PROTOCOL FOR SYSTEMATIC REVIEW ON REPORTING SUSPECTED ADVERSE DRUG REACTIONS
TITLE

Reporting suspected adverse drug reactions in patients: a systematic review of randomized controlled trials, observational and survey studies.

PROTOCOL INFORMATION¹:

Authors

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Contact person

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Preferred Reporting Items for Systematic Review and Meta-Analyses (‘PRISMA’)

This Protocol is primarily based on the 27-item checklist described in the PRISMA statement (Liberati et. al., 2009). The empirical and methodological research literature will be reported following the PRISMA (Moher, Liberati, and Altman, 2009) standards.

¹ (Higgins and Green, 2008).
ABSTRACT

The systematic review report will include a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants; interventions; study appraisal and synthesis; methods; results; limitations; conclusions; implications of key findings; and PRISMA registration number.

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CHAPTER 1

INTRODUCTION

Rationale

There is limited scientific research on:

a) the systems of reporting suspected (‘ADRs’) by patients and healthcare professionals (‘HCPs’);

b) patients’ and HCP’s knowledge, understanding, and experiences of reporting suspected ADRs;

c) factors that affect or could affect such reporting; and

d) how the above issues may be improved.

This review intends to bridge the current gaps and make recommendations, which can benefit patients, HCPs, and policy makers in worldwide populations, especially low-middle income countries (The World Bank, 2016), where this unmet human need may be most felt.

Patients use marketed drugs to treat diseases that continue to threaten the world’s populations such as cancer and diabetes. Unfortunately, some drugs continue to cause serious ADRs in patients. This means there are present and future needs to detect, assess, understand and prevent (Stephens, 2012) ADRs in patients and one way to achieve this is to reform the existing systems of reporting suspected ADRs to help to ensure that when
medicinal product safety problems arise prompt action is taken to keep worldwide populations safe from serious harm (MHRA, 2015a).

Under-reporting and the quality of data reported by patients and HCPs pose problems in the UK and internationally (Cornelius et. al., 2012; Stephens, 2012), while the extent to which definitive ADRs are under-reported is not known. Other current problems include: false positives/negatives created by reported data; proving causation after reports are made; inconsistent standards of reporting; background noise in the reporting databases, which obscures/confuses data that may lead to a signal; and limited incentives for HCPs and patients to report suspected ADRs.

These problems hinder the detection, assessment, understanding, and prevention of ADRs, which are often serious enough to result in admission to hospital (Pirmohamed et. al., 2004) and place a significant burden on health services and account for morbidity, mortality and extra costs (Pirmohamed et. al., 2004). For example, the percentage of hospital admissions due to ADRs was circa 10%; in France, two studies showed prevalence rates of 10.3% and 13.0% respectively (Moore et. al., 1998; Imbs et. al., 1999). In a UK prospective observational study of 18,820 hospital patients there were 1,225 admissions related to an ADR; a prevalence rate of 6.5%; an ADR directly led to admission in 80% of cases; the median bed stay was eight days, accounting for 1 in 16 hospital admissions, which was 4% of hospital bed capacity; and the overall fatality was 0.15% (Pirmohamed et. al., 2004).

In the USA it has been estimated that deaths attributable to ADRs accounted for the 4th-6th largest cause of mortality (Lazarou et. al., 1998) and ADR death rates based on reported US vital statistics increased between 1999 and 2006, with clear associations with age, race and urbanization subgroups (Shepherd et. al., 2012). In the USA between 2006 and the first quarter of 2015 the Food and Drug Administration’s Adverse Events Reporting System (‘AERS’) showed a steady increase in the rate of the seriousness of the adverse events
reports made (U.S. FDA, 2015). This is shown in Figure 1. The potential signals of serious risks/new safety information identified from the AERS for the period 2008 to the first quarter of 2016 suggest that a significant number of these reports relate to suspected ADRs (U.S. FDA, 2016a). However, there is no certainty that any reported event was actually due to the implicated drug (U.S. FDA, 2016b). The FDA does not require that a causal relation between a drug and an event be proven and reports do not always contain enough detail to evaluate an event properly (U.S. FDA, 2016b). In some cases the reports may relate to duplicate reporting, owing to factors such as follow-up reports received on a case or different persons reporting on the same patient case (U.S. FDA, 2015). Furthermore, the FDA does not receive reports of every adverse event or medication error that occurs with a drug (U.S. FDA, 2016b). The AERS system has a number of weaknesses, but the exact extent of the magnitude of the problem in the USA and other worldwide jurisdictions is not known.

**Figure 1.** Patient outcome(s) for reports in AERS from 2006 to the first quarter of 2015 (U.S. FDA, 2015).
Adverse drug reactions are a financial burden to worldwide National Health Services (‘NHS’). For example, in some countries 15-20% of hospital budgets have been spent on dealing with drug complications (White et. al., 1999, cited by WHO, 2002). Adverse drug reactions increase costs due to increased hospitalization, prolongation of hospital stay and additional clinical investigations in more serious cases (Sultana et. al., 2013). In the USA the economic burden resulting from ADRs (Sultana et. al., 2013) has been conservatively estimated at $US30 billion dollars annually (White et. al., 1999; Sultana et. al., 2013) and could exceed $US130 billion in a worst-case scenario (White et. al., 1999). In a UK observational study the projected annual cost of ADRs hospital admissions to the UK NHS was £466m (€706m, $847m) (Pirmohamed et. al., 2004). There are also indirect costs for patients and their caregivers, e.g. missed days from work and/or patient morbidity and anxiety due to the ADR(s) (Wu and Pantaleo, 2003, cited by Sultana et. al., 2013). Adverse drug reactions may also trigger prescription cascades when new medications are prescribed for conditions that are a consequence of other medications, which is often an unrecognized ADR (Sultana et. al., 2013).

These problems can adversely affect patients’ quality of life and can also cause patients to lose confidence in the healthcare system (MHRA, 2015b). If they are not tackled they will compound, because the world population of 7.3 billion, in 2015, is expected to reach 8.5 billion by 2030, 9.7 billion in 2050 and 11.2 billion in 2100 (United Nations, 2015).

**Aims**

*Primary*

We intend to critically evaluate the reporting of suspected ADRs by patients and HCPs.
Secondary

This review intends to investigate: what is known; what is unknown; patients and HCPs knowledge, understanding and experiences of reporting suspected ADRs; factors that affect them/could affect them in making reports; and how the above issues may be improved.

Objectives (questions)

Question 1

Given the current weaknesses of the systems for patients and HCPs to report suspected ADRs, what systems exist, can better models be created or implemented and would such models be practicable and cost effective in practice?

Table 2 describes how research question 1 was formulated by applying the PICOS criteria: Population; Intervention or Indicator; Comparison; Outcome; and Study Design (Richardson et al., 1995) framework mnemonic.

| P: Population/Patient/Problem | Patients\(^2\) and HCPs\(^3\) in any population. The reporting systems problems include: under-reporting; data quality; difficulties in detecting signals after reports are made; duplication of reports; subjective bias of reporters; poor contribution of reporting data to signal detection; false positives/negatives; data background noise; and limited harmonized reporting |

\(^2\) This includes in and out patients and patients with any disease types.

\(^3\) This review will research: doctors; nurses; pharmacists; and dentists.
standards.

I: Intervention or indicator  New reporting systems or no intervention.

C: Comparison/control  Existing reporting systems or no comparison/control.

O: Outcome of interest  The systems that exist, the creation or implementation of new models and their practicable and cost effective feasibility in practice.

S: Study Design  Randomized controlled trials; observational and survey studies on reporting suspected ADRs.

**Question 2**

What is the understanding, knowledge and experiences of patients and HCPs in the UK and internationally about reporting suspected ADRs, what factors affect them or could affect them in making reports and how might they be improved?

**Table 3** describes how research question 2 was formulated by applying the PICOS criteria: Population; Intervention or Indicator; Comparison; Outcome; and Study Design (Richardson et. al., 1995) framework mnemonic.

P: Population/Patient/Problem  Patients⁴ and HCPs⁵ in any population. The problems are: a lack of understanding, and knowledge about reporting suspected

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⁴ Op. Cit. 2.
⁵ Op Cit. 3.
ADRs and negative practical, psychological and emotional factors that influence reporting.

I: Intervention or indicator
New reporting systems designed to improve understanding, knowledge, experience and factors that affect or could affect patients and HCPs reporting or no intervention.

C: Comparison/control
Existing understanding, knowledge, experience and factors that affect or could affect patients and HCPs reporting or no comparison/control.

O: Outcome of interest
Patients’ and HCPs knowledge, understanding and experiences of reporting and factors that affect or could affect them in making reports and how these issues, including the problems identified in ‘P’ above, might be improved to benefit them.

S: Study Design
See Table 2.
CHAPTER 2

METHODS

Protocol and registration

This Protocol will be registered on PROSPERO (CRD, 2015), which is an international prospective register of systematic reviews. Protocol details, including the registration number can be viewed on: http://www.crd.york.ac.uk/PROSPERO/. Non-research theoretical literature reviews (and scoping reviews) are not eligible for inclusion in PROSPERO (CRD, 2015). Therefore, the separate Protocol for the non-research theoretical systematic literature review will not be registered and published in PROSPERO (CRD, 2015).

Eligibility criteria

The criteria set out below are consistent with the aims and objectives of the review set out in Chapter 1 and the assumption is that this strategy may provide evidence that will enable them to be achieved. To facilitate making comparisons between the characteristics of studies retrieved and the study characteristics of this review, the types of studies included must have been designed by using PICOS, and have a minimum length to follow up of 1 month (Liberati et. al., 2009).

Types of studies

The following are eligible: randomized controlled trials, observational and survey studies (CRD, 2009), which examine:
• systems for participants to report suspected ADRs;

• participants’ understanding, knowledge and experiences of reporting suspected ADRs; and

• factors that affect or could affect participants reporting suspected ADRs.

The eligible studies will be restricted to English language only. No jurisdictional limits or publication status restrictions will be imposed on studies, except, unpublished material and abstracts will be excluded from the review (Liberati et. al., 2009). The language restriction is imposed due to limited resources to transcribe non-English studies. The exclusion of unpublished material and abstracts may provide greater consistency, reliability and quality of eligible included studies, which are beneficial to the robustness of the scientific evidence base available for analysis and reaching conclusions. The following publication date restriction will be imposed: all studies will be restricted to the period from 1st January 2006 to 20th September 2016.

Non-randomized controlled trials are excluded in order to raise the quality of the inclusion criteria and to mitigate a substantial and disproportionate number of search results arising from a research scoping exercise. Case series and case reports are excluded from the review owing to the high risk for bias in these study designs (CRD, 2009). Case-control studies, economic evaluations (CRD, 2009) and other secondary data e.g. letters to the editor (Liberati et. al., 2009) will also be excluded for the aforementioned reasoning in the preceding paragraph for the exclusion of unpublished material and abstracts.

**Types of participants**

Patients and HCPs aged ≥18.
**Types of interventions**

- New reporting systems.
- New reporting models designed to improve the attitude and behaviour of patients and HCPs.
- No intervention.

**Types of outcome measures**

Studies will be excluded from this review if they do not meet at least one of the primary outcome measures.

*Primary*

- The extent to which the reporting systems are effective or ineffective as measured by the outcomes of the eligible studies.
- Participants’ knowledge, understanding and experiences of the reporting systems as measured by the outcomes of the eligible studies.
- Propensity and rates of reporting suspected ADRs incidents in accordance with:
  
i. mechanistic schemes to classify ADRs called: Extrinsic, Intrinsic, Distribution, Outcome, Sequela (‘EIDOS’); Dose relatedness of the reaction, Time-course of the reaction, and individual Susceptibility factors (‘DoTS’) and the type A and type B
pharmacological classification (Aronson and Ferner, 2003; Ferner and Aronson, 2010; Stephens, 2012); guidance; personal knowledge/experience/judgment;

ii. seriousness, which is defined and measured as an adverse event or suspected adverse reaction that results in any of the following outcomes: death; a life threatening adverse event; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant incapacity; or substantial disruption of the ability to conduct normal life functions; or a congenital anomaly/birth defect (Department of Health and Human Services, 2010);

iii. intensity (severity) of suspected ADRs as defined and measured by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (National Cancer Institute, 2010); and

iv. harm to patients or patients prevented from harm as measured by the outcomes of the eligible studies.

• Propensity of under-reporting of suspected ADRs as measured by the outcomes of the eligible studies.

• Statistical comparisons within and between population groups of the likelihood of reporting suspected ADRs e.g. doctor vs nurse, senior vs junior HCPs, men vs women, younger people (≤40 yrs.) vs older people (≥65 yrs.); age ranges (18-24; 25-39; 40-65; ≥66 yrs.); patient vs HCPs; patient group comparisons.

• Whether the results of trials carried out in primary health care settings are the same as trials carried out in hospital settings.
• The type of data reported.

• The quality of data reported as measured by the outcomes of the eligible studies.

• The extent of duplicated reporting.

• The incidents of reporting false positives/negatives.

• The extent to which reporting systems result in poor signal detection as measured by the outcomes of the eligible studies.

• The extent to which reporting system databases contain background noise as measured by the outcomes of the eligible studies.

• The extent to which subjective bias exists in the reporting of suspected ADRs as measured by the outcomes of the eligible studies.

• The extent to which eligible studies find that limited international harmonization impedes suspected ADRs reporting.

• The extent to which practical, psychological and emotional factors impede participants making suspected ADRs reports as measured by the outcomes of the eligible studies.
• Recommendations for reforms to tackle perceived problems and cost effectiveness of them in practice e.g. the affect of under-reporting of ADRs on healthcare to patients and the impact on national and private sector health service resources.

• Any cost or resource implications reported in the eligible studies (CRD, 2009).

Secondary

The extent to which the scientific evidence base supports simultaneous empirical studies that are being prepared and will be undertaken on the review topic from 2017.

Information sources

Research studies will be identified mainly by searching electronic databases and scanning reference lists of included articles from these online electronic searches (Liberati et. al., 2009). The electronic databases search criteria will be applied to the following 10 listed online resources for the period 1st January 2006 to 20th September 2016:

1. CINAHL (Cumulated Index of Allied Health Literature);
2. Cochrane Library;
3. Embase;
4. EMA (European Medicines Agency);
5. FDA (U.S. Food and Drug Administration);
6. MHRA (Medicines & Healthcare products Regulatory Agency);
7. Medline;
8. PsycInfo;
9. Web of Science; and
10. WHO International Clinical Trials Registry Platform (WICTRP).
OVID will be used as the primary search interface for the electronic databases (Liberati et al., 2009). The review will report, in Tables, the electronic databases searched, the start and end dates they were searched, the location of the data searched within the database and the statistical result i.e. the number of items found (Liberati et al., 2009). The dates of the first and last search will be reported (Liberati et al., 2009).

For the period 1st January 2006 to 20th September 2016 hand searches will be made of the following books: (Waller, 2010; Cobert, 2007 and 2012; Stephens, 2012; Ziebland et al., 2013).

The review will report who constructed, developed and conducted the searches (Zhang et al, 2006).

An updated search of 6/10\(^6\) medical science electronic sources, only, will be undertaken for the period 21st September 2016 to 21st September 2018 or thereafter (Saunders et al., 2004).

**Search**\(^7\)

The reporting systems problems include: under-reporting; data quality; proving causation; duplication of reports; subjective bias of reporters; poor contribution of reporting data to signal detection; false positives/negatives; data background noise; and limited harmonized reporting standards.

The following key search terms will be used to search the online resources:

1. Adverse drug reaction reporting systems.

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\(^6\) CINAHL, Cochrane Library, Embase, Medline, PsycInfo and WICTRP.

\(^7\) This is based on the 2 questions in Chapter 1, previous research knowledge, experience and consultations with medical science information retrieval specialist. Here, Boolean operators (‘and’; ‘or’; ‘not’), synonyms and other search symbols are omitted.
2. Adverse drug reaction.
3. Adverse drug event.
4. Side effect.
5. Toxic effect.
6. Reporting attitude.
7. Reporting perspective.
9. Reporting behaviour.
10. Randomized controlled trials for Nos.1-9 above.
11. Observational and survey studies for Nos.1-9 above.

An example of a search strategy using e.g. Medline will be included in the review report.

**Study selection**

The PRISMA flow diagram will be used to summarize study selection processes⁸.

In summary, the process for selecting studies from retrieved records will be based on:

a) screening and selection of all the titles and/or abstracts that match the predetermined eligibility criteria; and

b) for studies that appear to meet the inclusion criteria, or in cases when a definitive decision cannot be made based on the title and/or abstract alone, the full paper will be obtained for detailed assessment against the eligibility criteria (CRD, 2009; Liberati et. al., 2009).

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⁸ Adapted from (Moher, Liberati, and Altman, 2009)). See Appendix 1.
An assessment of eligibility will be undertaken independently by the review authors in an un-blinded manner (Liberati et. al., 2009). Disagreements between the review authors will be resolved through meetings and discussions, which is intended to reach consensus or by a 3rd party member of the review team, Professor Ashok Handa and/or Dr. Jeffrey Aronson, whose decision will be final (Shah et. al., 2005). The review will report the level of agreement between the review authors, how often arbitration about selection was required and what specified actions were taken to resolve disagreements e.g. seeking supervisory guidance from Professor Handa and Dr. Aronson; contacting the authors of the original studies (Liberati et. al., 2009).

The study selection process will be piloted by applying the inclusion criteria, to a sample of papers, in order to check that they can be reliably interpreted and can classify the studies appropriately (CRD, 2009). The pilot phase may be used to refine and clarify the inclusion criteria and ensure that the criteria can be applied consistently by both review authors (CRD, 2009). Piloting may also give an indication of the likely timeframe for the full selection process to be completed (CRD, 2009).

Data collection process

The review authors will use a data extraction form. However, the one included here is specifically designed for randomized controlled trials. Therefore, it may be modified before being pilot-tested on ten randomly selected included studies and it is likely that when the review starts it will be modified (Liberati et. al., 2009) to take into account that the review study designs include randomized controlled trials, observational and survey studies. Both review authors will extract the data from included studies independently (i.e. in duplicate) and then meet to check the extracted data (Liberati et. al., 2009). Any disagreements

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9 This will be based on the Centre for Reviews and Dissemination data extraction template (CRD, 2009). See Appendix 2.
between the review authors will be resolved as aforementioned in the previous section\(^\text{10}\) (Mistiaen and Poot, 2006).

The authors of studies included will be contacted, if necessary, to obtain or confirm data (Liberati et al., 2009). A draft copy of the review report will not be circulated to them in advance of publication. This reduces or eliminates the actual or perceived risk of the report being viewed by any member of the public as being influenced by any form of bias and/or lack of independence. Endnote for Mac software will be used to store electronic data, deleting duplicated studies and facilitating analysis of the data. The full text of all duplicated studies will be reviewed to establish if any inconsistencies exist, which will enable a judgment to be made on their significance (if any) to the review and any actions taken by the review authors to solve inconsistencies across these studies will be reported (Liberati et al., 2009).

**Data items**

Data will be listed and all variables defined following PICOS\(^\text{11}\) (Liberati et al., 2009). Information will be extracted from each included study on: (1) the characteristics of trial participants e.g. age, patient, doctor, pharmacist, nurse, dentist and the study’s inclusion and exclusion criteria; (2) type of intervention\(^\text{12}\) e.g. new reporting models designed to improve the attitude and behaviour of patients and HCPs; (3) type of outcome measure\(^\text{13}\) e.g. the affect of under-reporting of ADRs on healthcare to patients and the impact on NHS resources (Allen et al., 2009). If any assumptions or simplifications are made or any variables are added to those already pre-specified in this Protocol, they will be reported (Liberati et al., 2009).

\(^{10}\) See ‘Study selection’ above.

\(^{11}\) See PICOS criteria in Chapter 1.

\(^{12}\) See ‘Eligibility criteria’ above.

\(^{13}\) Ibid.
Risk of bias in individual studies

The review authors will report how they assessed the risk of bias, including, whether it was in a blind manner (Liberati et. al., 2009). The Cochrane risk of bias tool (Higgins and Green, 2008) will be used to facilitate the assessment. The review authors may have to use separate risk of bias tools and criteria for assessing the quality of the observational and survey studies e.g. (STROBE, 2009). To ascertain the validity of eligible studies, the review authors will work independently and their determinations will include: the adequacy of randomization and concealment of allocation, blinding of patients, HCPs, data collectors, and outcome assessors; and the extent of loss to follow-up (i.e. the proportion of participants in whom the investigators were not able to ascertain outcomes) (Tracz et. al., 2006).

To explore variability in study results (heterogeneity) and before conducting the data syntheses, the review authors hypothesize that the effect size may differ according to the methodological quality of the studies (Bucher et. al., 2000). The review authors will report any collaboration exercises among them that were undertaken (Liberati et. al., 2009).

The aforementioned points are subject to the caveat that the ultimate decision regarding which methodological features to evaluate will require consideration by the review authors of the strength of the empirical evidence, the theoretical rationale and the unique circumstances of the studies included (Liberati et. al., 2009).

Risk of bias across studies

The review authors will specify any assessment of risk of bias that may affect the cumulative evidence e.g. publication bias, selective reporting bias within studies (Liberati et. al., 2009). The review authors will report any pre-specified analyses for assessing risk of bias across studies that were not completed and the reasons e.g. too few included studies (Liberati et. al., 2009). The Cochrane risk of bias tool (Higgins and Green, 2008) will be
used to facilitate the assessment of the risk of bias across studies. Aforementioned, the review authors may have to use separate risk of bias tools and criteria for assessing the quality of the observational and survey studies.

Summary measures

The review authors will apply the risk ratio, odds ratio and risk difference to measure binary outcomes (Harris and Taylor, 2014; Higgins and Green, 2008). For continuous outcomes the difference in means will be measured (Higgins and Green, 2008) if the outcome measurements in all studies are made on the same scale (Liberati et al., 2009). The standardized difference in means will be applied if the studies do not yield directly comparable data (Liberati et al., 2009). The hazard ratio will be applied to measure time-to-event outcomes (Higgins and Green, 2008).

Planned method of analysis

The review authors will test for heterogeneity by using the method proposed by (Higgins et al., 2003) to measure inconsistency (termed $I^2$), which is the percentage of total variation across studies due to heterogeneity of the effects across interventions (Liberati et al., 2009). The review authors will report any reconstruction, imputation or conversations of data (Liberati et al., 2009).

Additional analyses

The review authors will conduct a sensitivity analyses for randomized controlled trials, observational and survey studies and compare the results. This will be used to explore the extent to which the main findings of the review are affected by changes in its methods or in the data used from the individual studies (e.g. study inclusion criteria, results of risk of bias assessment) (Liberati et al., 2009).
A subgroup analyses will be undertaken by dividing the studies (for study level characteristics) or participant data (for participant level characteristics) into subgroups and making indirect comparisons between them (CRD, 2009). The rationale is to analyze whether e.g. the effect of an intervention is the same among HCPs and patients; establishing if the results of trials carried out in primary health care settings are the same as trials carried out in hospital settings; and an international comparison of participants’ knowledge, understanding and experiences of reporting suspected ADRs (CRD, 2009).
CHAPTER 3

RESULTS

Study selection

The review will include the numbers of studies screened, assessed for eligibility and included in the review, with reasons for exclusions at each stage, with a flow diagram\(^{14}\) (Moher, Liberati, Tetzlaff and Altman, 2009).

Study characteristics

The data extracted will include for each study the: PICOS; size; duration; follow up; and citation (Liberati et. al., 2009). This data will be presented in a Table\(^{15}\).

Risk of bias within studies

The review authors will assess the risk of bias for each included study by using a standard approach with defined criteria\(^{16}\) and present the results of any such assessments in a Table\(^{17}\) (Devereaux et. al., 2005; Liberati et. al., 2009).

Risk of bias across studies

The review authors will specify any assessment of the risk of bias that may affect the cumulative evidence e.g. publication bias, selective reporting within studies (Liberati et. al., 2009).

\(^{14}\) See Appendix 1.

\(^{15}\) See Appendix 3.

\(^{16}\) See Chapter 2 ‘Risk of bias in individual studies’.

\(^{17}\) See Appendix 4.
Results of individual studies

For all outcomes considered the review authors will report for each study: (a) summary data for each intervention group\(^{18}\); and (b) effect estimates and confidence intervals, with a forest plot\(^{19}\) (Liberati et. al., 2009).

The review authors will indicate, if relevant, which results were not reported directly and had to be estimated from other information\(^{20}\) (Liberati et. al., 2009).

If the review authors find too many outcomes for full information to be included, the results for the most important outcomes (as determined by the pre-specified outcomes of the eligible studies) will be included in the review report with additional information provided as a web appendix (Liberati et. al., 2009). The choice of the information to report will be justified in light of what was stated in this Protocol (Liberati et. al., 2009). The review authors will expressly state in the report if the planned main outcomes cannot be presented due to a lack of information (Liberati et. al., 2009).

Synthesis of results

The review authors will report all the outcome measures that they set out to investigate\(^{21}\) (Liberati et. al., 2009). It is likely that the study designs, participants, interventions and reported outcome measures are likely to vary markedly, therefore, the review will focus on describing the studies, their results, their applicability and their limitations on a qualitative evidence synthesis rather than meta-analysis (Balk et. al., 2006). The review authors will apply a general framework to the synthesis of the results (Mays et. al., 2005; Popay et. al., 2006; CRD, 2009).

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\(^{18}\) See Table 6 in Appendix 5.
\(^{19}\) See Table 7 in Appendix 5.
\(^{20}\) See Chapter 2 ‘Summary measures’.
\(^{21}\) See Chapter 2 ‘Types of outcome measures’.
**Additional analyses**

The review authors will report the results of any additional analyses e.g. $P$ (probability) value, Incidence Rate Ratio (IRR), Point Prevalence Rate (PPR), Power (Harris and Taylor, 2014).

**Analyses of the quality of the evidence**

The review authors will rate or assess the overall body of evidence addressed in the review e.g. by using the GRADE system to assess any randomized controlled trials (Guyatt et. al., 2008) or general/specific frameworks to assess quality of the evidence (CRD, 2009). The review authors will tie the strength of their summary recommendations to their assessment of the quality of evidence (Liberati et. al., 2009).

**Software**

Software will be used to facilitate analysis of the results e.g. IBM SPSS Statistics (Griffiths, 2016; Pallant, 2016).
CHAPTER 4

DISCUSSION

Summary of evidence

The review authors will use an adapted framework for a structured discussion (Docherty and Smith, 1999; Drotar, 2009), which will enable them to report:

a) a statement of the main findings;

b) a critical comparison of the review with the existing body of literature, in particular, other systematic reviews and any differences;

c) the strengths and weaknesses of the review. This will include a critical: appraisal of the methodological quality of the review; discussion at study, outcome (e.g. risk of bias) and review levels (e.g. incomplete retrieval of identified research, reporting bias) (Drotar, 2009; Liberati et. al., 2009); and

d) the practical implications for future research, policy-makers and practice; the direction and magnitude of effects observed in the included studies; the applicability of the findings of the review; and any unanswered questions.
The conclusions will provide a critical interpretation of the results and make recommendations in the context of other evidence, including, implications for practice and future research (Liberati et al., 2009) e.g. one recommendation that will be made and designed is a checklist for this type of review\textsuperscript{22}. The presentation of the research recommendations will also use a structured format represented by the acronym EPICOT (Evidence, Population(s), Intervention(s), Comparison(s), Outcome(s), Time stamp). Timeliness (duration of intervention/follow-up) and study design will be considered by the review authors as optional additional elements of the structured format (CRD, 2009; Brown et al., 2006).

\textsuperscript{22} This was proposed by the second review author, Dr. Igho Onakpoya and both authors will work on its design, dissemination and publication.
CHAPTER 6

GOVERNANCE

Expert Review Group Members

A review group has been established to undertake and support the review. It will comprise: two reviewers, including, one with substantial expertise in undertaking systematic reviews and a clinical pharmacologist who is an expert in ADRs.

Consultants for review

A librarian, and a statistician will provide consultancy guidance to the Expert Review Group, as required.

Review supervision

The lead review author, Mr. Gary Greer, will be supervised by Professor Ashok Handa and Dr. Jeffrey Aronson. The supervisors are members of staff within the UO.

Integrity and ethics

The review authors will observe the highest standards of ethics and integrity in the conduct of their research in accordance with the UO’s policy on ‘Academic Integrity in Research: Code of Practice’ (University of Oxford, 2014) and the former named UK Department for Business, Innovation & Skills (replaced by the Department for Business, Energy & Industrial Strategy in July 2016) and Government Office for Science policy on ‘Rigour, Respect and Integrity: A Universal Ethical Code for Scientists’ (UK Department for Business Innovation etc., 2007).
Conflicts of interest

The review authors will assess and implement any conflicts of interest in accordance with the UO and the International Committee of Medical Journal Editors (‘ICMJE’) published policies on conflicts of interest (University of Oxford, 2015; ICMJE, 2016). No conflict of interest exists at the time of drafting this Protocol and none are anticipated on implementation of it. Nonetheless, this will be kept under careful review by the review authors who will report any conflict of interest that arise (CRD, 2009). This strategy ensures transparency and is important in maintaining the readers confidence in the review authors report (CRD, 2009).

Funding

None. At the time of drafting this Protocol this review will be undertaken independently of any sources of funding from any other party. If funding is secured the source of it will be reported.

Training

The review authors will attend technical training, if required, to support the review, which will be reported.

Dissemination and publication

The review authors will communicate the review findings to patients, HCPs and policymakers by using the CRD Dissemination Framework\textsuperscript{23} (CRD, 2009).

\textsuperscript{23} See Appendix 6.
Timetable

The timeframe for the review is set out in Appendix 7.
APPENDIX 1

PRISMA Flow Diagram

Figure 2 describes the flow of information through the different phases of a systematic review using the PRISMA 2009 Flow Diagram. Adapted from (Moher, Liberati, and Altman, 2009).

Identification

Records identified through database searching
(n = )

Additional records identified through other sources
(n = )

Records after duplicates removed
(n = )

Screening

Records screened
(n = )

Records excluded
(n = )

Eligibility

Full-text articles assessed for eligibility
(n = )

Full-text articles excluded, with reasons
(n = )

Included

Studies included in qualitative synthesis
(n = )

Studies included in quantitative synthesis
(n = )
APPENDIX 2

Data extraction form

General information

Researcher performing data extraction

Date of data extraction

Identification features of the study:

  Record number (to uniquely identify study)

  Author

  Article title

  Citation

  Type of publication (e.g. journal article)

  Country of origin

  Source of funding

Study characteristics

Aim/objectives of the study

Study design

Study inclusion and exclusion criteria

Recruitment procedures used (e.g. details of randomization, blinding)

24 Adapted from (CRD, 2009).
Unit of allocation (e.g. participant, GP practice, etc.)

**Participant characteristics**

Characteristics of participants at the beginning of the study e.g.

- Age
- Gender
- Ethnicity
- Socio-economic status
- Disease characteristics
- Co-morbidities

Number of participants in each characteristic category for intervention and control group(s) or mean/median characteristic values. (The reviewers will record whether it is the number eligible, enrolled, or randomized that is reported in the study)

**Intervention and setting**

Setting in which the intervention is delivered

Description of the intervention(s) and control(s) (e.g. how the intervention was developed, theoretical basis (where relevant))

Description of co-interventions

**Outcome data/results**

Unit of assessment/analysis

Statistical techniques used
For each pre-specified outcome:

Whether reported

Definition used in study

Measurement tool or method used

Unit of measurement (if appropriate)

Length of follow-up, number and/or times of follow-up measurements

For all intervention group(s) and control group(s):

Number of participants enrolled

Number of participants included in analysis

Number of withdrawals, exclusions, lost to follow-up

Summary outcome data e.g.

Dichotomous: number of events, number of participants

Continuous: mean and standard deviation

Type of analysis used in study (e.g. intention to treat)

Results of study analysis e.g.

Dichotomous: odds ratio, risk ratio, confidence intervals, and p-value

Continuous: mean difference, confidence intervals

As a subgroup analysis is planned the above information on outcome data or results will be extracted for each patient subgroup
Additional outcomes

Record details of any additional relevant outcomes reported

Costs

Resource use

Adverse events
APPENDIX 3

Example of summary of study characteristics

Table 4 describes a summary of included studies evaluating reporting suspected ADRs in patients. Adapted from (De Camp et al., 2008).

<table>
<thead>
<tr>
<th>Source</th>
<th>Setting</th>
<th>No. of patients</th>
<th>Age range</th>
<th>Inclusion criteria</th>
<th>Follow up</th>
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</table>
APPENDIX 4

Example of assessment of the risk of bias

Table 5 describes the assessment of the risk of bias of included studies evaluating reporting suspected ADRs in patients. Adapted from (Devereaux et. al., 2005).

<table>
<thead>
<tr>
<th>Trials</th>
<th>Concealment of randomization</th>
<th>Trial stopped early</th>
<th>Patients blinded</th>
<th>Healthcare providers blinded</th>
<th>Data collectors blinded</th>
<th>Outcome assessors blinded</th>
</tr>
</thead>
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</table>
APPENDIX 5

Example of summary of results

Table 6 describes a summary of results for binary and continuous outcomes for each study. Adapted from (Liberati et al., 2009).

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Frequency of event</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
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<td>I</td>
<td>C</td>
<td>I</td>
<td>C</td>
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</table>

**KEY:**

I = Intervention.

C = Control.
Table 7 describes a summary of results adapted from (Skalsky et al, 2008). Column 4 will show a forest plot for each study, which illustrates the effect estimates and confidence intervals graphically. Column 5 will show other data for each study as follows: the group specific summary data; effect size; confidence interval; and the percentage weight.

<table>
<thead>
<tr>
<th>Description</th>
<th>I</th>
<th>C</th>
<th>Forest Plot</th>
<th>Other data</th>
</tr>
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<tbody>
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</table>

**KEY:**

I = Intervention.

C = Control.
APPENDIX 6

Figure 3 describes an outline of the CRD Dissemination Framework. Adapted from (CRD, 2009).

![Diagram of CRD Dissemination Framework]

- **Review topic**
- **Message**
- **Audience**

**External factors:**

- **Source**
- **Tailoring of messages**

**Setting/context**

- **Communication channels selection**
- **Time**

**Resources:**

- **Implement dissemination strategy**
- **Evaluation/feedback**
APPENDIX 7

Timetable

Table 8 describes the timetable for the empirical and methodological literature review that will be reported using PRISMA. The estimated timeframe for completion of the review is 14 months, excluding preparations, consultations on the Protocol and dissemination and publication. Adapted from (Higgins and Green, 2008).

<table>
<thead>
<tr>
<th>Month</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>August &amp; September 2016</td>
<td>Preparations and consultations on Protocol (Circa 6 weeks)</td>
</tr>
<tr>
<td>September-January 2017</td>
<td>Final consultations, construction of search terms, pilot testing them, updated scoping searches, final list of search terms, review searches, data storage, registration and publication of Protocol on PROSPERO (CRD, 2015), pilot testing data selection process, data identification, screening and eligibility</td>
</tr>
<tr>
<td>January 2017</td>
<td>Pilot test of data collection Form(s) (2 weeks)</td>
</tr>
</tbody>
</table>

25 It is possible that the timetable may have to be extended due to e.g. the parallel non-research theoretical systematic literature review; parallel empirical studies; and unforeseen events that may arise.
<table>
<thead>
<tr>
<th>Time Period</th>
<th>Task Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>February-June 2017</td>
<td>Data collection, entry and follow up of any missing data</td>
</tr>
<tr>
<td>(5 months)</td>
<td></td>
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<tr>
<td>July-September 2017</td>
<td>Analysis of results, discussion, conclusions and recommendations</td>
</tr>
<tr>
<td>(3 months)</td>
<td></td>
</tr>
<tr>
<td>October-November 2017</td>
<td>Preparation of review report</td>
</tr>
<tr>
<td>(2 months)</td>
<td></td>
</tr>
<tr>
<td>November 2017 or thereafter</td>
<td>Dissemination and publication</td>
</tr>
<tr>
<td>(2-6 months minimum)</td>
<td></td>
</tr>
<tr>
<td>21st September 2018 or thereafter</td>
<td>An updated search of 6/10^26 medical science electronic sources only will be undertaken (Saunders et al, 2004) to identify any new studies for the period 21st September 2016 to 21st September 2018 or thereafter</td>
</tr>
<tr>
<td>(circa 6 months)</td>
<td></td>
</tr>
<tr>
<td>April 2019 onwards</td>
<td>Thesis writing, dissemination and publication</td>
</tr>
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</table>

ACKNOWLEDGEMENTS

The authors will acknowledge the people who provided support to the review.
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International Committee of Medical Journal Editors (2016) *Author Responsibilities – Conflicts of interest* [online] Available from URL


Mistiaen, P. and Poot, E. (2006) Telephone follow-up, initiated by a hospital-based health professional, for postdischarge problems in patients discharged from hospital to home.


conduct of narrative synthesis in systematic reviews a comparison of guidance-led narrative synthesis versus meta-analysis/links/5532159f0cf2f2a588ad67fd.pdf.


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