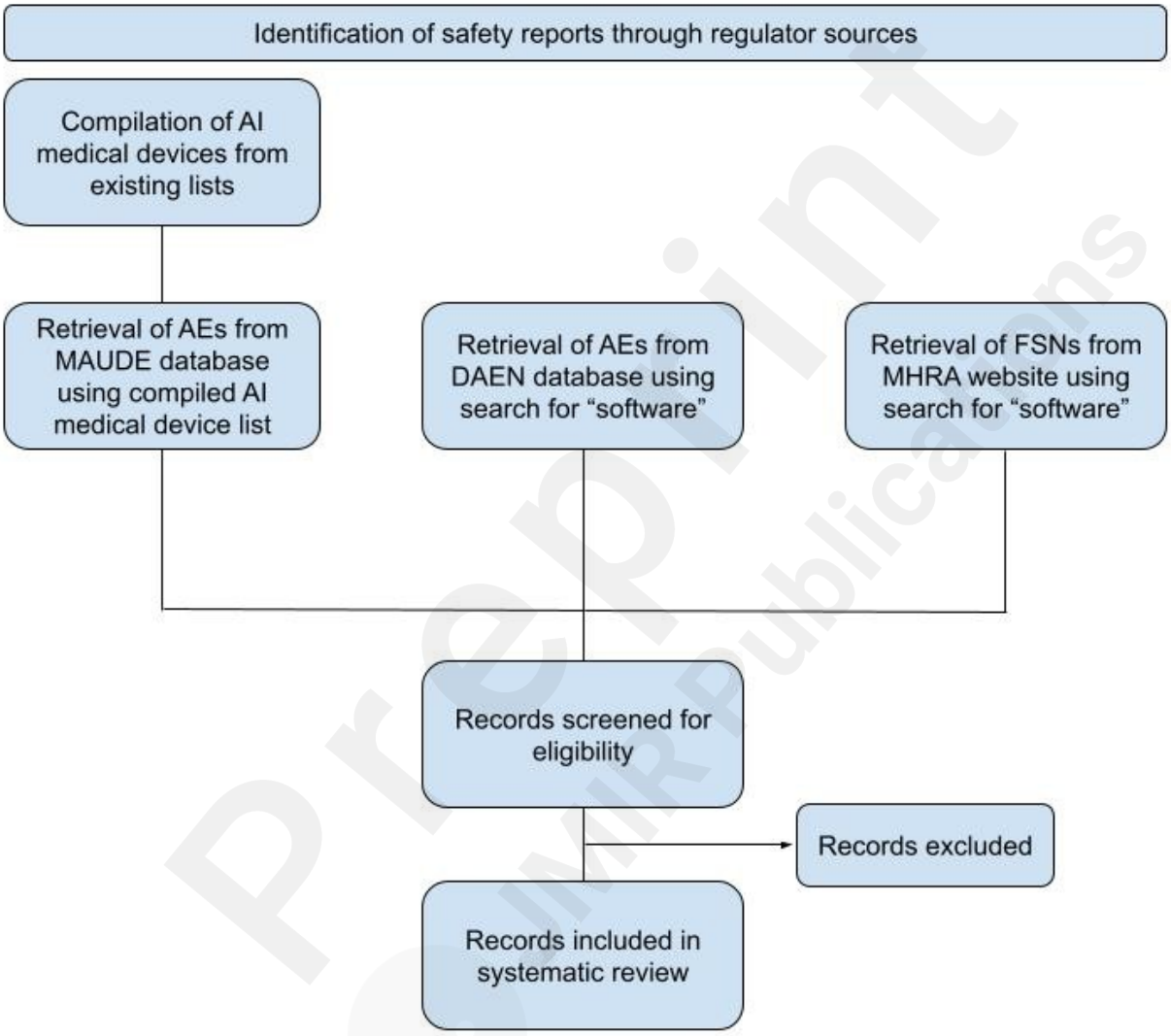

Figure 1: PRISMA flowchart to be populated during systematic review process

Risk of bias assessment and confidence in cumulative evidence

This systematic review focuses on real world data reported in regulatory databases. There are no formal risk of bias tools for this data, however the review will include a measure of completeness of data reported in adverse event reports. There will be no formal evaluation of confidence in cumulative evidence as the items included in this review are not research articles.

Data extraction

The data extraction process will involve three stages. The first stage relates to the MAUDE database (FDA). The openFDA API will be used to extract all AIaMD related reports into a local database. The data will then be tabulated and displayed in Microsoft Excel (Microsoft, Washington, UK). The second stage relates to the DAEN (TGA) and FSN (MHRA) information sources. For these, the data extraction process will be undertaken using a standardised data extraction form. Data will be entered into the extraction form using Microsoft Excel (Microsoft, Washington, UK). Two reviewers will extract this data independently using the agreed template and any disagreements will be escalated to a third arbitration reviewer. Lastly, available regulatory approval data will also be extracted where available for AIaMDs with reported AEs. For AIaMDs with reported AEs, published clinical evaluation studies will also be identified where available.

The following data will be extracted based on documentation available from the FDA, international medical device regulators forum (IMDRF), and published literature.[29,30]

Data points directly relating to safety reports:

- Type of report
- Date of event
- Date of report
- Patient demographics
- Patient outcome (Death, injury or malfunction without patient harm)
- Description of the event (Free text entry regarding the incident)
- Device brand name (Brand name of AI medical device involved in the AE report)
- Manufacturer name (Name of manufacturer for the AI medical device in question)
- Unique device identifier if available
- Operator of device
- Reporter occupation
- Response to AE from manufacturer where available (details regarding any investigation)
- Latency of response from manufacturer (time from AE report to manufacturer response)
- Recall data if available

Further data regarding the AIaMD will be identified from clinical evaluation data. Data points

relating to the medical devices in question:

Datapoint	**Explanation**
Approval number (if FDA approved)	Unique approval number assigned to devices acquiring regulatory approval
Approval pathway	The name of the regulatory pathway through which the AIaMD was approved. E.g. for the FDA this will be 510k, De novo or Premarket approval
Manufacturer origin country	The country of origin of the manufacturer
Medical specialty	The medical discipline which the device is intended for
Type of AI	The type of AI system e.g. deep learning
Autonomy level of AIaMD	Autonomy level will be graded based on the intended use of the device
Intended use of AIaMD	Intended purpose of the device and associated detail such as intended population and setting
Risk classification	The risk class of the AIaMD as approved by the regulator
Risk level	The risk level of the AIaMD determined according to IMDRF guidance
Validation sample size	The sample size of the validation cohort if available
Retrospective or prospective validation	The type of validation study that was conducted prior to regulatory approval
Reported demographics in validation	Any reported patient demographics reported in the validation study
Adverse events reported in clinical validation study	Whether or not any adverse events were reported within the validation study prior to regulatory approval

Data synthesis

A descriptive analysis of extracted data will be undertaken. Analysis of the variables described above will include comparison across 1) types of intended use (and risk level), 2) specialty area, and 3) regulatory territories (UK/USA/Australia). The comparison aims to identify whether there are certain types of AIaMD intended use (and risk level), specialty, or regulatory territory within which AEs are more commonly reported. The types of intended use for AIaMDs will be grouped into two broad categories based on clinical tasks. These will include 1) diagnostic and prognostic AIaMD and 2)

therapeutic AIaMD. Detected AEs and FSNs will be characterised according to AE terminology available from the IMDRF.[31]

Once AEs and FSNs have been characterised using AE terminology, rates of each type of AE will be quantified and compared between the groups described above. The following further analyses will also be considered:

- The number of AEs reported per year to identify trends in reporting
    - Rates of AEs reported for AIaMDs across the three jurisdictions mentioned will be calculated. This will be calculated for each group above, but also across groups to quantify trends in AE reporting.
- Completeness of adverse event reports
    - AE reports often vary in their completeness. For example some reports may not contain who reported the event, or what the final patient outcome was. Completeness of adverse event reports will be assessed against reference criteria, developed using existing guidance and adverse event reporting forms. The IMDRF (which has membership of several international regulators) provides guidance relating to AE reporting. This assists in standardisation of AE reports across globe. Therefore, it is likely that findings generated will apply to AE reporting both within and outside the three jurisdictions included in this study.
- Adverse event reporting party.
    - The source of the adverse event will be compared across groups to understand how reporting characteristics vary. E.g. reporting by manufacturers versus clinical staff versus patients.
- Availability of clinical evaluation data for medical devices with reported adverse events.
    - Where adverse events are reported for AIaMD, and clinical evaluation data is available (from regulatory or manufacturer websites), further analysis will be conducted. The types of AEs that are reported across different clinical studies will be identified and compared with AEs detected in adverse event databases.

The analysis aims to generate insights into the frequency of reporting of AIaMD associated AEs, but also the characteristics of the AEs in order to inform real world safety monitoring practices for AIaMD. Additionally, this systematic review aims to generate insights into how AE reporting may vary by region and regulatory authority. By understanding what types of AEs have been reported,

systems to detect relevant patient harms can be implemented in real world AI safety monitoring strategies.

Results

Scoping searches are being conducted with screening to begin in April 2024. Data extraction and synthesis will commence in May 2024, with planned completion by August of 2024. The review will highlight the types of adverse events being reported for different types of AI medical devices, and where the gaps are. It is anticipated that there will be particularly low rates of reporting for indirect harms associated with AIaMD.

Discussion

The systematic review outlined in this protocol aims to identify and characterise adverse events arising from AIaMDs as estimated through AE reporting systems. The review will highlight the types of adverse events being reported for different AI medical devices, and more importantly where the gaps are. It is anticipated that reporting will be poor overall with particularly low rates of reporting for indirect harms associated with AIaMD.

AEs are often poorly reported in the literature and are usually not the primary outcome of clinical research studies.[32] Once a medical device has gained regulatory approval and is in active use, AE reporting is an essential component of post-market safety monitoring. There is variable reporting of AEs for medicines and medical devices, and reporting can often be sporadic for the latter.[6,33] AI as a medical device has gained much interest recently, with many new commercially available AIaMDs ready for deployment. However, there remains a lack of consensus around how to ensure robust safety monitoring post-deployment. One key aspect is AE reporting for AIaMDs.

There is minimal awareness around what consists of an AE for AIaMDs and how these AEs should be reported. This systematic review protocol describes the methodologies for searching AE databases and highlights relevant information sources. The systematic review will outline the methodology for searching AE databases and highlight all reported AEs for AI as a medical device. The review will provide insights into the types of AEs that may occur for AIaMDs, the completeness of reporting, and the frequency of AE reports. Given the often variable AE reporting for many other types of medical devices, it is likely that AE reporting for AIaMDs will be equally variable if not even poorer. The data points listed in the previous section will allow analysis of frequency and types of AEs being

reported, in addition to the types of AI medical devices for which AEs are more commonly identified. Furthermore, for devices where validation data is available from regulators, analysis will highlight potential correlation between the level of evidence submitted for regulatory approval, and the likelihood of AEs being reported.

There are several limitations which need to be considered. First, the review described in this protocol focuses on real world evidence in the form of adverse events which have been reported through post-market surveillance pathways. This means that there will be variation in the quality of reports. As part of this review, the completeness of the report will be assessed, however there will not be a formal risk of bias assessment. Second, the scope of this review is focused on AI as a medical device There will be numerous AEs reported for software as a medical device without AI. Many of the AEs related to this group of devices could provide relevant insights for AI medical devices and there might be value in a review for these devices in the future. Finally, this study only examines publicly available data as access to additional data is reserved for medical device regulators only. It is anticipated that the review will highlight the need for transparent databases, providing a foundation for further work with regulators to reduce opacity of such data sources.

This review of adverse event databases comes at a key milestone in AIaMD regulation reform and aims to inform regulators and policymakers of the current state of AE reporting. The review will provide information such as the devices and types of algorithms for which AEs are most commonly reported, whether any use cases or specialties are frequently involved, and potentially the level of clinical validation associated with frequent AE reports if this is available. A companion systematic review is being conducted by our group investigating AE reporting in randomised controlled trials (RCTs) of AI medical devices. The companion review aims to assess the types of AEs being reported in RCTs, but also how algorithmic performance error analysis is conducted. Together, these systematic reviews will identify the current status of AE reporting across both clinical trial and real-world deployment phases. This work aims to generate insights into how AIaMD safety signals could be monitored going forward, whilst informing the decision making of multiple stakeholders including manufacturers, AIaMD deployment teams, regulators, and policymakers.

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Conflicts of Interest

The authors declare no conflicts of interest.

Author contributions

All authors have contributed to the design and development of this systematic review. AUK, XL, DJM, and AKD contributed directly to the drafting of the manuscript. AUK and RD developed the search strategy including API based searches of the openFDA database. All authors contributed to reviewing and redrafting of this manuscript. They have all approved the final version and agreed to be held accountable for all aspects of the work. AKD and DJM are joint senior authors.

Abbreviations

AI- Artificial Intelligence
AE- Adverse Event
AIaMD- Artificial Intelligence as a Medical Device
DAEN- Database of Adverse Event Notifications
FDA- Food and Drug Administration
FSN- Field Safety Notice
MHRA- Medicines and Healthcare products Regulatory Agency
TGA- Therapeutic Goods Agency

Multimedia Appendix 1: PRISMA-P 2015 Checklist

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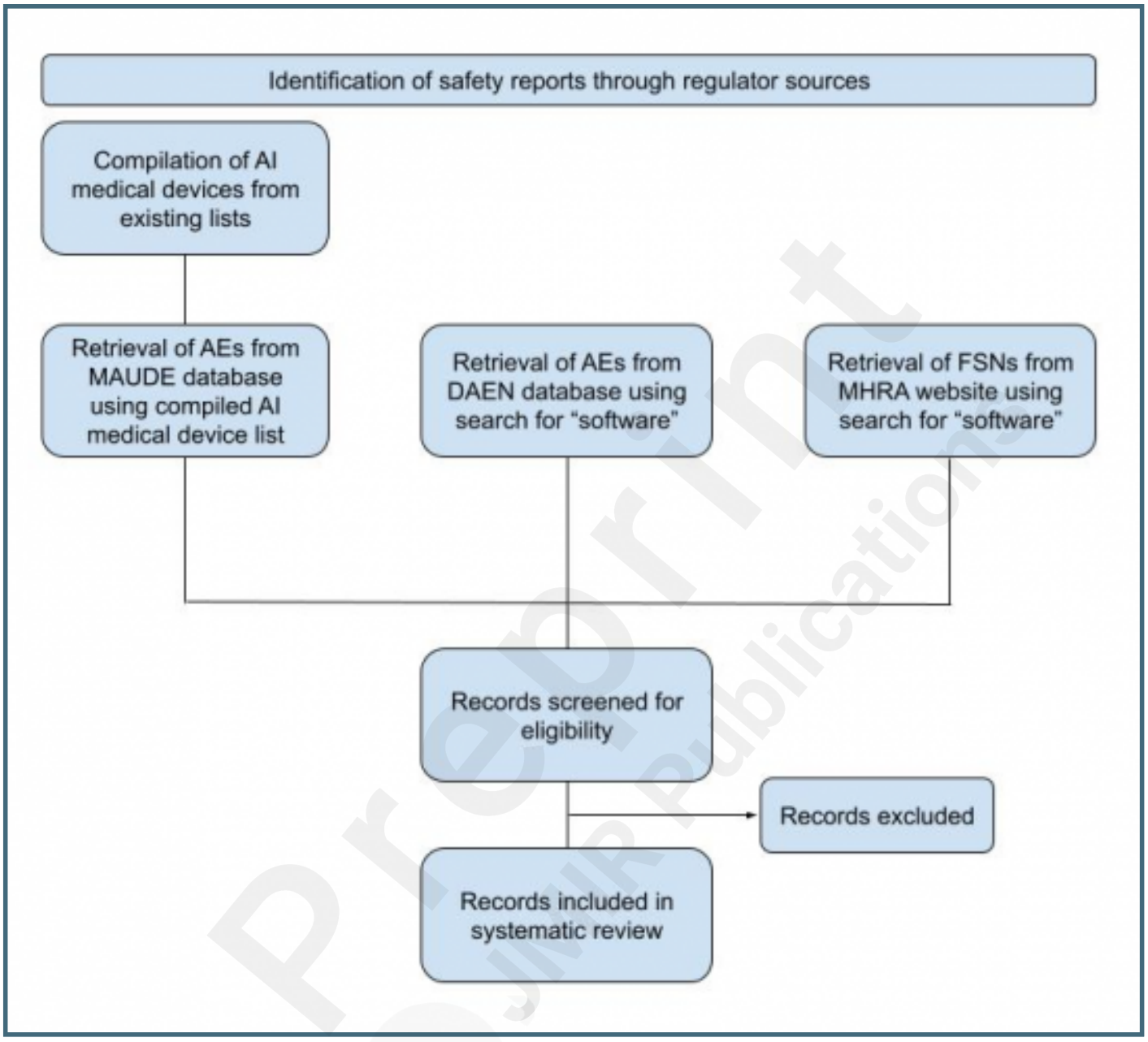
Supplementary Files

Figures

PRISMA flowchart to be populated during systematic review process.



Multimedia Appendixes

PRISMA-P Checklist.
URL: http://asset.jmir.pub/assets/55a6991f656601884c6b20c29269a465.docx