Comparative Clinical Effectiveness of Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia

Research Protocol

TABLE OF CONTENTS

BACKGROUND, OBJECTIVES, AND RESEARCH QUESTIONS

Background

Tardive dyskinesia (TD) is a movement disorder with a delayed onset that is related to prolonged use of medications that block the dopamine receptor, most commonly antipsychotic drugs.[1] Though initially associated with older antipsychotic agents, termed "first-generation" antipsychotics, TD also occurs with newer agents, termed "second-generation" or "atypical" antipsychotics.[2] Other medications associated less commonly with TD include metoclopramide and antidepressants (e.g., amoxapine).[3]

The movements associated with TD can be localized or diffuse and can result in physical and psychological impairment. TD is a hyperkinetic, involuntary movement disorder that can include a range of clinical manifestations. Classic TD involves the mouth and face region which can present as lip smacking or pursing, chewing, facial grimacing, and tongue movements inside the mouth or tongue popping out. TD can also involve the limbs and trunk. This may manifest as repetitive foot tapping, finger movements, dystonic postures of the neck and trunk that can include torticollis, rocking and rotatory movements, as well as shoulder shrugging. Patients may not be aware of these involuntary movements, especially when involving the face, and thus the condition can be socially stigmatizing. To assess the severity of TD symptoms and the impact of treatment, the Abnormal Involuntary Movement Scale (AIMS) has been used in clinical and research settings.[4] Though there is currently no validated measure that reflects the impact of TD on a patient's quality of life, the Abnormal Involuntary Movement Scale (AIMS) has been used in clinical and research settings to assess the general severity of symptoms and the impact of treatment.[4]

The term "tardive" implies a delayed onset, commonly after at least 3 months of exposure to offending agents,[5] but examples of symptoms developing after shorter time periods have been observed. This may in part be related to the onset of TD being insidious and difficult to recognize at first. Among patients on antipsychotics, prevalence rates of TD have been estimated to be 25%,[6] with a range of 20-50%.[7] Prevalence is higher for first generation (30%) than for second generation (13-20%) agents.[6] Antipsychotic agents are most frequently used for patients with schizophrenia and schizoaffective disorder but are also used in serious mood disorders such as bipolar disease and major depression. It is estimated that there are six million individuals with these diagnoses on antipsychotics in the U.S.[8] Other uses can be for those with personality disorders, post-traumatic stress disorder (PTSD), insomnia and dementia. The incidence of new TD is reported to be around 5% per year with first generation antipsychotics and 3% per year with second generation antipsychotics.[9,10] Higher rates are seen in older and female patients.[11]

Treatment recommendations have been developed by the American Psychiatric Association and the American Academy of Neurology.[5,12] Avoiding long-term use of antipsychotic agents for conditions where evidence of benefit is lacking or other treatment options are available is preferred. Therapy for TD has primarily focused on decreasing and then stopping the offending agent, and switching to a

different antipsychotic if such agents are still deemed necessary. It is often not possible to stop the antipsychotic immediately because TD symptoms can worsen upon withdrawal. Though patients with TD symptoms may improve with these changes, complete resolution of symptoms is rare, and long-lasting or permanent symptoms can be seen, even in patients who successfully are taken off antipsychotics.[13,14] Therefore, other treatments have been sought to decrease symptoms of patients with TD, and guideline recommendations may change with the availability of safer and more effective treatment options.

Though a wide range of pharmacologic treatments for TD have been studied, few therapies have been shown to produce more than a slight to moderate benefit.[2,15] Tetrabenazine, approved for Huntington's disease in 2008, is a VMAT2 inhibitor that has been used off-label for TD. VMAT2 inhibition depletes dopamine storage in pre-synaptic vesicles, resulting in less dopamine release. Several small controlled and observational studies of tetrabenazine have shown varying improvement in symptoms, but the need for three-times per day dosing and side effects, including sedation and worsening of depression and anxiety have limited its usefulness. Other drugs used have included clozapine, benzodiazepines, anti-cholinergic agents, and a number of different vitamins and homeopathic therapies. Given the limited evidence of therapeutic benefit from available treatments, there is a clear need for new therapeutics for patients with disabling symptoms due to TD.

No FDA approved drugs were available prior to the approval of valbenazine in April 2017. Like tetrabenazine, valbenazine (Ingrezza™, Neurocrine Biosciences, Inc.) is a VMAT2 inhibitor, but is dosed once a day and may have a favorable side-effect profile compared to other off-label agents. Deutetrabenazine (Austedo™, Teva), a modification of tetrabenazine that slows metabolism and clearance, was approved for the treatment of Huntington's disease in April 2017, and is currently under review for a TD indication.

Overview

This review will evaluate the comparative clinical effectiveness of the VMAT2 inhibitors valbenazine, deutetrabenazine, and tetrabenazine for the treatment of adults with tardive dyskinesia. Evidence will be collected from available randomized controlled trials, non-randomized clinical trials, and high-quality systematic reviews; comparative observational studies will also be included if available. We will limit our review to those studies that capture the outcomes of interest; however, when assessing adverse events and harms, we will also look for randomized trials of the VMAT2 inhibitors for conditions other than tardive dyskinesia. We will not restrict studies according to study duration or study setting; however, we will limit our review to those that measure the outcomes of interest and include at least 10 patients. We will supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[16]

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair*: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor*: Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.*

PICOTS Inclusion Criteria

All search algorithms for the systematic literature review will be generated utilizing PICOTS-related elements: Population, Interventions, Comparisons, Outcomes, Timing, and Setting.

Population

The primary population of focus for the review will be adults ages 18 and older with symptoms of tardive dyskinesia for at least three months and history of use of dopamine receptor antagonists. However, population with conditions other than tardive dyskinesis that use the intervention of interest will also be assessed when assessing adverse events and other potential harms.

We will also seek evidence on key subpopulations of interest, including: (a) patients with incident or new onset tardive dyskinesia; (b) patients with localized vs. generalized tardive dyskinesia symptoms; (c) patients with schizophrenia/schizoaffective disorders vs. other underlying conditions that may be associated with TD. Other subgroups of interest will include age, gender, and severity of symptoms as assessed by both clinicians and patients (i.e., mild, moderate, or severe).

Interventions

We will consider all VMAT2 inhibitors including those with FDA indications for TD as well as one investigational therapy presently undergoing FDA review and one drug used off-label. Interventions of interest are listed below.

- Valbenazine (Ingrezza™, Neurocrine Biosciences, Inc)
- Deutetrabenazine (Austedo™, Teva [investigational])
- Tetrabenazine (Xenazine®, Lundbeck and generics [off-label use])

Comparators

We will examine studies comparing VMAT2 inhibitors to placebo or other types of active medications that are used off-label to control TD symptoms. Wherever possible, we will evaluate head-to-head trials of the interventions. If suitable data are available, the review may include head-to-head comparisons through methods such as network meta-analysis.

Outcomes

This review will examine key clinical outcomes associated with TD. However, when assessing adverse events and harms, we will also look for randomized trials of the interventions of interest for conditions other than tardive dyskinesia. We will engage with patient groups and clinical experts to ascertain which outcomes are of greatest importance to patients, and seek patient-reported outcomes or other evidence sources to enrich the available data. Initial discussion with patients, patient groups, and clinicians indicate that clinical trials are often lacking robust information on patient-reported outcomes and burdens associated with tardive dyskinesia.

Outcomes of interest will include:

- Symptom improvement (Abnormal Involuntary Movement Scale [AIMS], Clinical Global Impression of Tardive Dyskinesia [CGI-TD])
- Patient reported outcome (Patient Global Impression of Change [PGIC])
- Health-related quality of life
- Treatment-related adverse events (e.g., somnolence, suicide, worsening of underlying mental health illness)
- Discontinuation due to adverse events
- Costs and cost-effectiveness

We will also look for evidence on additional patient-reported outcomes as available. Importantly, long-term use of antipsychotics is also associated with the development of other extrapyramidal symptoms and movement disorders, but the focus of this assessment will be on TD symptoms only.

Evidence tables will be developed for each selected study and results will be summarized in a qualitative fashion; meta-analysis will be used to quantitatively summarize outcomes for the therapies of interest. In addition, we will consider network meta-analysis to combine direct and indirect evidence of effectiveness if available data permit.

Timing

Evidence on intervention effectiveness will be derived from studies of any duration if they meet the study design criteria set forth above and measure the outcomes of interest.

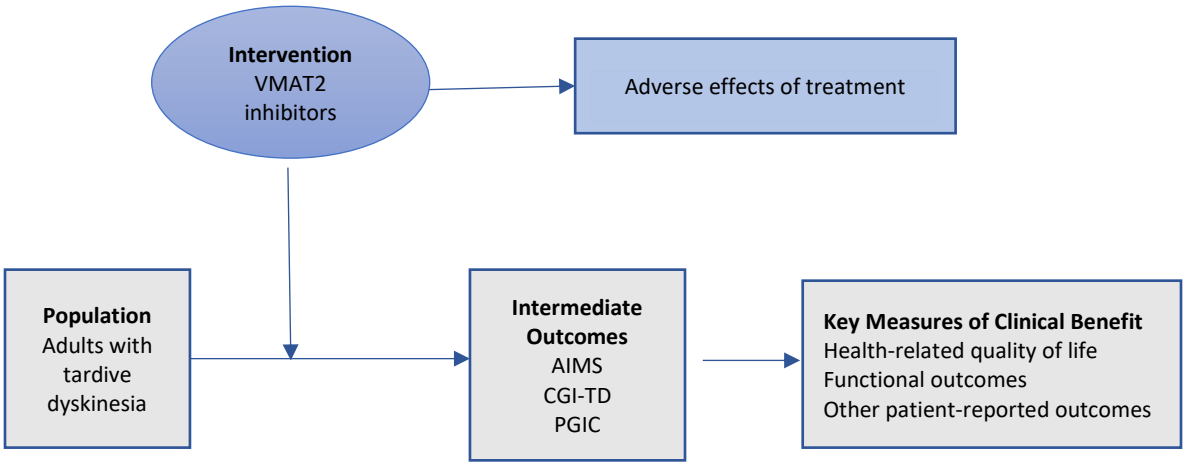
Setting

All relevant settings will be considered, including outpatient/clinic, office, and home settings.

Analytic Framework

The proposed analytic framework for this project is depicted below.

Figure 1. Analytic Framework: Vesicular Monoamine Transporter 2 Inhibitors for Tardive Dyskinesia



VMAT2: vesicular monoamine transporter 2; AIMS= Abnormal Involuntary Movement Scale; CGI-TD= Clinical Global Impression of Tardive Dyskinesia; PGIC= Patient Global Impression of Change

EVIDENCE REVIEW METHODS

Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on VMAT2 inhibitors for tardive dyskinesia will follow established best methods.[17,18] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE, EMBASE, PsycINFO, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials for relevant studies. Each search will be limited to English-language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items.

The search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Tables 1-2 on the following pages. We will also include abstracts from conference proceedings in the literature search. To supplement the above searches and ensure optimal and complete literature retrieval, we will perform a manual check of the references of recent relevant reviews and meta-analyses.

Table 1: Search Strategy of Medline 1996 to Present with Daily Update, Psych INFO and Cochrane Central Register of Controlled trials

1	exp tardive dyskinesia/
2	(tardive adj3 (dyskine$ or diskine$ or syndrome$ or dystonia$)).ti,ab.
3	1 or 2
4	(movement* adj disorder*).mp.
5	((involuntary* or abnormal* or hyperkinetic) adj3 movement*).mp.
6	3 or 4 or 5
7	exp tetrabenazine/
8	(Tetrabenazine or Xenazine).mp.
9	(Deutetrabenazine or Austedo).mp.
10	(Valbenazine or ingrezza).mp.
11	7 or 8 or 9 or 10
12	vesicular monoamine transporter adj3 inhibitor.mp
13	11 or 12
14	6 and 13
15	(animals not (humans and animals)).sh.
16	14 not 15
17	limit 16 to english language
18	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education

	handout or periodical index or personal narratives or portraits or practice guideline or review or videoaudio media).pt.
19	17 not 18
20	remove duplicates from 19

Table 2. Search strategy of EMBASE SEARCH

#1	'tardive dyskinesia'/exp
#2	(tardive NEAR/3 (dyskine* OR diskine* OR dystonia* OR syndrome*)):ab,ti
#3	#1 OR #2
#4	'movement disorder*':ab,ti
#5	((involuntary* OR abnormal*) NEAR/3 movement*):ab,ti
#6	#3 OR #4 OR #5
#7	'tetrabenazine'/exp OR tetrabenazine:ab,ti OR xenazine:ab,ti
#8	'deutetrabenazine'/exp OR deutetrabenazine:ab,ti OR austedo:ab,ti
#9	'valbenazine'/exp OR valbenazine:ab,ti OR ingrezza:ab,ti
#10	#7 OR #8 OR #9
#11	'vesicular monoamine transporter' NEAR/3 inhibitor*
#12	#10 OR #11
#13	#6 AND #12
#14	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#15	'human'/exp
#16	#14 AND #15
#17	#14 NOT #16
#18	#13 NOT #17
#19	#18 AND ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#20	#18 NOT #19
#21	#20 AND [english]/lim
#22	#21 AND [medline]/lim
#23	#21 NOT #22

Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will screen the titles and abstracts of all publications identified through electronic searches according to the inclusion and exclusion criteria defined by the PICOTS elements; a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract-level screening due to insufficient information. For example, a study that does not report an outcome of interest in its abstract would be accepted for further review of full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

Data Extraction Strategy

For the systematic literature review, the data extraction will be performed in the following steps:

1. Three reviewers will extract information from the full articles.
2. Extracted data will be reviewed for logic, and a random proportion of data will be validated by a fourth investigator for additional quality assurance.

Information from the accepted studies will be extracted into data extraction forms.

Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, multiple assessments of publication bias will be performed. We will first scan the ClinicalTrials.gov site to identify studies completed more than two years ago which would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

Evidence Synthesis

Data on relevant outcomes will be summarized in evidence tables, and synthesized qualitatively in the text of the report. Evidence table shells are presented in Appendix B.

In addition, network meta-analysis (NMA) for indirect comparisons will be considered where possible. We will evaluate the feasibility of NMA by exploring for the presence of any clear indicators of study heterogeneity conferred by variation in study populations, study design, reported outcomes or analytic methods which would preclude meaningful quantitative synthesis. We do not anticipate including tetrabenazine in any quantitative comparisons, due to the anticipated small number of adequately-controlled studies, and other major differences in study design (e.g., use of nonstandard clinical measures of outcome).

If quantitative analyses are deemed feasible based on the structure of available evidence, they will focus on assessing the effects of the regimens of interest on symptom improvement and/or other key outcomes, using a random effects approach. We will evaluate the presence of statistical inconsistency in the data, by using both the local and global approaches. Specifically, we will use the loop-specific approach[20] to detect loops of evidence that might present important inconsistency as well as the node-splitting approach[21] to detect comparisons for which direct estimates disagree with indirect evidence from the entire network. Transitivity assumptions will be examined by assessing the comparability of the

distribution of the treatment effect modifiers across comparisons. Mean baseline AIMS scores and treatments for the underlying conditions that may be associated with TD are examples of potential effect modifiers that will be considered.

References

1. Li P, Snyder GL, Vanover KE. Dopamine Targeting Drugs for the Treatment of Schizophrenia: Past, Present and Future. *Current topics in medicinal chemistry.* 2016;16(29):3385-3403.

2. Cloud LJ, Zutshi D, Factor SA. Tardive dyskinesia: therapeutic options for an increasingly common disorder. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics.* 2014;11(1):166-176.

3. Waln O, Jankovic J. An update on tardive dyskinesia: from phenomenology to treatment. *Tremor and other hyperkinetic movements (New York, NY).* 2013;3.

4. Gharabawi GM, Bossie CA, Lasser RA, Turkoz I, Rodriguez S, Chouinard G. Abnormal Involuntary Movement Scale (AIMS) and Extrapyramidal Symptom Rating Scale (ESRS): cross-scale comparison in assessing tardive dyskinesia. *Schizophrenia research.* 2005;77(2-3):119-128.

5. Bhidayasiri R, Fahn S, Weiner WJ, Gronseth GS, Sullivan KL, Zesiewicz TA. Evidence-based guideline: treatment of tardive syndromes: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2013;81(5):463-469.

6. Carbon M, Hsieh CH, Kane JM, Correll CU. Tardive Dyskinesia Prevalence in the Period of Second-Generation Antipsychotic Use: A Meta-Analysis. *The Journal of clinical psychiatry.* 2017;78(3):e264-e278.

7. Association AP. *Diagnostic and statistical manual of mental disorders (5th edition).* Washington, DC2013.

8. Patrick M. Neurocrine Biosciences' Valbenazine Launch: What You Need to Know. *Neurocrine Biosciences: The Formula for 2016 Valuations* 2016; http://marketrealist.com/2016/03/neurocrine-biosciences-expected-submit-nda-tardive-dyskinesia-drug-valbenazine-2016/.

9. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *The American journal of psychiatry.* 2004;161(3):414-425.

10. Vijayakumar D, Jankovic J. Drug-Induced Dyskinesia, Part 2: Treatment of Tardive Dyskinesia. *Drugs.* 2016;76(7):779-787.

11. Woerner MG, Correll CU, Alvir JM, Greenwald B, Delman H, Kane JM. Incidence of tardive dyskinesia with risperidone or olanzapine in the elderly: results from a 2-year, prospective study in antipsychotic-naive patients. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2011;36(8):1738-1746.

12. Association AP. Tardive dsykinesia: A Task Force Report of the American Psychiatric Association. *Psychiatric Services.* 1992;44(2):190.

13. Glazer WM, Morgenstern H, Schooler N, Berkman CS, Moore DC. Predictors of improvement in tardive dyskinesia following discontinuation of neuroleptic medication. *The British journal of psychiatry : the journal of mental science.* 1990;157:585-592.

14. Glazer WM, Morgenstern H, Doucette JT. The prediction of chronic persistent versus intermittent tardive dyskinesia. A retrospective follow-up study. *The British journal of psychiatry : the journal of mental science.* 1991;158:822-828.

15. Rana AQ, Chaudry ZM, Blanchet PJ. New and emerging treatments for symptomatic tardive dyskinesia. *Drug design, development and therapy.* 2013;7:1329-1340.

16. *U.S. Preventive Services Task Force Procedure Manual.* Agency for Healthcare Research and Quality; July 2008. Publication No. 08-05118-EF.

17. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.

18. *Cochrane Collaboration Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011].* The Cochrane Collaboration and John Wiley & Sons Ltd; 2008.

19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *International journal of surgery (London, England).* 2010;8(5):336-341.

20. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of clinical epidemiology.* 1997;50(6):683-691.

21. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in medicine.* 2010;29(7-8):932-944.

22. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj.* 2009;339:b2700.

APPENDIX A. PRISMA CHECKLIST

The checklist below is drawn from Moher et al. 2010.[19] Additional explanation of each item can be found in Liberati et al. 2009.[22]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

doi:10.1371/journal.pmed.1000097.t001

APPENDIX B. DATA EXTRACTION SUMMARY TABLE SHELLS

Author & Year of Publication (Trial Name) Quality rating	Study Design and Duration of Follow-up	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Patient Characteristics	Outcomes	Harms