

How to do a systematic review

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Abstract

High quality up-to-date systematic reviews are essential in order to help healthcare practitioners and researchers keep up-to-date with a large and rapidly growing body of evidence. Systematic reviews answer pre-defined research questions using explicit, reproducible methods to identify, critically appraise and combine results of primary research studies. Key stages in the production of systematic reviews include clarification of aims and methods in a protocol, finding relevant research, collecting data, assessing study quality, synthesizing evidence, and interpreting findings. Systematic reviews may address different types of questions, such as questions about effectiveness of interventions, diagnostic test accuracy, prognosis, prevalence or incidence of disease, accuracy of measurement instruments, or qualitative data. For all reviews, it is important to define criteria such as the population, intervention, comparison and outcomes, and to identify potential risks of bias. Reviews of the effect of rehabilitation interventions or reviews of data from observational studies, diagnostic test accuracy, or qualitative data may be more methodologically challenging than reviews of effectiveness of drugs for the prevention or treatment of stroke. Challenges in reviews of stroke rehabilitation can include poor definition of complex interventions, use of outcome measures that have not been validated, and poor generalizability of results. There may also be challenges with bias because the effects are dependent on the persons delivering the intervention, and because masking of participants and investigators may not be possible. There are a wide range of resources which can support the planning and completion of systematic reviews, and these should be considered when planning a systematic review relating to stroke.

Keywords

Systematic review, methods, protocol, Cochrane, synthesis, rehabilitation

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Introduction

Why do a systematic review in stroke?

In order to provide patients with the best possible care and treatment, healthcare decisions should be based on up-to-date, high-quality research evidence.^{1,2} However, there is an unmanageably large and continually growing body of research evidence, and healthcare practitioners do not have time to keep up to date with this evidence base.^{3,4} There has also been an exponential increase in the amount of stroke research over the last 50 years (see Figure 1). In April 2017, the Cochrane Stroke Group trials register contained 24,084 references to 9975 randomized or controlled clinical trials relating to stroke, and a search of any key electronic bibliographic database reveals that there are tens of thousands of non-randomized studies relating to stroke. Yet, despite important advances in evidence-based stroke care,^{5,6} stroke survivors still do not always get the best possible care.⁷ High quality up-to-date systematic reviews of primary research studies, addressing questions which are of recognized importance to stroke survivors, carers, and clinicians are therefore

essential.^{8,9} Systematic reviews are also important for the avoidance of research waste, by ensuring that new primary research is done with full knowledge of what has already been done, and that new research evidence is interpreted in the light of what is already known.^{10–12}

What is a systematic review?

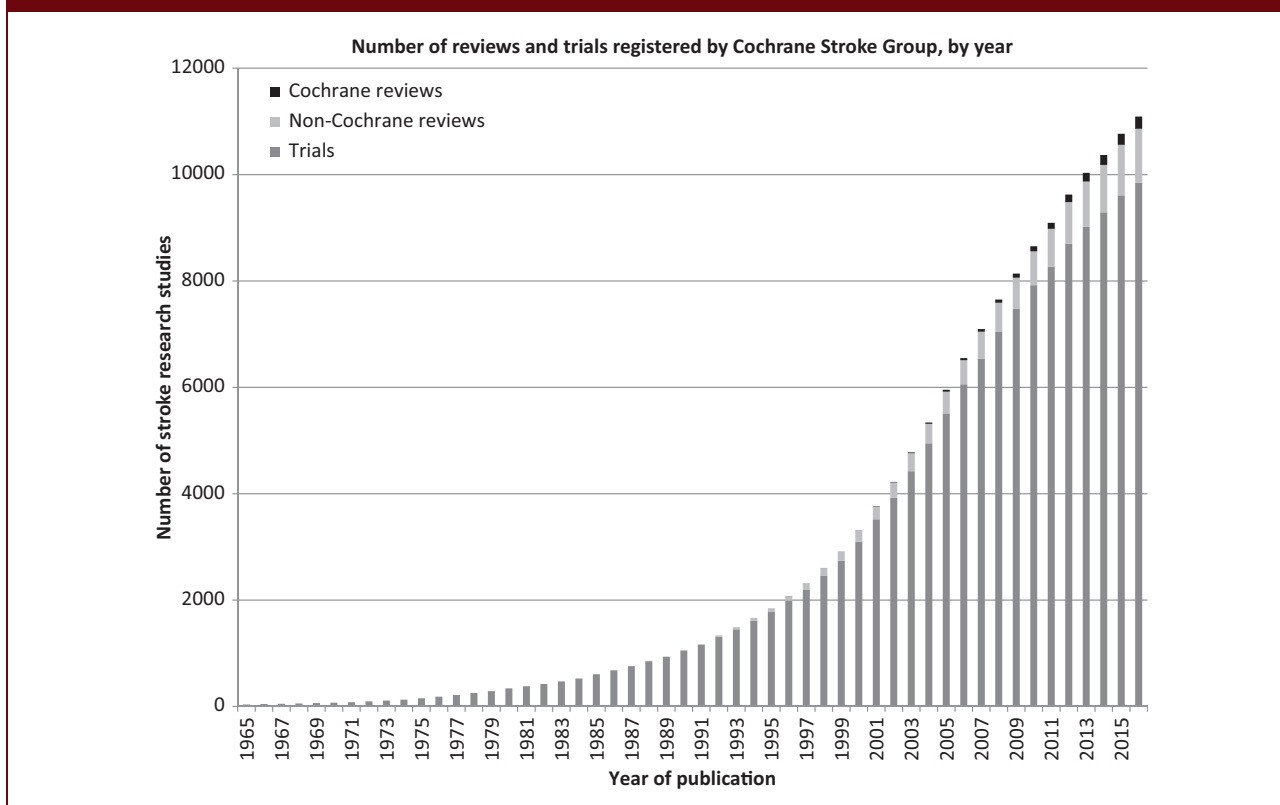
A systematic review aims to bring evidence together to answer a pre-defined research question. This involves the identification of all primary research relevant to the defined review question, the critical appraisal of this research, and the synthesis of the findings.¹³ Systematic reviews may combine data from different

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Figure 1. Number of reviews and trials registered by Cochrane Stroke Group, by year.

research studies in order to produce a new integrated result or conclusion, or they may bring together different types of evidence in order to explore or explain meaning.¹⁴

Systematic reviews can address any defined research question. Table 1 provides examples of questions that have been addressed in published reviews relating to stroke, and examples of resources relating to different types of reviews. The table illustrates that there are different types and methods of systematic review for different types of questions. This is the same as when selecting a method for primary research, where the type of research question influences selection of an appropriate method (e.g. a question about the effect of an intervention may be best answered by a randomized controlled trial, or a question about prognosis best answered by an observational cohort study). A high quality systematic review will try to identify all primary research studies that are relevant, both published and unpublished, carried out all over the world and written in different languages. The quality of the identified research will be critically appraised, and the results of studies will be systematically brought together in order to provide the best possible answer to the review question; this process may involve the statistical

combination of study results (meta-analysis) or other approaches to data synthesis. In this way, a systematic review of evidence should support the delivery of optimal healthcare interventions and research.

Essential features of systematic reviews include explicit, reproducible methods for identification of primary research studies and critical assessment and synthesis of studies that meet the eligibility criteria.^{3,20,51,52} Systematic reviews should be distinguished from “non-systematic” reviews which do not have these features, and which are sometimes also described as a “conventional literature review,”⁵³ “scoping review,”⁵⁴ or “narrative review.”⁵⁵ In the past, there has been considerable confusion and inconsistency in the terminology used around systematic reviews,⁵⁶ in part because historically the term “systematic review” had often been associated specifically with the bringing together of data from quantitative research studies. However, it is now widely recognized that a “systematic review” refers to the process of systematically bringing together the results of any research, including qualitative or mixed methods research studies.^{57,58}

There is growing recognition of the importance of patient and public involvement to the value and relevance of systematic reviews,⁵⁹ and some key

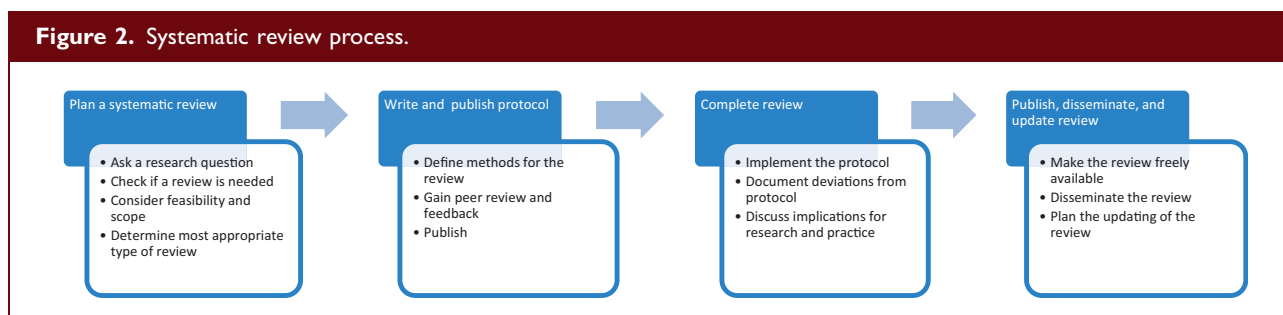
Table 1. Types of systematic reviews, frameworks for review questions, and resources to support protocol development, quality assessment of studies and review reporting

Type of research question	Type of systematic review	Published examples from the field of stroke	Framework for systematic review questions	Resources for protocol development	Tools for quality assessment of included studies	Reporting guidelines
What is the effectiveness of an intervention (e.g. a treatment, service or policy)?	Intervention review	What is the safety and effectiveness of thrombolytic therapy for the treatment of acute ischaemia stroke? ¹⁵ What is the effect of stroke unit care, as compared to alternative forms of care for people following a stroke? ¹⁶ Does fitness training after stroke reduce death, dependence and disability? ¹⁷	PICO: Population, intervention, comparison, outcome PICOS: Population, intervention, comparison, outcome, study type PICOT: Population, intervention, comparison, outcome, timeframe ¹⁸ PICOC: Population, intervention, comparison, outcome, context	Cochrane Handbook for intervention reviews ¹⁹ Joanna Briggs Institute (JBI) Reviewers' manual ²⁰ Standards for Systematic Reviews of Comparative Effectiveness Research ²¹ Methodological Expectations of Cochrane Intervention reviews (MECIR) ²²	Cochrane risk of bias tool ²³ JBI Critical appraisal tools ²⁴	Preferred reporting items for systematic reviews and meta-analyses (PRISMA) ²⁵ Methodological expectations of cochrane intervention reviews (MECIR) ²²
What is the accuracy (sensitivity or specificity) of a diagnostic test?	Diagnostic test accuracy (DTA) review	What is the accuracy of MRI for the detection of acute hemorrhagic lesions within 12 hours of stroke symptoms? ²⁶ What is the accuracy of cognitive diagnosis of multidomain, cognitive impairment/dementia in stroke survivors? ²⁷	PICOT: Population, index test, comparator, outcome, target condition PPIRT: Population, prior tests, index tests, reference standard, target condition	Cochrane Handbook for DTA reviews ²⁸	Quality assessment of diagnostic accuracy studies (QUADAS-2) tool ²⁹ Critical Appraisal Skills Program (CASP) diagnostic checklist ³⁰ Centre for evidence based medicine (CEBM) diagnostic study appraisal worksheet ³¹ JBI critical appraisal tools ²⁴	PRISMA-DTA: Checklist for reporting of diagnostic test accuracy systematic reviews (in development) ³²
What is the prognosis / prevalence / predictors of a recovery of a condition?	Observational studies review	What is the worldwide incidence of stroke? ³³ What is the prevalence of pre-stroke dementia and the prevalence and incidence of post-stroke dementia and their associated risk	PEO: Population, exposure, outcomes PCO: Population, context, outcome PICo: Population, interest, context	Cochrane Methods: Prognosis (resources and publications) ³⁶	CASP cohort study checklist ³⁰ CEBM Prognosis appraisal worksheet ³¹ JBI Critical appraisal tools ²⁴	Meta-analysis of observational studies in epidemiology (MOOSE) ³⁷

(continued)

Table 1. Continued

Type of research question	Type of systematic review	Published examples from the field of stroke	Framework for systematic review questions	Resources for protocol development	Tools for quality assessment of included studies	Reporting guidelines
		<p>factors?³⁴ What are the predictors of upper limb recovery following stroke?³⁵</p>				
What is the accuracy of an outcome assessment or measurement tool?	Review of measurement instruments	<p>What is the validity and reliability of the Modified Rankin Scale?³⁶ What are the psychometric properties of outcome measures used in stroke self-management interventions?³⁹</p>	<p>De Vet 2011, Chapter 9: Systematic reviews of measurement properties⁴⁰ COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN)⁴¹</p>	<p>COSMIN checklist⁴¹; Also potentially relevant: OMERACT filter⁴²</p>	COSMIN ⁴¹	
What are the views or experiences of people with a condition?	Qualitative review	<p>What are stroke survivors' experiences of rehabilitation?⁴³ What are carers' experiences of caring for stroke survivors?⁴⁴</p>	<p>SPIDER: Sample, phenomena of interest, design, evaluation, research type⁴⁵ SPICE: Setting, perspective, intervention, evaluation⁴⁶ ECLIPS: Expectations, client group, location, impact, professionals involved, service⁴⁷</p>	<p>Cochrane Handbook Chapter 20 (Qualitative research and Cochrane reviews)⁴⁸ JBI Reviewers' manual²⁰</p>	<p>CASP qualitative checklist³⁰ JBI Critical appraisal tools²⁴</p>	<p>Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ⁴⁹ Realist and meta-narrative evidence synthesis – evolving standards (RAMESES) publication standards⁵⁰</p>



organizations now identify patient and public involvement as an essential feature of a systematic review (e.g. EPPI Centre⁵¹). Patient and public involvement within systematic reviews is increasingly asked for by funders of health research (e.g. NIHR⁶⁰ and European Science Foundation,⁶¹ including stroke research (e.g. Stroke Foundation⁶²).

Systematic reviews in stroke

Most systematic reviews in stroke are reviews of interventions for prevention, acute treatment, and rehabilitation.⁶³ While reviews of the effectiveness of drugs to prevent or treat stroke may arguably be relatively straight-forward, reviews of complex interventions, such as rehabilitation, are more complicated, as are reviews of diagnostic test accuracy or qualitative data. Challenges in reviews of stroke rehabilitation can include poor definition, implementation, and description of complex rehabilitation interventions⁶⁴⁻⁶⁷; inconsistent use of outcome measures, or use of outcome measures that have not been validated⁶⁸; or poor generalizability of results (for example, because of exclusion of participants with aphasia or cognitive impairment⁶⁹). Furthermore stroke rehabilitation research has particular challenges because the effects are dependent on the person delivering the intervention, and blinding of participants and staff to randomized interventions may not be possible within some studies.

In this article, our objective is to outline the systematic review process, from the planning of the review, through the writing of the protocol and the completion, publication, and dissemination of the review (Figure 2). We focus primarily on reviews of the effect of interventions for prevention, acute treatment and rehabilitation of stroke, but we also incorporate and discuss other types of systematic reviews, such as reviews of diagnostic accuracy and reviews of qualitative data. We use an example from stroke rehabilitation⁷⁰ to illustrate methodological challenges, since reviews of rehabilitation are often more methodologically complex than reviews of prevention and acute treatment.

Box 1. What is the research question?

Background and question: My patient has recently had a stroke, and can only walk with assistance. Many physiotherapists have a preference for a specific approach to rehabilitation.^{71,72} These approaches include the Bobath approach^{73,74} and the motor learning approach.⁷⁵ What specific physiotherapy approach should I use in order to best improve the walking of my patient?

Forming the PICO question:

- **Patient:** Patients with acute stroke (less than six weeks) with reduced mobility.
- **Intervention:** Any specific approach to physiotherapy.
- **Control:** No physiotherapy.
- **Outcome:** Independence in activities of daily living; ability to walk independently.

PICO question: In patients with a recent acute stroke (less than 6 weeks) with reduced mobility, is any specific physiotherapy approach method more beneficial than no physiotherapy at improving independence in activities of daily living and gait speed?

Planning a systematic review

What is the research question?

A systematic review should be prompted by an interest in a topic, and a wish to answer a specific question. The question should clarify the problem to be addressed, specifying the particular population to which the question applies, as well as any intervention and outcomes of interest. How to form a systematic review question is considered further below. Box 1 illustrates how an initial interest in the effect of rehabilitation interventions was formulated into a research question.

Is a systematic review needed?

For any research to be justified, including systematic reviews, the research question must address what is

important to patients and clinicians.¹¹ If a research question is of low priority to the people affected by the condition, or important outcomes are not considered, or the intervention is considered unacceptable to patients, or too costly to deliver, then further research can be wasteful.^{10,11} There are a number of reports which highlight key topics and research questions which are considered of greatest importance by stroke survivors, carers, and health professionals working in stroke care.^{76–81}

In addition, if a research question has already been answered by a systematic review, another review of the same evidence will be wasteful and creates challenges for clinicians and policy makers seeking systematic reviews to inform their clinical decision making.⁸² There are currently (March 2017) at least 1385 systematic reviews relating to stroke.⁶³ An overview of reviews relating to stroke upper limb rehabilitation identified multiple overlapping reviews, with over 10 published systematic reviews of evidence relating to constraint-induced movement therapy and electrical stimulation.⁸²

It is sometimes argued that an additional criterion to consider is whether there is published research relevant to the research question. A systematic review which does not find and include any relevant studies can be referred to as an “empty review.”⁸³ These empty reviews arguably are of little value in aiding clinical decisions, and subsequently careful consideration should be given to embarking on what may be an empty review. However, where the intention is to complete a systematic review in order to confirm the absence of primary research, prior to the planning and conduct of a primary research study, there remains clear justification for a systematic review.

Feasibility and scope of the systematic review

It is estimated that a typical systematic review will take at least 12 months to complete, although this could be less, depending on the review and the available resources.⁸⁴ Data from the Cochrane Stroke Group demonstrate that completion time for a Cochrane systematic review, from initial registration of a title to publication of a completed review, is a median of 158 weeks (interquartile range 105 to 209). Although the scope of a systematic review will largely be determined by the research question which has been formulated, there may be opportunities to broaden or narrow a research question in an attempt to make the planned review manageable within the available time and resources.⁸⁵ A broader review question (sometimes known as a “lumping” review) has the advantage that it will be applicable to a wider range of settings or populations (or interventions or outcomes), and provides greater potential for exploration of consistency

of research findings, with less opportunities for chance findings.^{86,87} Furthermore, broad reviews arguably make systematic review findings more accessible to clinical decision makers, who often have to choose between a variety of interventions for delivery to a number of different patients. However, when resources are limited, a narrower review (or “splitting” a review) may make completion more feasible, and the increased homogeneity of the included studies may provide a more focused answer to the specific (narrow) research question.⁸⁷ Box 2 gives arguments for a broad and for a narrow review, using the example of rehabilitation interventions.

What sort of systematic review best suits the research question?

The type of research question which has been asked will be central to determining the most appropriate type of systematic review (Table 1). The research questions in Box 1 and Box 2 require an intervention review.

Write and publish a protocol

A protocol is an essential part of the review process,^{20,25,88–90} and should include sufficient information to enable independent replication of the methods. Adherence to a pre-defined protocol is a key method with which to avoid the introduction of selection bias, as it ensures that all important decisions have been made in advance of knowledge of the results.^{25,89–91} Peer review and feedback from key stakeholders are important,^{20,52,90} and a protocol should be published prior to starting on the systematic review, for example in a repository, electronic library (e.g. within the Cochrane Library,⁹² PROSPERO,⁹³ or Joanna Briggs Database⁹⁴), or in a journal. Publication helps ensure transparency within the review process, enabling any deviation from review protocol to be easily identified.^{21,90,91} For example, prior publication of a protocol will enable selective outcome reporting to be identified if this occurs within the final review.^{88,89,91} Furthermore, publication is a key step to avoid research duplication and waste, ensuring that other researchers are aware that the review is being completed.^{89–91} Figure 3 illustrates the key stages for writing a protocol and completing a systematic review. Each stage is briefly discussed below, and key resources highlighted (Table 1).

Clarify review aims and objectives

A clear research question, like the one in Box 1, will help clarify the eligibility criteria for inclusion of relevant studies (and exclusion of irrelevant studies). For relatively simple systematic reviews of effectiveness of

Box 2. Should the review be broad or narrow?

PICO question: In patients with a recent acute stroke (less than six weeks) with reduced mobility, is any specific physiotherapy approach more beneficial than no physiotherapy at improving independence in activities of daily living and gait speed?

Arguments in favor of a broad review:

- Limiting the review to patients who had a stroke during the last six weeks will arguably result in a fairly “narrow” review, and potentially large volumes of evidence arising from other patients would be excluded. A broader review would result in a review of a greater volume of evidence.
- Assessing the effects of different physiotherapy approaches (not only the Bobath approach) will be clinically relevant to clinicians, who have to consider all available approaches when reaching a treatment decision. Limiting the review to only one specific approach (e.g. the Bobath approach) does not answer the clinical question relating to the relative effects of different approaches.
- Considering control groups other than just a “no physiotherapy” control group will reflect the choice faced by many clinicians, who have to choose between two or more different approaches, rather than between one approach or no physiotherapy.
- A broader review will have more data from additional studies, making it possible to perform meaningful subgroup analyses.

Example of a broader review question: In patients with stroke with reduced mobility, is any specific approach to physiotherapy more beneficial than no physiotherapy or any other physiotherapy approach at improving independence in activities of daily living and gait speed?

Arguments in favor of a narrow review:

- The broad review would be more work (more articles to screen, more data to extract, more analyses to be done, more results to discuss).
- There would be a need to consider the generalizability of results arising from this broad population to the sub-population of primary interest for this review (patients with stroke during the last six weeks).
- A review focused on just one physiotherapy approach (e.g. the Bobath approach) will be more concise and of greater interest for readers interested in this specific approach.

Example of a more narrow review question: In patients with a recent acute stroke (less than six weeks) with reduced mobility, is the Bobath approach more beneficial than the motor learning approach at improving independence in activities of daily living and gait speed?

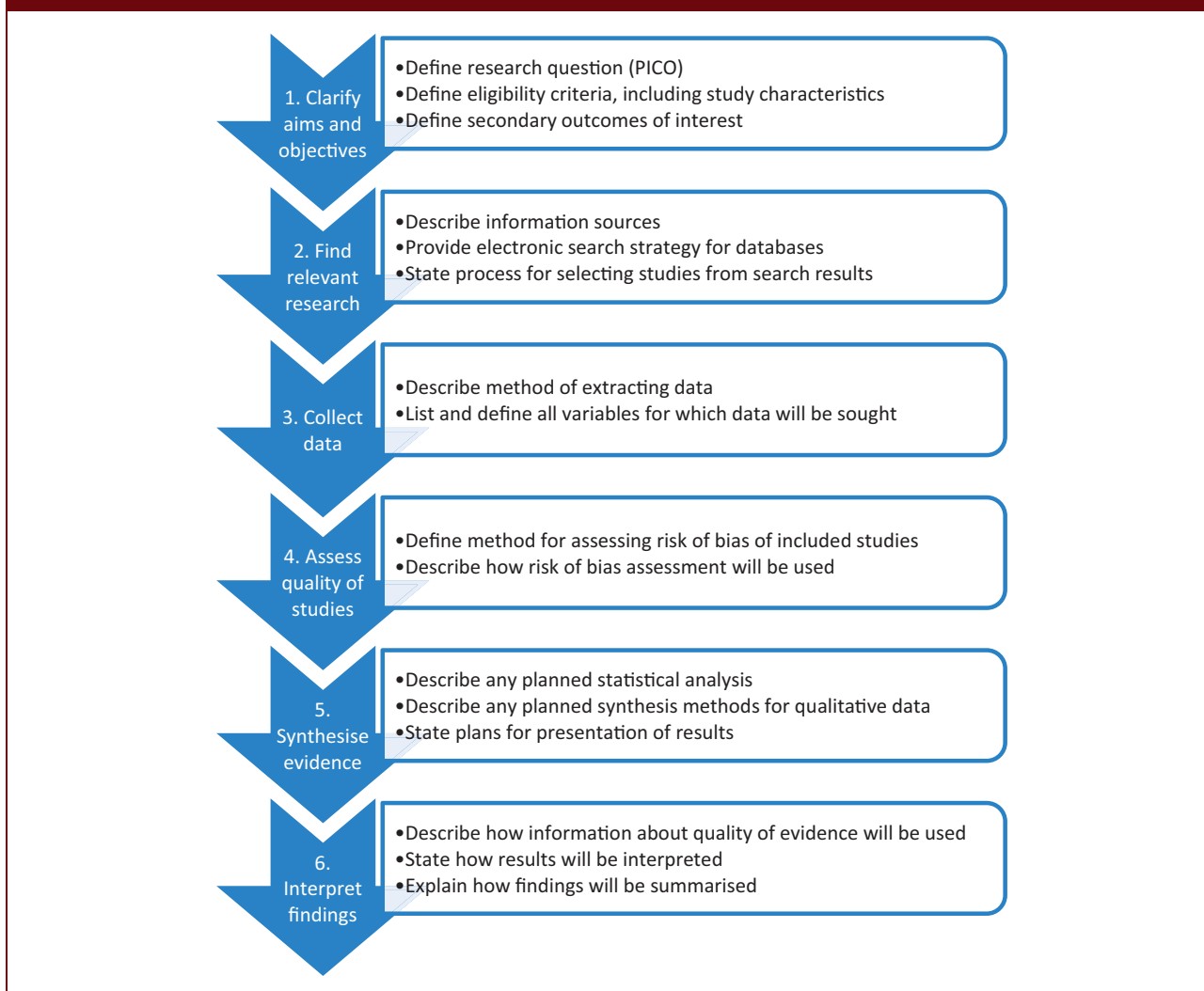
interventions, the systematic review question is often informed by the “PICO” framework, but there are a range of other frameworks which can inform the questions for more complex reviews (Table 1).⁹⁵

There are some specific considerations relating to systematic reviews in stroke. For example, when defining the population (P), it may be important to state how stroke is defined or diagnosed, or to define a specific subset of participants (e.g. participants with aphasia), or those within a specific care setting. Sometimes it may be appropriate to broaden the scope of the review by including other relevant populations in addition to stroke (e.g. other non-progressive brain diseases/injuries).

Defining interventions (I) used in stroke care, particularly non-pharmacological interventions, can be complex, and careful consideration should be given to describing the key components of the intervention. The TIDieR checklist⁹⁶ may provide a useful guide to clarifying the intervention, and ensuring a structured definition. Careful consideration should be given to the “dose” of complex interventions, clarifying how this will be defined, and acknowledging that this can be a complex combination of total number of treatment sessions over the study duration, number of treatment

sessions per day, week or month, length of treatment sessions, intensity of treatment (possibly measured in a range of ways such as number of repetitions, or a measure of exertion). Where a comparison or control (C) intervention is defined, it is important to consider that within some stroke research studies, a control group which receives no active treatment may be unlikely (perhaps for ethical reasons), and consequently an active intervention may be compared to a variety of alternative interventions. These could include “standard care” (which would need to be defined fully for the purposes of the review) or another active intervention, or the same active intervention delivered at a different dose or intensity. It is important that the protocol states whether studies which deliver interventions in combination (e.g. constraint induced movement therapy plus electrical stimulation) will be eligible and, if so, how these studies with combined interventions will be brought together with studies of single interventions.

Outcomes (O) that are of interest to the research question should be defined; these ought to be outcomes which are meaningful to patients and other key stakeholders, and it may be appropriate to consider the views of stroke survivors, carers and/or health

Figure 3. Key stages for a protocol and systematic review completion.

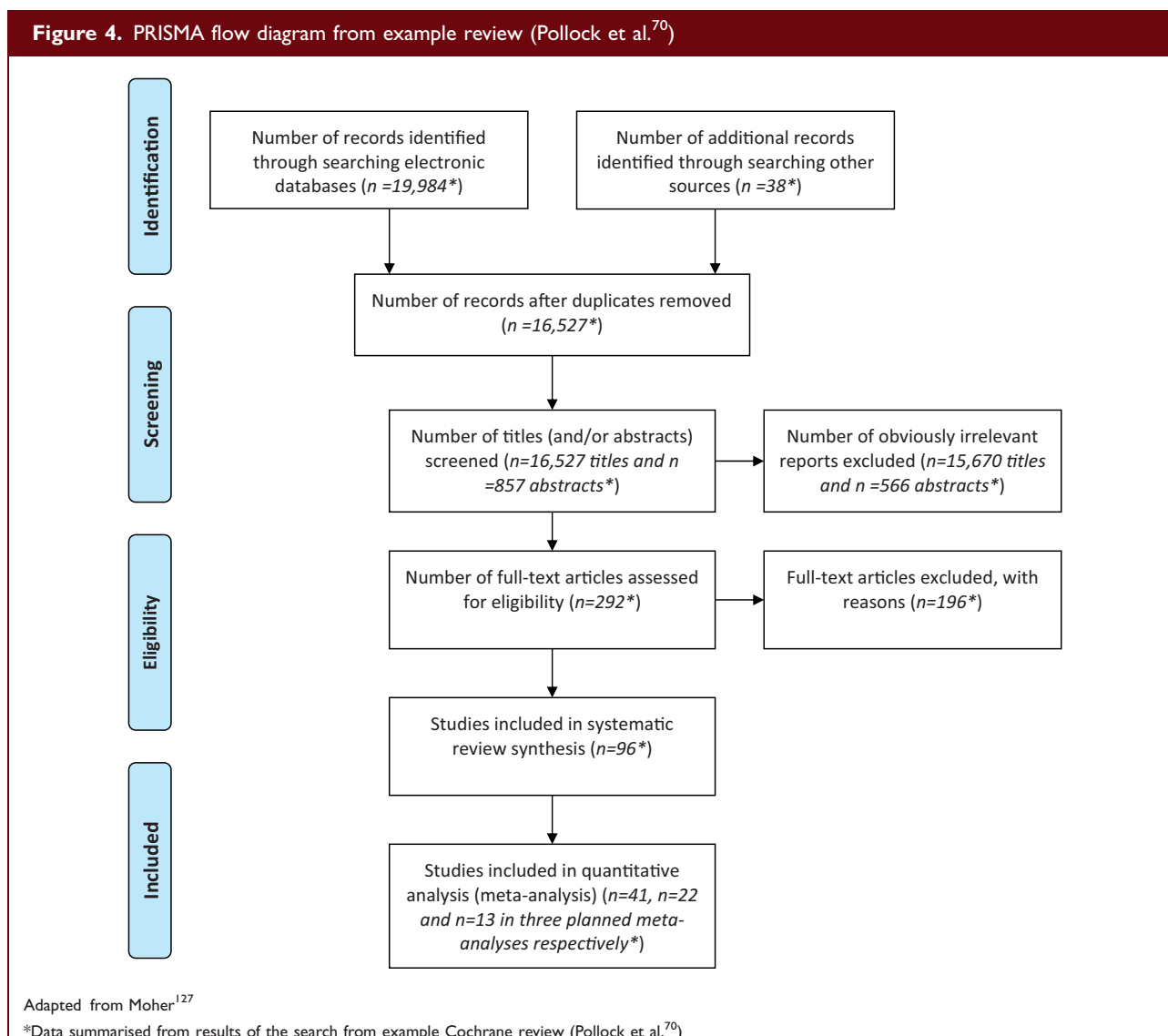
professionals when determining what outcomes are most important.⁹⁷ Acceptable methods for measuring an outcome should be stated, including any objective measures (e.g. blood pressure, number of strokes, number of falls, walking speed) or subjective scales (e.g. Barthel Index, Fugl-Meyer Assessment, quality of life scales). To avoid the introduction of bias, the outcome of greatest interest should be defined as the primary outcome, and additional outcomes as secondary outcomes. The timing of the outcome of interest should be clearly defined, and consideration given to how measurements taken at different times in the research study, and at different times post stroke, will be included.

Another key parameter to be defined is the types of study design which will be included in the systematic review. For Cochrane intervention reviews, this is often limited to randomized controlled trials, but

other reviews may include other types of study (e.g. observational studies). For example, considering the question relating to physical rehabilitation in Box 1, the question could be broadened to consider issues relating to stroke survivors' views and experiences of rehabilitation therapies, resulting in the inclusion of qualitative research studies (e.g. studies reporting results from interviews and/or discussions in focus groups).

Find relevant research

The protocol should include the full search strategy, which ought to be developed with appropriate expert advice or support from an information specialist, and description of electronic databases, and any other sources, which are to be searched. There are a wide-range of health-related bibliographic databases, some



covering broad areas of healthcare research (e.g. MEDLINE⁹⁸ and EMBASE⁹⁹), while some focus on specific study designs (e.g. the Cochrane Database of Systematic Reviews¹⁰⁰), more narrow specialist areas (e.g. PsychINFO for behavioural and social science research,¹⁰¹ PEDro for physiotherapy related trials, reviews and guidelines,¹⁰² REHABDATA for rehabilitation research¹⁰³) or a particular language or geographical area of publication (e.g. Wangfangdata, a database of Chinese studies¹⁰⁴). In general, multiple electronic databases should be used, in an attempt to be comprehensive and avoid introduction of reporting bias.¹⁰⁵

Consideration should be given to how the search results will be managed, including use of any bibliographic or data management software. For example,

adequate records of the results of the search and application of eligibility criteria must be kept, in order to complete a detailed PRISMA flowchart (Figure 4). The methods for identifying studies for inclusion should detail processes for screening of titles or abstracts in order to remove irrelevant reports, application of eligibility criteria to abstracts or full texts, and final decision making. It should be clear which of these processes will be carried out by two independent reviewers, and if there are independent reviewers what the process will be if there is disagreement. The use of two independent reviewers at key stages in the review process is considered an important approach in order to avoid one single reviewer introducing a biased (or flawed) interpretation of review criteria. At the end of this stage of

the review process, the final list of included studies will have been identified.

Collect data

“Data” refer to any information within the included studies, including information relating to the characteristics of the study as well as to quantitative and/or qualitative results. The protocol should define the data which will be extracted from each study, who will extract it and in what format. Methods to avoid the introduction of errors (e.g. entering wrong numerals into a spreadsheet; failure to identify required data from a study report) or bias should be considered, and may involve the use of two independent reviewers. Information extracted relating to stroke populations could incorporate data associated with stroke diagnosis (e.g. type, severity of stroke; lesion site; date or time since stroke; measures of initial impairment or disability) and demographic variables (e.g. age, gender, socioeconomic status, level of education, handedness). The TIDieR template⁹⁶ may be a useful tool for extraction of data relating to complex interventions, and could be incorporated into data extraction plans. Data should also be systematically collected relating to the design and conduct of the research study, such as the method of randomization and allocation concealment in the case of a randomized controlled trial. The protocol should also state which specific statistical variables (e.g. mean, confidence intervals, standard deviation) will be extracted.

Assess quality of included studies

A key stage within a systematic review is the assessment of the methodological quality of the included studies. This process involves critical appraisal and judgment relating to whether there were any potential risks of bias within the study. A bias is a “systematic error, or deviation from the truth, in results or inferences,”²³ and this can lead to findings which do not reflect the true result.¹⁰⁶ Table 2 summarizes common sources of bias, summarizing methods which can be used to avoid or limit the introduction of bias, and giving examples of bias identified in studies included in our example review.⁷⁰ Within stroke research, bias is a common risk when masking of study participants and investigators is not possible, as is the case when testing many non-pharmacological interventions. For example, outcome assessors may inadvertently provide greater encouragement during the measurement of walking speed in the intervention group than in the control group (performance bias), or may record more positive

outcomes for those in the treatment group when using a subjective rating scale or questionnaire (detection bias). Bias can also result if dropouts (for example, due to death or subsequent stroke) occur more often in one group than the other (attrition bias), or if studies or outcomes are reported selectively, depending on the results (reporting bias).

There are a large number of tools available to support critical appraisal of study quality (Table 1).¹⁰⁷ These tools can be “scales” which score quality components and provide a summary score. Despite the existence of a wide number of scales to assess quality,¹⁰⁸ the use of scales is explicitly discouraged by Cochrane²³ as the validity and transparency of such summative scales can be questioned.¹⁰⁹ The Cochrane risk of bias tool is now recommended for use within all Cochrane reviews, and is widely used by non-Cochrane reviews of randomized controlled trials. Figure 5 shows how risk of bias can be presented, using our example review.⁷⁰

The risk of reporting bias can be assessed using a funnel plot, which shows estimates of effect size from included studies against a measure of each study’s size or precision. An asymmetrical funnel plot can indicate reporting bias, for example if a search strategy had failed to identify small unpublished studies which did not show statistically significant effects, while larger published studies with statistically significant effects were identified. The presence of funnel plot asymmetry is often judged subjectively through visual inspection, but a number of statistical tests have been proposed.¹¹⁰ It is important to note that asymmetry within a funnel plot can be due to reasons other than reporting bias, for example poor methodological quality.¹¹⁰ Funnel plots are not recommended if there are less than 10 studies in a meta-analysis,¹¹⁰ and in these cases, the potential impact of reporting bias should be considered without statistical analysis.

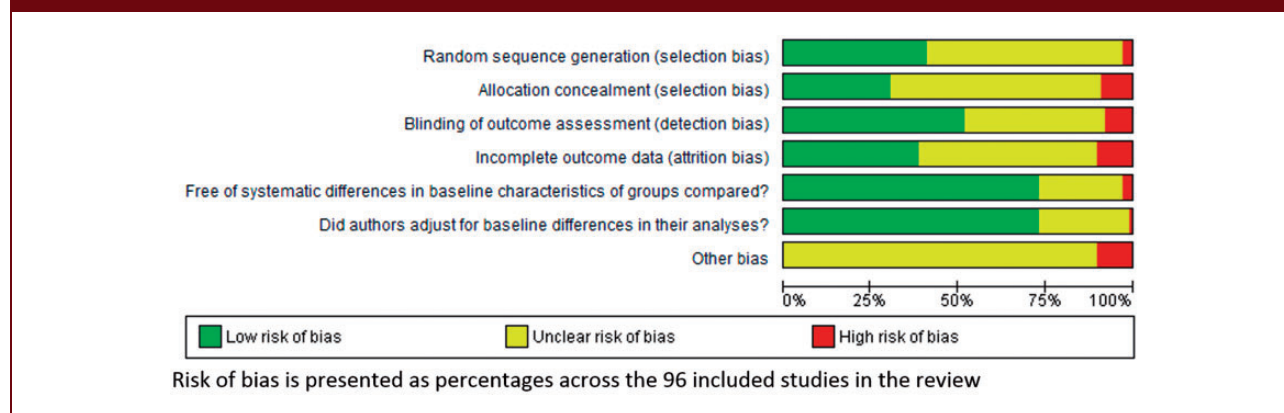
Assessment of quality requires adequate reporting of information in the individual study reports. The protocol should detail how absence of information (i.e. lack of reporting) will be incorporated into the assessment of risk of bias, and consider how to distinguish between a study for which risk of bias is unclear, and a study for which there is clear evidence of specific bias. The protocol may also describe methods to attempt to seek missing information, such as contacting research authors or imputing alternative values.

In addition to describing how risk of bias will be assessed, the protocol should also state how the risk of bias assessment will be used. Some systematic reviews may exclude studies which are judged to be of poor methodological quality, or at high risk of bias,

Table 2. Common sources of bias in stroke research

Common sources of bias	Description of bias ²³	Methods to avoid introduction of bias	Examples from review of physical rehabilitation approaches ⁷⁰
Selection bias	The groups of participants who are being compared have differences at baseline, due to the way that participants have been allocated to groups.	Randomization (allocation of participants to groups based on a random process, or sequence, with the order of allocation concealed from all people involved in the study)	Zhu 2006 ^a allocated participants to groups "according to time of hospital admission." This method introduced a risk of selection bias as the characteristics of participants could vary according to time, and the researchers could potentially influence the allocation of a participant to a specific treatment group.
Performance bias	The groups of participants receive differences in care, other than differences in the intervention which is being tested.	Masking (blinding) of participants and personnel (concealment) to the study treatment being delivered	Dean 2000, Chan 2006 and Gelber 1995 ^a did not use masking of person delivering the intervention, who could therefore be more enthusiastic and encouraging towards patients in the intervention group than the control group.
Detection bias	The way outcomes are measured in the groups of participants differs.	Masking (blinding) of outcome assessor to the study treatment being delivered	Salbach 2004 ^a un-masked outcome assessors, introducing a high risk of detection bias.
Attrition bias	There are differences in retention / withdrawals between the groups of participants.	Complete data collection in both groups. The reasons for missing data must be reported for each treatment group, so that any differences between groups can be explored.	Fang 2003 ^a had more drop-outs from one group than the other.
Reporting bias (including publication bias, and selective outcome reporting)	There are systematic differences between reported and unreported findings.	Comprehensive searching for all eligible studies (regardless of publication status) can help avoid publication bias. Pre-specification of outcome measures within a published protocol can help avoid selective outcome reporting. Statistical methods can be used to aid detection of reporting biases (funnel plots and sensitivity analyses).	Trials published in non-English language and in Chinese journals may not all have been identified ⁷⁰

^aFor references see Pollock et al.⁷⁰

Figure 5. Risk of bias graph from example review (Pollock et al.⁷⁰)

from subsequent synthesis. However, a more comprehensive and transparent approach is arguably to maintain all included studies and perform sensitivity analyses to explore the impact of excluding studies which have been judged to be at high risk of bias.

Synthesize evidence

All systematic reviews should include a synthesis of the data that have been found. Data synthesis can involve summarizing results (quantitative and/or qualitative findings) in tables, or producing narrative summaries.

Systematic reviews of quantitative data may include statistical pooling (meta-analysis). Figure 6 shows a typical Forest plot used in most reviews of quantitative data, using our example review.⁷⁰ In this example, the data being combined comprise a number of continuous outcome scales and the statistical effect measure determined is the standardized mean difference; if only one outcome scale was used, a mean difference may be calculated and if outcome data are dichotomous, the effect measure selected may be an odds or risk ratio, or risk difference. Key components which ought to be specified at the protocol stage include; the comparisons (meta-analyses) which are planned, the types of data and outcome measures which will be combined, the statistical method for pooling data and effect measure which will be used, and how heterogeneity will be assessed and interpreted. For example, the choice of statistical method for pooling data will depend on whether the heterogeneity between effect estimates is most likely due to clinical or methodological diversity between studies (in which case a fixed-effect method should be used), or whether it is most likely due to random variation (in which case a random-effect method should be used).¹¹¹ The protocol should also specify which subgroup and sensitivity analyses are planned. Examples of subgroup analyses that were considered relevant and

carried out within our example review,⁷⁰ are given in Box 3. Where statistical pooling is not planned (for example within systematic reviews of observational studies), tables summarizing results of individual studies can be useful.

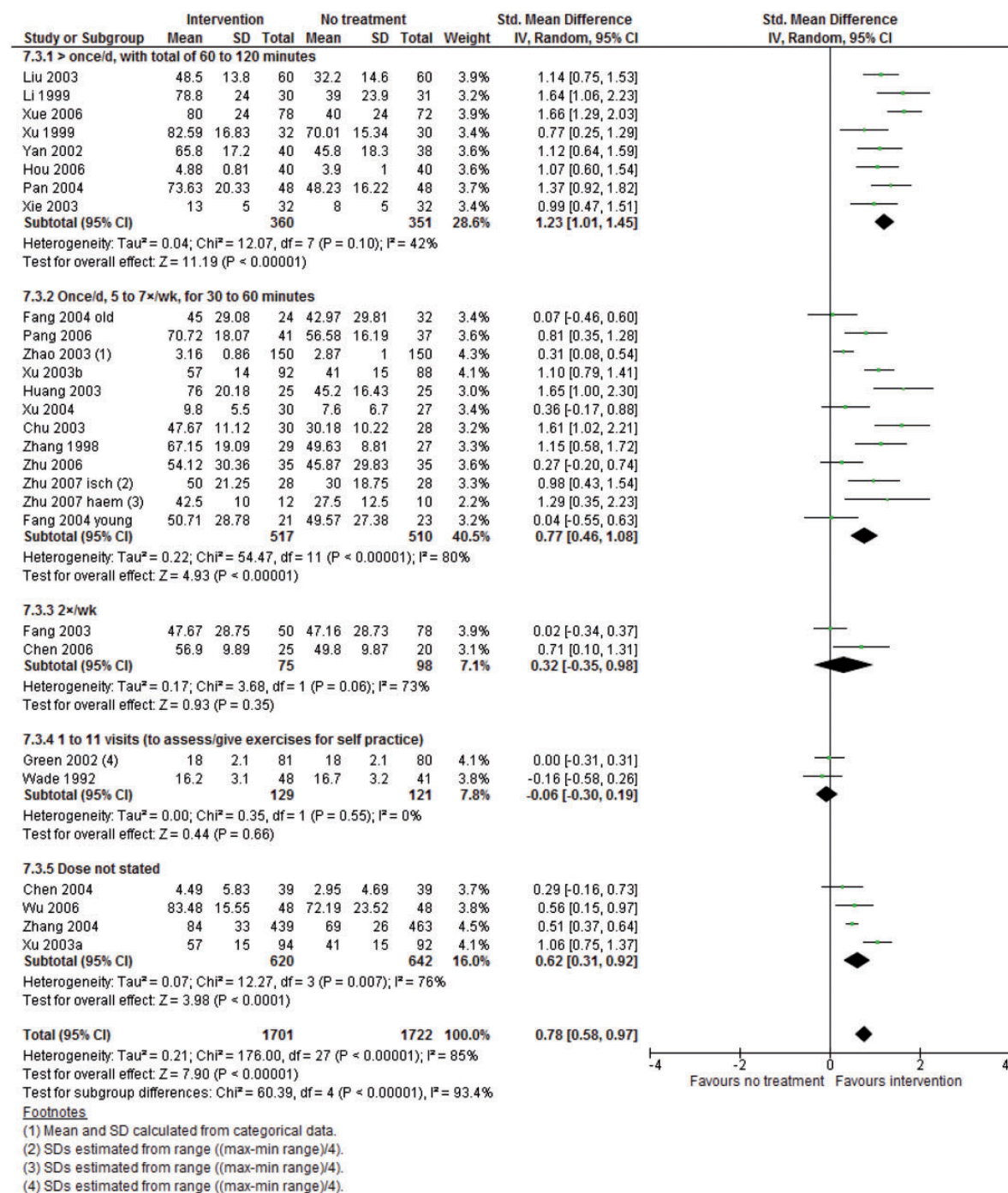
Systematic reviews including qualitative studies may adopt a number of different formal synthesis methods.^{57,58,112–114} Readers are referred to appropriate texts relating to specific synthesis techniques; however, there is considerable confusion in the published literature in relation to the terminology used to describe methods of synthesizing qualitative or mixed method studies.^{56,115} Cochrane does not recommend a specific synthesis approach for inclusion of qualitative evidence, highlighting that evaluation of the robustness of different methods is lacking.⁴⁸

Interpret findings

A plan for summarizing key findings is an essential part of a systematic review. This is often in the form of a table that summarizes the key findings and the overall quality of the data, and it is good practice to decide what will go in this at the protocol stage.¹¹⁶ The GRADE approach is being widely used within systematic reviews,^{117,118} but other approaches are available (e.g. Weight of Evidence framework^{106,119}). Table 3 shows a summary of findings table from our example review, using the GRADE approach.

Complete the systematic review

Following peer review and publication of the systematic review protocol, the review can be carried out, informed by the methods described in the protocol. Ideally, there will not be any differences between the protocol and review; however if there are any deviations from protocol, then these should be clearly

Figure 6. Forest plot from example review (Pollock et al.⁷⁰).

Data presented in subgroups according to dose/frequency of intervention.

documented, justified, and reported within the final systematic review.⁸⁹

A discussion within a completed systematic review should address a number of key points, including the

quality and completeness of the data. Any potential biases in the review process and any deviations from protocol should be discussed, as should any agreements or disagreements between the review findings and other

Box 3. What subgroup analyses are relevant?

PICO question: In patients with a recent acute stroke (less than six weeks) with reduced mobility, is any specific physiotherapy approach more beneficial than no physiotherapy at improving independence in activities of daily living and gait speed?

Relevant subgroup analyses to consider:

- Effects of therapy given at different times after stroke (<1 week, 1–3 weeks, or 3–6 weeks).
- Effects of therapy in different parts of the world (Europe, Australasia, America, Asia).
- Effects of therapy at different doses/intensities (> 45 min/day, 30–45 min/day, 15–30 min/day, <5 sessions/week, <2 sessions/week).
- Effects of therapy delivered by different professions (physiotherapist, nurse, assistant therapist, carer/family member).
- Effect of different specific therapy approaches (e.g. Bobath approach, motor learning approach, orthopedic methods).

Table 3. Summary of findings table from example review

PICO question: In patients with a recent acute stroke (less than six weeks) with reduced mobility is any specific physiotherapy method more beneficial than no physiotherapy at improving independence in activities of daily living and gait speed?				
Selected outcomes	Standardized mean difference (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Independence in ADL scales	0.58 (0.11 to 1.04)	9 studies 540 participants	⊕⊕⊕ ⊖moderate	Quality of evidence downgraded as there was substantial statistical heterogeneity in results ($I^2 = 85\%$)
Gait velocity	−0.06 (−0.29 to 0.18)	3 studies 271 participants	⊕⊕⊖ ⊖low	Quality of evidence downgraded twice as dose of physiotherapy varied substantially between studies, and 1/3 studies were carried out in China (and a significant subgroup effect relating to geographical location of the study was identified)

Note: This table is adapted from the summary of findings table within our example review,⁷⁰ for the purpose of this article.

relevant reviews, guidelines or policies. The generalizability of the evidence to the original research question, and the implications of the review findings to clinical practice should be considered. However, systematic reviews ought to avoid giving specific recommendations for clinical practice, since local circumstances, such as status of the health care system, costs of the intervention, and patients' preferences must always be considered when making clinical decisions based on systematic review evidence. Involvement of key stakeholders, including patients, carers and health professionals, may be beneficial at this stage, helping to interpret findings in a way that is meaningful to the

users of the review.^{120–122} Often a systematic review will highlight gaps in the evidence, or in the quality of the evidence, in which case specific implications for research should be derived. This should move beyond a statement that “more research is needed” discussing the need for different types of study designs and proposing research questions which need to be addressed.

After review completion: Publication, dissemination and up-dating

After the systematic review has been reviewed and approved, it should be made freely available through

publication in a journal, electronic repository, or other resource. The publication should highlight any sources of funding for the review, and any competing interests between the review authors, funders, or other related organizations in the review production. Systematic review authors should consider strategies for effective dissemination,¹²³ and involvement of patients and the public seems to be important for successful implementation of research findings.^{61,121,122} The need for further work to highlight effective strategies for implementation in the field of stroke care has been highlighted.^{124,125}

Ideally, systematic reviews will be updated regularly in order to incorporate new studies, although decisions to update have to take many factors into account, including the importance of the topic, whether there is new evidence and the likelihood of this changing the conclusions of the review.¹²⁶ Regular updating of a systematic review is generally recommended and is a more efficient use of resources than embarking on a new review addressing the same question.¹²⁶

Conclusions

Systematic reviews in stroke are necessary to ensure that healthcare and research decisions are informed by the best possible, up-to-date research evidence, and that patients are provided with the best possible care. A protocol is an essential part of all systematic reviews, ensuring rigorous, transparent methods. Key stages in systematic reviews include the formulation of the research question, the identification of relevant research, data extraction, assessment of risk of bias, data synthesis, summary and interpretation of the findings. The review process should include strategies for dissemination. Updating a systematic review after completion is important to ensure that the conclusions remain valid.

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