Methods Research Report

Supplemental Project To Assess the Transparency of Reporting Requirements: Tympanostomy Tubes in Children With Otitis Media

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by e-mail to epc@ahrq.hhs.gov.

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Supplemental Project to Assess the Transparency of Reporting Requirements: Tympanostomy Tubes in Children With Otitis Media

Structured Abstract

Introduction. Despite efforts to spur pediatric research, there is a paucity of pediatric-specific research data available to guide clinical decisionmaking. Searching the grey literature improves the identification of evidence not found in the peer-reviewed literature and may prove particularly valuable for pediatric research synthesis. The objective of this methodology report is to examine the feasibility and additional utility—in terms of impact on risk of bias and strength of evidence assessments—of comprehensive searches of trials registries to supplement the evidence identified in an ongoing systematic review on tympanostomy tubes in children with otitis media conducted by the Brown Evidence-based Practice Center (EPC).

Data sources. We conducted searches in ClinicalTrials.gov and the International Clinical Trials Registry Platform, using terms that matched those used in the original review database searches.

Results. Six studies were identified in both the registries and the original review. Overall the agreement for design, arm information, baselines, and results was very close, but prespecified outcomes in almost all of the records differed from the outcomes in the publications based on those records. Twenty studies were screened in via registry searches but not found in the original review. Two gave results, but we were unable to incorporate them in to the analysis, due to the fact that they had no statistical analyses. The results of these trials would not have changed our initial meta-analyses, risk of bias, or strength or evidence assessments. Seven of the records without results indicate studies with completion dates in the future or recent past. The information about these studies can be used to inform future research needs. We were able to find a registry record for only four of the 178 studies in the original review.

Conclusions. This project yields limited evidence on the utility of searching ClinicalTrials.gov, because only six records were found that matched papers in the report, along with two others that yielded new results. Based on the evidence we found, there does not appear to be an impact on the conclusions or strength of evidence in the report of including records from ClinicalTrials.gov and ICTRP. One way in which conducting a registry search is of value to a systematic review project is in identifying ongoing research, as well as gaps in knowledge, and facilitating prioritization of future research to reduce redundancy.

Contents

Background and Objectives

As described in our Omega-3 Fatty Acids and Cardiovascular Disease report, Systematic reviewers have pursued two methods approaches for dealing with information bias: (1) detecting (and correcting results for) information bias using only the identified studies (e.g., using funnel-plot based methods[1-4] or various selection models[5-7]) and (2) examining trial registries, surveying researchers, and perusing the grey literature to identify unpublished study results or ongoing studies. Empirical analyses of prospective registry data can inform on the time between study completion and publication, the number of unpublished studies, the fidelity of studies to registered protocols, and the congruence of study results between result registries and publications.[8-11]

Despite efforts to spur pediatric research, children remain "therapeutic orphans" [12] for whom a paucity of pediatric-specific research data is available to guide clinical decision making. Searching the grey literature improves the identification of evidence not found in the peer-reviewed literature and may prove particularly valuable for pediatric research synthesis. Empirical evidence suggests that FDA regulated and/or industry sponsored research are more likely to be found in trial registries, but compliance with mandated ClinicalTrials.gov requirements remains poor, including low rates of timely registration and posting of results.[13] Efforts to incentivize pediatric research have resulted in modest impact toward increasing available data on pediatric drugs and devices.[14] Studies conducted outside the United States may not be registered with ClinicalTrials.gov but may be found in a local registry (e.g., ICTRP). For these reasons, we propose to search and evaluate studies from both sources.

The objective of this methodology report is to examine the feasibility and additional utility—in terms of impact on risk of bias and strength of evidence assessments—of comprehensive searches of the ClinicalTrials.gov and ICTRP registries to supplement the evidence identified in an ongoing systematic review on tympanostomy tubes in children with otitis media conducted by the Brown Evidence-based Practice Center (EPC).[15]

Methods

Overview

This report is based on a systematic review that is currently being conducted by our EPC on the relationship between tympanostomy tubes and a variety of outcomes, including hearing, developmental outcomes and quality of life, adverse events, and otorrhea. The ongoing systematic review (hereafter referred to as "original review") is being conducted in accordance to IOM standards and AHRQ guidance.

Terminology

We use the term study to refer to the conducted research. Information about the design or results of studies may be reported in publications or in registry records. It is possible that studies identified through the registry search have no associated publications; and that studies identified in the original review have no records in ClinicalTrials.gov or ICTRP.

Registry Searches

Because the registry databases are not indexed, queries can only include text words. Thus, it was necessary to translate the search of the original review, which includes text words, as well as controlled-vocabulary (MeSH) terms, to a semantically equivalent query using the ClinicalTrials.gov and ICTRP interfaces. The ClinicalTrials.gov search interface allows only for queries with a limited number of characters, and documentation on advanced searching options, such as truncation and adjacency searching, is sparse.[16, 17] We were able to keep the PubMed search strategy intact for the ClinicalTrials.gov search, merely translating MeSH terms to text words. However, to run the search in the ICTRP interface, which does not allow for nested queries, we were forced to search only on intervention terms. Appendix A includes the literature searches from the original review and the specific search strategies to be used in ClinicalTrials.gov and ICTRP.

Analysis

Registry searches were categorized as follows (1) included in the original review but not found in the registry, (2) included in the original review and found in a registry but with no new results data, (3) included in the original review and found in a registry with new data, and (4) identified via the registry but not found in the original review. Though we planned to document rationale for study discontinuation, none were provided for studies included in our analysis. We focus on the value of results data identified via registry searches, and thus highlight the congruence, or lack thereof, among data identified via the registry and found in the original review in light of additional study data identified via registry searches.

For studies included in the original review that also have a registry record, the additional information in the registry records pertains to their design (if the registry record includes protocol information) or their findings (if the record includes results). Information found in records was examined against information obtained from publications to judge whether important changes in the analysis plan occurred. We made such comparisons only with respect to 1) general design items used to inform risk of bias assessments and 2) the analysis plan of the

eligible exposure-outcome relationships. The risk of bias of each study result in the original review will be evaluated based on predefined questions. We assessed whether the additional information in the registry records changed the risk of bias assessments in the original review. In the assessment for changes in the analysis plan, we looked for changes in the population studied, the effect measure (e.g., difference in means, odds ratios for specific categorizations of continuous outcomes), and maximum follow up recorded; we also looked for differences in the estimation procedure (the prescribed statistical learning procedure) and the plan for handling missing values, where the records give sufficient information.

We have described whether registry records and publications describe the same outcomes. Because no records with matched publications gave results, we were unable to assess whether the results agreed. Registry records of newly identified studies not included in the original review are summarized in narrative form and extracted into spreadsheets based on the original review's extraction form. We applied the same risk of bias assessments as in the original review, where it is possible to assess risk of bias, and report results, as well as whether the new results can be incorporated into the analyses of the original review.

Risk of Bias for the Evidence Base and Strength of Evidence

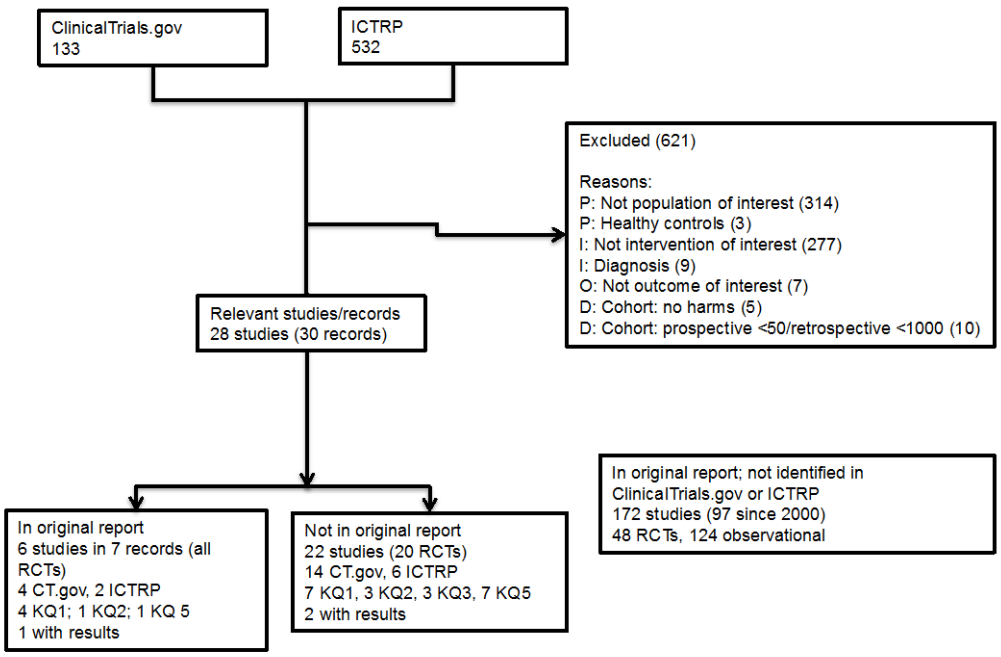
For outcomes with new data from the registries, we have reassessed the risk of bias of the evidence base and the strength of evidence using the same methodology used for the original review. We assess whether the new studies fall within the range of the similar studies from the original review and whether the additional data are likely to directly impact the strength of evidence or the assessment of risk of bias for the evidence-base.

Results

Registry Search Yield

As can be seen in Figure 1, the searches of ClinicalTrials.gov and ICTRP returned 665 records, of which 29 studies in 30 records were determined to be relevant for the project. Of these, four matched papers cited in the original review, none with results. Twenty-three did not have matching papers in the original review, and two of these had results reported in the trial registry. The greatest amount of that time was in the screening of the 665 records retrieved and in the matching and evaluation of the relevant records. The time screening could have been reduced by (1) searching only ClinicalTrials.gov, but relevant records from ICTRP would have been missed; or (2) searching ClinicalTrials.gov, using the advanced search function with the otorrhea terms in the population field and tympanostomy terms in the intervention field. This strategy returned only 77 records, and that set included all of the records eventually screened in as relevant. This was a project where the limitations of the ICTRP search interface were apparent, requiring that we use a very general search for only the intervention terms and screen over 500 records to find the 10 eventually included in the analysis.

Figure 1. Literature flow



RCT: randomized controlled trial; CT.gov: ClinicalTrials.gov; ICTRP: International Clinical Trials Registry Platform; NRCS: non-randomized comparative study; KQ: key question.

Comparison of Registry Searches with Original Review

The original review included 178 studies, 11 (studies) of which were identified in the registry record search. Table 1 gives basic information on all 28 relevant records from the registry searches, with the six that were also in the original review at the top.

Table 1. Overall description of studies found

Study Identifier	Papers Author, year, PMID	Registry	Prospective/ retrospective	Dates	Target N	Key Question
In report						
NCT00365092	Paradise 2001 11309632	CT.gov	Retrospective	2002-2006	400	1
ISRCTN35793977	MRC Multicentre Otitis Media Study Group 2012 (TARGET) 22443163	ICTRP/ISRCTN	Retrospective	1994-1997	590	1
ISRCTN57358603	Maw, 1999, 10459904	ICTRP/ISRCTN	Retrospective	1994-1997	NR	1
NCT00629694	Vlastos 2011 21205368 5/2007-5/2008 Greece	Ct.gov	Retrospective	2007-2009	52	1
NCT00162994	Kujala, 2014, 24445832; Kujala, 2012, 22466327	CT.gov	Retrospective	2002-2005	300	2
NCT01949142 and NCT01949155	Mair, 2016, 26985629	Ct.gov (identified through ICTRP)	Prospective	2013-2014	530	5
Not in report, with results						
NCT01404611		CT.gov	Prospective	2011-2013	331	5
NCT01908803		CT.gov	Prospective	2013-2014	84	5
Not in report, no results						
NCT02546518		CT.gov	Prospective	2015-2016	80	1
NCT00016497		CT.gov	Retrospective	1997-2007	No data	1
NCT01071902		CT.gov	Prospective	2010-2011	400	1
NCT02490332		CT.gov	Prospective	2015-2020	400	1
ACTRN12613000102774		ICTRP/ANZCTR	Prospective	2014-	280	1
NCT00809601		CT.gov	Prospective	2008-2015	400	1,2
ACTRN12611001073998		ICTRP/ANZCTR	Prospective	2014-	200	1,2
NCT02038400		CT.gov	Prospective	2013-	140	2
NCT02567825		CT.gov	Prospective	2015-2021	240	2
ACTRN12611000380998		ICTRP/ANZCTR	Prospective	2011-	200	2,3
NCT01111877		CT.gov	Prospective	2010-2011	1389	3
NCT01437436		CT.gov	Retrospective	2010-2012	120	3
NCT02165384		CT.gov	Retrospective	2014-2016	250	3
NCT00578474		CT.gov	Retrospective	2005-2008	911	5
NCT00578773		CT.gov	Retrospective	2007-2009	303	5

Study Identifier	Papers Author, year, PMID	Registry	Prospective/ retrospective	Dates	Target N	Key Question
NCT00579189		CT.gov	Retrospective	2006-2009	776	5
NCT01994642		CT.gov	Prospective	2013-2016	203	5
IRCT2013112315496N1		ICTRP/IRCT	Retrospective	2006-	530	5
EUCTR2009-017319-13-BE		ICTRP/EUCTR	Prospective	2011-	1300	5
EUCTR2010-023239-40-ES		ICTRP/EUCTR	Retrospective	2011-	330	5

CT.gov: ClinicalTrials.gov, ICTRP: International Clinical Trials Registry; ANZCTR: Australian New Zealand Clinical Trials Registry; IRCT: Iranian Registry of Clinical Trials; ISRCTN: International Standard Registered Clinical/soCial sTudy Number; EUCTR: European Union Clinical Trails Registry; PMID: PubMed Identifier.

Studies Included in the Original Review, With a Registry Record

Only six studies (in seven records) matched papers in the original review. All were identified based on the papers attached to the registry record. Matching based on trial title, author, study title, and population information helped us identify one study that did not have an NCT number in the MEDLINE record or publication listed in the registry record (NCT00629694). Only one record gave baseline data and results, but we were able to compare design, interventions, and outcomes across the all six studies, which were published in eleven papers. We also performed risk of bias analysis based on the limited information included in the records, comparing that to the risk of bias information from the papers.

Study Design

Table 2 includes the basic design characteristics that were extracted for the original review. Other than level of detail given and occasional differences in the age ranges, the study descriptions were very close between the records and the resulting papers. There is little indication of reporting bias in the papers, and in fact the only instance in which funding source did not agree was in Paradise, where the record indicated only government funding and the paper referred to both government and industry funding.

Table 2. Design characteristics

Study	Study design	Funding source	Inclusion criteria	Age range (y)	Number of assessments/ followup duration (weeks)
NCT00365092	RCT	Government	Persistent middle-ear effusion, otherwise healthy.	<0.17 at enrollment (<4 at randomization)	nr/572
Paradise 2001 11309632 [18-22]	RCT	Government/ Industry	Middle ear effusion that appeared substantial in quantity and persisted despite treatment with anti-microbial drugs for 90 days in the case of bilateral effusion or 135 days in the case of unilateral effusion.audiometric examinations;	0.04-1.17	nr/572
ISRCTN35793977	RCT	Government	No previous ear or adenoid surgery, having B+B or B+C2 tympanograms and a bilateral average hearing threshold greater than 20 dB, plus an air-bone gap greater than 10 dB HL. Excluded: Children with severe general disease, craniofacial abnormalities, sensorineural losses, parents with	3.5-7	NR

Study	Study design	Funding source	Inclusion criteria	Age range (y)	Number of assessments/ followup duration (weeks)
			language or literacy problems. A few children are also excluded if a consultant feels it would be unethical to randomise them into the study.		
MRC Multicentre Otitis Media Study Group 2012 (TARGET) 22443163[23]	RCT	Government	Bilateral OME over 12-week watchful waiting period; excluded History of ear or adenoid surgery	3.25-6.75	5/104
ISRCTN57358603	RCT	Government	Confirmed bilateral otitis media with effusion (OME). Bilateral hearing impairment of 25-70 dB of at least 3 months' duration	DOB 4/1/1991-DOB 12/31/1992	NR
Maw 1999 10459904[24]	RCT	Government	Confirmation of bilateral OME by otoscopy; disruptions to speech, language, learning, or behaviour	DOB 4/1/1991-DOB 12/31/1992	2/78
NCT00629694	RCT	Academic Hospital	Inclusion Criteria: children operated for their adenoid hyperthrophy with an adenoid size of 3 (measured in a scale of 1-3 intraoperatively or from lateral neck x-ray) and otitis media with effusion causing an average air-bone gap of greater than 20db. Children should be otherwise healthy with an ASA score of I and between 3-12 years old of age Exclusion Criteria: other health problems especially related with the condition eg cleft palate	3-12	NR/52
Vlastos 2011 21205368 5/2007-5/2008 Greece[25]	RCT	Not reported	The diagnosis of OME was based on otoscopy, tympanography and pure tone audiometry. Specifically, the presence of an opaque or thickened tympanic membrane, air–fluid level, or bubbles, or the inability to visualize the incudostapedial joint, were considered signs of OME, in children with a type B tympanogram (compliance <0.2 ml) and an audiogram with an air–bone gap of 20 dB or a hearing loss of 30 dB but no more than 55 dB in at least one frequency in both ears. Absence of the light reflex was not regarded as a specific sign of OME.; Absence of the light reflex was not regarded as a specific sign of OME; Absence of the light reflex was not regarded as a specific sign of OME	3-7	3/52
NCT00162994	RCT	Academic/Hospital	Inclusion Criteria: at least 3 otitis media episodes during the last half year; address near (< 50 km) the university hospital of Oulu Exclusion Criteria:	0.83-2	

Study	Study design	Funding source	Inclusion criteria	Age range (y)	Number of assessments/ followup duration (weeks)
			otitis media effusion lasting longer than two months without acute exacerbations; prior adenoidectomy or tympanostomy; head or neck malformation; retarded child serious disease; chemoprophylaxis for another disease		
Kujala 2012 22466327, 24445832 3/2002-6/2004 Finland[26, 27]	RCT	Academic/Hospital	Inclusion Criteria: at least 3 AOM episodes during the past 6 months; Exclusion criteria: Cranial abnormalities, chronic otitis media with effusion, a prior adenoidectomy or tympanostomy tubes, documented immunological disorders or ongoing antimicrobial prophylaxis for a disease other than AOM	0-2	>3/>52
NCT01949142 and NCT01949155	RCT	Industry	Inclusion Criteria clinical diagnosis of bilateral middle ear effusion requiring tympanostomy tube placement Subject's caregiver is willing to comply with the protocol and attend all study visits Exclusion Criteria Subject has a history of prior ear or mastoid surgery, not including myringotomy or myringotomy with tympanostomy tube placement Subject has a history of sensorineural hearing loss Subject has a history of chronic or recurrent bacterial infections other than otitis media that likely will require treatment with antibiotics during the course of the study	0.5-17	4/4
Mair 2016 26985629 4/2014-6/2014 U.S. [28]	RCT	Industry	Key inclusion criteria: Clinical diagnosis of bilateral MEE requiring TTP, and ability to provide assent for participation in the trial Key exclusion criteria hstory of ear or mastoid surgery; designation for any other surgical procedure that would occur concurrently with TTP; history of sensorineural hearing loss, chronic or recurrent bacterial infections, tympanic membrane perforation, immunodeficiency disease, or abnormality of the tympanic membrane or middle ear; use of topical nonsteroidal otic agents within 1 day of randomization; use of a topical or otic corticosteroid within 3 days of randomization or a systemic corticosteroid within 7 days of randomization; any infection requiring systemic antimicrobial or antifungal agents;	0.5-17	4/4

Study	Study design	Funding source	Inclusion criteria	Age range (y)	Number of assessments/ followup duration (weeks)
			use of topical or systemic antimicrobial or antifungal agents before approximate washout intervals; concurrent use of oral anti-inflammatory agents; history of allergy to ciprofloxacin; menarche or postmenarche (among girls); and being the sibling of or residing in the same household as another participan		

RCT: Randomized controlled trial; AOM: acute otitis media; DOB: date of birth; NR: not reported; OME: otitis media with effusion; MEE: middle ear effusion; TTP: tympanostomy tube placement

Arm Details

Table 3 shows the arm details information for the studies with both a registry record and papers. Again, the agreement between the record and the data extracted from the papers was, in general, well matched. One record, ISRCTN35793977, indicated a third "watchful waiting" arm that was not reflected in the publication. A second record, NCT00162994, did not provide study arm details, though the resulting paper indicated three arms, tympanostomy tubes, tympanostomy tubes and adenoidectomy, and no treatment.

Table 3. Arm details

Study	Arm description
NCT00365092	TT inserted promptly
	TT inserted up to 9 months later if effusion persisted.
Paradise 2001 11309632	Early TT
	TT six months later if bilateral effusion persisted or nine months later if unilateral effusion persisted
ISRCTN35793977	TT and adenoidectomy
	TT
	Observation and medical management
MRC Multicentre Otitis Media Study Group 2012 (TARGET) 22443163	TT and adenoidectomy
	TT
ISRCTN57358603	Early TT
	Watchful waiting for a period of nine months with analysis by intention to treat
Maw 1999 10459904	TT within 6 weeks
	Watchful waiting for 9 months then TT if needed
NCT00629694	TT and adenoidectomy
	Myringotomy and adenoidectomy
Vlastos 2011 21205368	TT and adenoidectomy
	Myringotomy and adenoidectomy
NCT00162994	Procedure: adenoidectomy and tymapanostomy Study arms not provided.
Kujala 2012 22466327	TT
	TT and adenoidectomy
	No treatment
NCT01949142 and NCT01949155	OTO-201: One injection of 6 mg OTO-201 (ciprofloxacin in poloxamer 407) into each ear during surgery.
	Sham: Simulated single, intratympanic injection
M air 2016 26985629	OTO-201: One injection of 6 mg OTO-201 (ciprofloxacin in poloxamer 407) into each ear during surgery.

Sham: Simulated single, intratympanic injection

TT: Tympanostomy tubes

Risk of Bias

Table 4 shows the risk of bias assessments for the studies, based on the records and the papers. Because of the nature of the records, there was very little data on which to base these assessments, particularly with the ICTRP records, but where the data was adequate the agreement was good. Both ClinicalTrials.gov records indicated the intention to include blinding, but the publications were judged as high risk of bias for this, because they did not explicitly indicate blinding. Likewise, all four records indicated that the trials were randomized controlled trials (RCTs), but none explicitly discussed how randomization would be achieved, so all were rated as unclear based on the criteria used in the original review. Selective reporting bias, group similarity at baseline, and compliance could not be evaluated in the records, as they do not include any information about how the study actually progressed, so those columns have been removed from this table.

Table 4. Risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel/care providers	Blinding of outcome assessor	Incomplete outcome data	Intention-to-treat-analysis	Co-interventions	Timing of outcome assessments
ISRCTN35793977	Unclear	Unclear	High	High	High	Unclear	Unclear	Unclear	Low
MRC Multicentre Otitis Media Study Group 2012 22443163	High	Unclear	High	High	High	Low	Low	Unclear	Low
ISRCTN57358603	Unclear	Unclear	High	High	High	Unclear	Low	Unclear	Low
Maw 1999 10459904	Unclear	Unclear	High	High	High	High	Low	Unclear	Low
NCT00365092	Unclear	Unclear	Low	High	High	Unclear	Unclear	Unclear	Low
Paradise 2001 11309632	Low	Low	High	High	High	Low	Low	Unclear	Low
NCT00629694	Unclear	Unclear	High	High	Unclear	Unclear	Unclear	Low	Low
Vlastos 2011 21205368	Low	Unclear	High	High	Unclear	High	Low	Low	Low
NCT00162994	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear	Low
Kujala 2012 22466327, 24445832	Low	Low	High	High	High	Low	Low	Unclear	Low
NCT01949142 and NCT01949155	Unclear	Low	Low	Low	Low	Unclear	Low	Unclear	Low
M air 2016 26985629	Low	Low	Low	Low	Low	Low	Low	Low	Low

Outcomes

Overall, the outcomes appeared to match across the records and studies with a few exceptions. In four cases, there were more outcomes listed in the records than reported in the papers, indicating possible selective reporting bias for these studies. This is particularly notable because all of these records were retrospectively entered. In general, the results not reported were

quality of life outcomes (See bolded text in Table 5), though the Vlastos record (NCT00629694)[25] called for secondary tympanogram outcomes that were not reflected in the paper. The exception is the Paradise study, which across four papers reported on more quality of life measures than were called for in the record.

Table 5. Outcomes

Study	Outcomes
NCT00365092	Auditory continuous performance test Child Behavior Checklist Children's version of the Hearing in Noise Test Comprehensive Test of Phonological Processing Disruptive Behavior Disorders Rating Scale Impairment Rating Scales Number of words in a grade-level passage read correctly in one minute Visual continuous performance test Wechsler Abbreviated Scale of Intelligence Woodcock Reading Mastery Tests-Revised-Normative Update Woodcock-Johnson III Tests of Achievement, Standard Battery
Paradise 2001 11309632	Auditory Continuous Performance Test Child Behavior Checklist Children's Version of the Hearing in Noise Test Comprehensive Test of Phonologial Processing Disruptive Behavior Disorders Rating Scale Impairment Rating Scales McCarthy General Cognitive index McCarthy Verbal Subscale Mean Length of Utterance in Morphemes Nonword repetition test Number of Different Words Oral Reading Fluency Test Parenting Stress Index Peabody Picture Vocabulary Test–Revised Percentage of Consonants Correct–Revised Screening Test for Auditory Processing Disorders Social Skills Rating System Visual Continuous Performance Test Wechsler Intelligence Scale for Children Woodcock Reading Mastery Tests Woodcock-Johnson III Tests of Achievement
ISRCTN35793977	Behavioral assessment Economic impact General health Hearing Quality of life
MRC Multicentre Otitis Media Study Group 2012 (TARGET) 22443163	Hearing
ISRCTN57358603	Behavioral difficulty Hearing
Maw 1999 10459904	Behavioral difficulty Expressive language Hearing Middle ear effusion Verbal comprehension
NCT00629694	Primary: OM-6 burden of disease Secondary: Tympanogram type B
Vlastos 2011 21205368	OM-6 burden of disease
NCT00162994	Primary: Number of acute otitis media episodes

Study	Outcomes
	Quality of life Secondary: Number of days of middle ear effusion Speed of recovery of each otitis media episode Time to first recurrence
Kujala 2012 22466327, 24445832	Number of acute otitis media episodes Time to first recurrence
NCT01949142 and NCT01949155	Primary Treatment failures defined as the occurrence of any of the following events: otorrhea as determined by a blinded assessor on or after 3 days post-surgery, otic or systemic antibacterial drug use for any reason any time post-surgery, as well as patients who missed visits or were lost-to-follow-up. Secondary Adverse events, otoscopic exams, audiometry, and tympanometry Microbiological response
Mair 2016 26985629	Treatment failure: (1) the presence of postoperative otorrhea in one or both ears during the visual external ear examination on or after 3 postoperative day (day4); (2) the patient received otic antibiotic drops any time after surgery and before otorrhea confirmation by the blinded assessor; (3) the patient received a systemic antibiotic any time after surgery and before confirmation of otorrhea by the blinded assessor; (4) loss to follow-up; or (5) the patient did not return to the clinic for a blinded assessment Treatment-emergent adverse events (TEAEs), otoscopy for the presence of bilateral effusion, audiometric testing, tympanometry, evaluation of tube occlusion, physical examination, and vital sign measurement

Bold indicates an outcome not in the other source.

Studies Containing Results

One record contained results and could be matched to a paper (NCT01949142). Table 6 shows the baselines that were reported in both the record and the paper. The record gave far less baseline information than the paper, but what was reported matched exactly. Results that were reported in both the record and the paper are in Table 7. Again, the paper gave much more detail and included statistical analyses not reported in the record, but the limited information given for the efficacy outcomes of interest matched exactly between the paper and the record. The adverse event results were harder to correlate, because they were reported very differently in the record and the resulting paper. In general, there were few serious adverse events and many other adverse events. The paper reported higher numbers for all types of adverse events than did the record, and both consistently showed more adverse events in the intervention group.

Table 6. Baselines

Study	Arm (N)	Age (y), mean (SD)	Male gender n/N (%)
NCT01949142	OTO-201 (179)	2.392 (2.0710)	104/179 (58.1)
	Sham (87)	2.463 (2.1176)	56/87 (64.4)
Mair 2016 26985629	OTO-201 (179)	2.4 (2.1)	104/179 (58.1)
	Sham (87)	2.5 (2.1)	56/87 (64.4)

Table 7. Results

Study	Outcome	Timepoint	Arm (N)	Percentage
NCT01949142	Percentage of Participants Who Were Treatment Failures	Day 15	OTO-201 (179)	24.6
			Sham (87)	44.8
Mair 2016 26985629	Percentage of Participants Who Were Treatment Failures	Day 15	OTO-201 (179)	24.6 (44/179)
			Sham (87)	44.8 (39/87)

NCT01949142	Audiometry Patent tubes	Day 29	OTO-201 (179)	98.3 (left ear), 96.0 (right ear)
			Sham (87)	94.1 (left ear), 96.5 (right ear)
Mair 2016 26985629	Audiometry Patent tubes	Day 29	OTO-201 (179)	At least 94%
			Sham (87)	At least 94%

Relevant Studies Identified via Registry Searches and Not Found in Original Review

Of the 27 records found, 22 did not have a corresponding publication in the original review. Of these, two contained results, and 20 did not.

Studies Containing Results

Two records contained results, but had no matching reports in the published literature. One (NCT01404611) is noted in the registry as having been completed in 2013. It is likely that a publication of these results is forthcoming. The second (NCT01908803) is noted as having been terminated by management decision in 2014. Both studies address Key Question 5: Treatments for in-tube otorrhea. Both studies are industry funded. Details are in Table 8. Risk of bias assessments are in Table 9. In general, the records did not provide sufficient information to make judgments on risk of bias, but where sufficient information was reported, the risk of bias was generally low.

NCT01404611 gives results for 330 patients for time to cessation of otorrhea and adverse events up to 22 days. The adverse events reported include: mastoiditis, respiratory syncytial virus infection, otorrhea, pyrexia, upper respiratory tract infection, nasopharyngitis, and cough.

NCT01908803 gives results for 68 patients for proportion of subjects with sustained clinical cure at day 3 visit and adverse events, including serious adverse events (not defined), other adverse events (not defined), and acute OME.

NCT01404611 indicates that ciprofloxacin and fluocinolone acetonide have the shortest time to cessation of otorrhea (median 4.94 days, 95% CI 3.74 to 5.52), when compared to ciprofloxacin alone (median 6.83 days, 95% CI 5.49 to 7.74) or fluocinolone acetonide alone (median 22 days, 95% CI 13.93 to 22). However, because these are time-to-event data, we would need hazard ratios to perform a meta-analysis and the record does not include any formal statistical comparison. Thus, we were unable to compare these results with the analysis for this key question in the original review. NCT01908803 gives no results for this outcome, citing the early termination of the study.

NCT01908803 indicates that similar percentages had a sustained clinical cure at day 3. The group that got finafloxacin and dexamethasone had a cure rate of 38.5 percent, and the ciprofloxacin and dexamethasone arm a cure rate of 31.8 percent. No statistical analysis is provided, and because these are the same treatment types (antibiotic and glucocorticoid drops), we were not able to add it to our network meta-analysis for this outcome in the original review. The study record indicates that proportion of subjects with microbiological success at the day 8 visit was an outcome of interest, but gives no results for this outcome, citing the early termination of the study. NCT01404611 gives no results for either of these outcomes.

Table 8. Effectiveness of various interventions to treat TT Otorrhea

Study	Intervention Details	Responders	N
NCT01404611	DF289 (ciprofloxacin 0.3%) ear drops	NR	104
	DF277 (fluocinolone acetonide 0.025%) ear drops	NR	89
	DF289 (ciprofloxacin 0.3%) + DF277 (fluocinolone acetonide 0.025%) ear drops	NR	106
NCT01908803	AL-60371 (finafloxacin 0.3%)/AL-817 (dexamethasone) otic suspension (200 µL in affected ear(s) through tympanostomy tube on Day 1)	15	39
	Ciprofloxacin 0.3%/dexamethasone 0.1% otic suspension (Four drops in affected ear(s) twice daily through tympanostomy tube for 7 days)	7	22

NR: not reported

Table 9. Risk of bias of new studies

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of personnel/care providers	Blinding of outcome assessor	Incomplete outcome data	Intention-to-treat-analysis	Co-interventions	Timing of outcome assessments	Selective reporting bias	Group similarity at baseline	Compliance
NCT01404611	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear	Low	Low	Unclear	Unclear
NCT01908803	Unclear	Unclear	High	High	Low	Low	Low	Unclear	Low	High	Unclear	Unclear

Studies Without Results

Twenty studies were identified with no results and no related publications. Fourteen of these were listed in clinicaltrials.gov and therefore had an estimated completion date; ICTRP does not require this. Four of the 14 ClinicalTrials.gov records indicated terminated studies (one with no reason given, two as a management decision, and one because of a change in FDA guidance). Five records indicated active studies with completion dates in the future, and five indicated active status but have a completion date in the past. Of these five, three apparently related records were identified in ClinicalTrials.gov and reported completion dates between 2008 and 2009, one was a cohort study that was supposed to be completed in June 2013, and the last was an RCT with a completion date in September 2015. It is possible that one or both of these studies will be published in the near future. The six studies identified through ICTRP were all noted as ongoing, with first enrollment dates ranging from 2006 to 2014.

Studies Included in the Original Review with No Registry Record

The original review's 178 publications addressed five key questions:

Question 1: For children with chronic otitis media with effusion, what is the effectiveness of tympanostomy tubes, compared to watchful waiting, on resolution of middle ear effusion, hearing and vestibular outcomes, quality of life and other patient-centered outcomes?

a. What factors (such as age, age of onset, duration of effusion, comorbidities, and sociodemographic risk factors) predict which children are likely to benefit most from the intervention?

b. Does obtaining a hearing test help identify which children are more likely to benefit from the intervention?

Question 2: For children with recurrent acute otitis media, what is the effectiveness of tympanostomy tubes, compared to watchful waiting with episodic or prophylactic antibiotic therapy, on the frequency and severity of otitis media, quality of life, and other patient centered-outcomes? What factors (such as age, age of onset, number of recurrences, presence of persistent middle ear effusion, comorbidities, and sociodemographic risk factors, history of complications of acute otitis media, antibiotic allergy or intolerance) identify children who are most likely to benefit from the intervention?

Question 3: What adverse events, surgical complications, and sequelae are associated with inserting tympanostomy tubes in children with either chronic otitis media with effusion or recurrent acute otitis media?

Question 4: Do water precautions reduce the incidence of tympanostomy tube otorrhea, or affect quality of life?

Question 5: In children with tympanostomy tube otorrhea, what is the comparative effectiveness of topical antibiotic drops versus systemic antibiotics or watchful waiting on duration of otorrhea, quality of life, or need for tube removal?

Of the total 172 studies not found in either registry 75 were published before the inception of ClinicalTrials.com in 2000 and ICTRP in 2005 and thus cannot be expected to be in the registries. No nonrandomized studies were found in the registry searches. Six of 54 RCTs in the report were found in the registries: four for key question 1, one RCT for key question 2, and one for Key Question 5. No studies were identified for key questions 3 or 4. In looking at the 48 RCTs that were included in the report but not found in the registry searches, 35 would not have been expected in ClinicalTrials.gov for the following reasons: 22 had enrollment or publication dates that predated ClinicalTrials.gov's 2000 launch date, and 13 were not U.S. studies. A search of the MEDLINE records of the studies included in the report did not identify any records that were not identified in the CT.gov or ICTRP searches.

Discussion

Summary of Findings

Relevant Studies Identified via Registry Searches and Found in Original Review

Six studies were identified in both the registries and the original review. Overall the agreement for design and arm information was very close, as in the one record that reported it is the agreement for baselines and results.

Prespecified outcomes in almost all of the records differed from the outcomes in the publications based on those records. Several other studies have reported on discrepancies between prespecified outcomes in registry records and the resulting published studies. [29-32] We did not find any new information in any of these records that would change our initial meta-analyses, risk of bias, or strength or evidence assessments.

Relevant Studies Identified via Registry Searches and Not Found in Original Review

Twenty studies were screened in via registry searches but not found in the original review. Two gave results, but we were unable to incorporate them in to the analysis, due to the fact that they had no statistical analyses. The results of these trials did not change our initial meta-analyses, risk of bias, or strength or evidence assessments. Seven of the records without results indicate studies with completion dates in the future or recent past. The information about these studies can be used to inform future research needs.

Studies Included in the Original Review with No Registry Record

We were able to find a registry record for only four of the 178 studies in the original review. The records we found were all for RCTs that addressed key questions 1 and 2.

Process Limitations

Despite the relative ease of conducting registry searches in our study, the searches yielded no new information that would change our initial risk of bias or strength or evidence assessments. When available, study design, baselines, adverse events reporting, and results reported in the registry and publication typically aligned. Data identified via registry searches generally provided insufficient evidence to make judgments on specific risk of bias items. It was also difficult to draw any conclusions about publication bias based on our analyses.

Study outcomes information had highest number of discrepancies, potentially indication selective reporting bias. However, because many of these studies are relatively recent, it is also possible that information on these outcomes has not been published yet, but will be, indicating time lag, but not publication, bias

This project has a few limitations. The most significant of which is that much of the screening and data extraction was done by a single person, which means that it is possible that studies were missed or data incorrectly extracted. However, the results have been checked

against those of the original review and reviewed by the project lead on that report, as well as double-checked in places by other members of the team.

Conclusion

Our study demonstrated that the EPC systematic review process was amenable to adaptions required for searching, abstracting, and analyzing registry search yields. We used a very broad search and screened out a large number of records, requiring more staff time than is spent on registry searching for typical EPC systematic reviews. More precise searching may reduce associated study costs and sensitivity of the search. In general, we found that registry records were easy to screen and extract – often easier than the resulting publications. Study design and interventions information was readily identifiable and in almost all cases matched that of the papers. However, the patient-level information (baselines and outcomes) was limited in scope and detail. The addition of individual patient data to these records could be very valuable

This project yields limited evidence on the utility of searching ClinicalTrials.gov, because only six records were found that matched papers in the report, along with two others that yielded new results. Based on the evidence we found, there does not appear to be an impact on the conclusions or strength of evidence in the report of including records from ClinicalTrials.gov and ICTRP.

One way in which conducting a registry search is of value to a systematic review project is in identifying ongoing research, as well as gaps in knowledge, and facilitating prioritization of future research to reduce redundancy. Several of the studies not found in the original review but identified through registry searches were unfinished or in progress at the time of the search, these studies should be taken in to account when evaluating the state of the literature and calling for future research.

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Appendix A. Search Strategy

ClinicalTrials.gov search 2/9/16

Note, with the n-3 project, we searched very broadly and spent a lot of time screening out irrelevant abstracts. In this search, I am going to use clinicaltrials.gov's advance search features to limit the scope of the search.
In Interventions: tympanostomy OR grommet OR grommets OR tube OR tubes OR ventilation OR t-tube OR tubulation OR otologic surgical procedures
In Conditions: otitis OR "glue ear" OR middle ear OR OME OR SOM OR AOM
Limit to child
71 records retrieved

Searching the basic interface with the same terms:
(tympanostomy OR grommet OR grommets OR tube OR tubes OR ventilation OR t-tube OR tubulation OR otologic surgical procedures) AND (otitis OR "glue ear" OR middle ear OR OME OR SOM OR AOM)
Not limited to adults.
133 records retrieved
36 were labeled adult or adult/senior
26 remaining non-overlapping (any relevant?)

WHO ICTRP search 2/9/16

(tympanostomy OR grommet OR grommets OR tube OR tubes OR ventilation OR t-tube OR tubulation OR otologic surgical procedures) in the intervention
AND
(otitis OR "glue ear" OR middle ear OR OME OR SOM OR AOM) in the condition
Select recruitment status as ALL
Select all countries under countries of recruitment
Does not work

Had to search only on the condition:
otitis OR "glue ear" OR middle ear OR OME OR SOM OR AOM

retrieved 586 records

Original report searches

MEDLINE (5/26/15 6553 citations)

Population

(otitis)
OR

(“glue ear”)
OR
"Otitis Media with Effusion"[Mesh]
OR
"Otitis Media, Suppurative"[Mesh]
OR
"Ear, Middle/secretion"[Mesh]
OR
(middle and ear and (effusion* or infect* or inflame* or disease*))
OR
((OME OR SOM or AOM) AND (otitis OR ear))
OR
((mucoid* AND middle AND ear) OR (mucous AND middle AND ear) OR (seromuc* AND middle AND ear))

AND

Intervention

tympanostomy
OR
grommet*
OR
((ear or “pressure equalization” or PE or myringotomy or ventilating or ventilation) and (tube or tubes))
OR
“Otitis Media with Effusion/surgery”[mesh]
OR
"Middle Ear Ventilation"[Mesh] OR ((middle AND (ear OR tympanic)) AND (tube or tubes))
OR
"Otologic Surgical Procedures"[Mesh]
OR
T-tube or tubulation