Searching trials registers to identify studies for Cochrane Reviews

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YHEC
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Methods' Groups' Workshops

- Presented on behalf of the Cochrane Information Retrieval Methods Group
- Based on material from the 'Unpublished and ongoing studies' section of:
- Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.

  Available from: http://handbook.cochrane.org/

Conflict of Interest Statement

- "Julie Glanville, Carol Lefebvre and Gordon Dooley have no actual or potential conflict of interest in relation to this presentation."

Overview of the workshop

- Brief overview of trials registers and registration (Carol)
  - What are trials registers / trials results registers?
  - Why are they useful in the context of systematic reviews?
  - How have they developed?
- Demonstrations of key registers (Julie)
  - ClinicalTrials.gov
  - WHO ICTRP
  - Which should I use?
- **Gordon??**
- Summary

Trials registers and registration – background and development

What are trials registers?

- Databases of trial records
- Record is trial information –

  not published citation
- Typical *citation* record:

  AU, TI, SO, YR
- Typical *trials register* record:

  PI, study name, recruitment status etc.

Types of trials (results) registers

- National, regional and international trials registers
  e.g. ClinicalTrials.gov
- http://www.clinicaltrials.gov

- Subject-specific trials registers
  e.g. NCI's List of Cancer Clinical Trials
- http://www.cancer.gov/clinicaltrials

- Industry trial registers
  e.g. GlaxoSmithKline (GSK) Clinical Study Register
- http://www.gsk-clinicalstudyregister.com/

Searching for Studies chapter: *The Cochrane Handbook*

Why are they useful in the context of systematic reviews?

- Identifying studies for systematic reviews
  - to reduce biases (e.g. publication bias)
  - to inform decisions on when to undertake / update SRs
  - to help ensure studies can be included in a SR when completed
  - to obtain data from sponsor / investigator if trial is not published and / or not completed
  - to obtain data ahead of publication
  - to increase robustness of existing SRs with additional data

Trials registration developments (1)

- 1992 - subject specific trials registers (e.g. cancer)
- 1997 - Schering is sharing too! *Cochrane News* 1997;10:9.
  - outline details of 30+ trials submitted to CENTRAL by Schering Health Care Ltd
  - now accessible in the Bayer HealthCareTrial Finder web site
  - http://healthcare.bayer.com/scripts/pages/en/research_development/clinical_trials/trial_finder/index.php
- 1998 - GSK announced access to trial information.
  - Being a modern pharmaceutical company. BMJ 1998;317:1172-1180
  - 'GlaxoWellcome will register information on its future clinical trials protocols on its R&D website'
  - now available in GSK Clinical Study Register
  - http://www.gsk-clinicalstudyregister.com/

Trials registration developments (2)

- 1998 - Current Controlled Trials web site launched
  - Current Controlled Trials *meta*Register of Controlled Trials (*m*RCT)
  - The International Standard Randomised Controlled Trial Number Register scheme launched as the first online service that provided unique numbers for randomized controlled trials in all areas of health care and from all countries around the world
  - http://www.controlled-trials.com/mrct/
- 2000 - ClinicalTrials.gov - launched as a result of the Food and Drug Administration Modernization Act (of November 1997)
- 2004 - Support of trial registration at inception by the leading medical journal publishers (ICMJE) and their refusal to publish subsequently reports of trials not properly registered (De Angelis 2004, JAMA)

Trials registration developments (3)

- 2007 - World Health Organization (WHO) launched the International Clinical Trials Registry Platform (ICTRP) Search Portal to search across a range of trials registers
  - http://www.who.int/ictrp/search/en/

- 2008 - US National Institutes for Health (NIH) voluntary Public Access Policy **changed**
  - Now requires that 'all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine's PubMed Central **an electronic version of their final, peer-reviewed manuscripts** upon acceptance for publication to be made publicly available no later than 12 months after the official date of publication'.
  - http://publicaccess.nih.gov/FAQ.htm#753

  - Other national and funder initiatives w.r.t. open access publication

Trials registration developments (4)

- 2008 - U.S. Public Law 110-85 or the Food and Drug Administration Amendments Act of 2007 (FDAAA)

  (enacted 2007 w.e.f. 2008)

- The law includes a section on clinical trial databases (Title VIII) that **expands the types of clinical trials** that must be registered in ClinicalTrials.gov, **increases the number of data elements** that must be submitted, and also **requires submission of certain results** data (including adverse events).

- http://grants.nih.gov/clinicaltrials_fdaaa/faq.htm

Trials registration developments (5)

- 2011 - MECIR - mandatory standards for Cochrane Reviews – searching for studies
- http://www.editorial-unit.cochrane.org/mecir

- Searching Trials Registers – mandatory standard

- 'Search trials registers and repositories of results, where relevant to the topic through ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) portal and other sources as appropriate.'

Trials registration developments (6)

- Rationale for the 'searching trials registers' standard

- 'Searches for studies should be as extensive as possible in order to reduce the risk of publication bias and to identify as much relevant evidence as possible.'

- 'Although ClinicalTrials.gov is included as one of the registers within the WHO ICTRP portal, it is recommended that both ClinicalTrials.gov and the ICTRP portal are searched separately due to additional features in ClinicalTrials.gov.'

Trials registration developments (7)

- Ottawa Statement
  - http://ottawagroup.ohri.ca/index.html
- +AllTrials campaign
  - "All trials registered. All results reported."
  - http://www.alltrials.net/
- Science and Technology Commons Select Committee inquiry into clinical trials and disclosure of data: Joint response from The Cochrane Collaboration & CRD http://www.parliament.uk/documents/commons-committees/science-technology/Clinical%20trials%20combined.pdf
- Cochrane Collaboration Access to Data statement
  - recent consultation

Demonstrations of key registers

- Retrieval issues when searching registers
- Demonstrations of searching
  - ClinicalTrials.gov
    - http://clinicaltrials.gov/
  - WHO ICTRP
    - http://apps.who.int/trialsearch/
- Which do I need to search?

Typical retrieval issues (1)

- Lack of sophisticated interfaces
  - May not be able to translate MEDLINE structured searches adequately
    - PICO breakdown may not be replicable
  - Synonym searching may be time consuming
    - May not be able to use OR to link synonyms
    - May not be able to use parentheses and nest searches
    - May not be able to combine sets
  - Some interfaces offer categorization searching

    e.g. by disease
    - May be useful
    - Granularity may be too coarse or too fine
    - How far do we rely on the categorization?

Typical retrieval issues (2)

- Each trial register interface is different
  - ‘Memory overload’
- Updating searches is problematic
  - May not have clear entry / update codes
  - Even if there are entry / update codes, they may not be an option within the search
- Record selection options are rare
  - Copy all and scan offline?
  - Assess online and copy only those relevant – may make independent checking difficult and may be too many to assess in one sitting?
- Search history options are rare
- Saved searches options are rare
- Overlap across databases is not clearly established

Strategy adaptation

- Reduce number of PICO elements used
- Identify lowest yield concept and use that first
- Make use of disease/ intervention coding if necessary and if available
- With Google-type interfaces, may need to exclude previous terms using NOT
  - first search: dementia
  - second search: alzheimers (not dementia)
  - to reduce number of records already seen
- Set up alerts / RSS feeds where available to ease searching for updates

Demonstration topic

- Aricept is a drug used to treat Alzheimer's and other forms of dementia
- How can we search for ongoing and recently completed trials of Aricept?
- P (Patient group)
  - People with Alzheimer's disease / dementia
- I (Intervention)
  - Aricept
- C (Comparator)
  - ???
- O (Outcomes)
  - Delay onset / progression of Alzheimer's disease???

ClinicalTrials.gov

- First stage: search on aricept in all fields
- To see the effect of the search and how to develop it further, click on
  - 'Search details' tab
- Select 'Modify this search'
  - Add 'donepezil'
- Select 'Expert search'
  - Limit to alzheimers OR dementia
- Consider just searching Intervention field to achieve focus
  - if the terminology is very standard and you know all the alternatives?
- 195 results

ClinicalTrials.gov export

- Use ‘Download’ option to export records
  - Tab or comma delimited
    - Load into Excel
    - Load into Endnote with a tab delimited filter
  - Export as XML

WHO ICTRP

- http://apps.who.int/trialsearch/
- Difficult to combine search terms because the interface doesn't support parentheses
- Automatic synonym matching (as long as we don't use truncation)
  - but we can't tell how this is achieved
- Need to do multiple combinations of search terms
- Aricept OR donepezil
- 558 records of 342 trials

Search terms	results	What might be happening?
Aricept AND alzheimer	77	Mapping to variants of alzheimer
Aricept AND alzheimer*	77	Truncating alzheimer but not mapping to variants
Aricept AND alzheimer* OR dementia	1280	Searching for (aricept AND alzheimer) OR dementia
Aricept AND alzheimer* OR aricept AND dementia	90	(aricept AND alzheimer*) OR (aricept AND dementia)
aricept AND alzheimer* OR aricept AND dementia OR donepezil AND alzheimer*	185	(aricept AND alzheimer*) OR (aricept AND dementia) OR (donepezil AND alzheimer*)
aricept AND alzheimer* OR aricept AND dementia OR donepezil AND alzheimer* OR donepezil AND dementia	200	(aricept AND alzheimer*) OR (aricept AND dementia) OR (donepezil AND alzheimer*) OR (donepezil AND dementia)

Which should we search?

- Since ICTRP is included in ClinicalTrials.gov, do we need to search both ICTRP and ClinicalTrials.gov?
- We have investigated this
- Searching ClinicalTrials.gov and the International Clinical Trials Registry Platform to inform systematic reviews: what are the optimal search approaches?
- Glanville JM, Duffy S, McCool R, Varley D.
- J Med Libr Assoc. 2014 Jul;102(3):177-83. doi: 10.3163/1536-5050.102.3.007

YHEC Research: Objectives

- To explore two aspects of retrieval from ICTRP and ClinicalTrials.gov
- Does varying the **sensitivity** of the strategy assist with identifying relevant studies?
- Does using the **basic** or **advanced** search options assist with improving sensitivity or precision of searches?

YHEC Research: Methods

Identify Gold standard

- Identified eight recently updated Cochrane Reviews
- Identified included studies in those reviews which had matching trials records in ICTRP and/or ClinicalTrials.gov

Test strategies

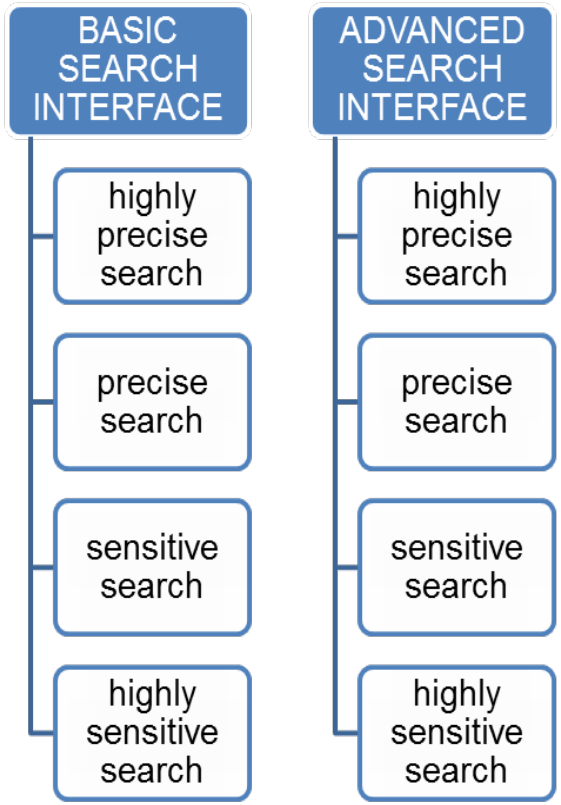
- Reran or adapted the systematic review search strategies to find the identified studies in each register
- Tested different search approaches

Assess strategy yield

- Identified yield of search approaches in ICTRP and/or ClinicalTrials.gov
- Explored the value of using basic and advanced search options in those registers

YHEC testing strategies

- A highly (specific) precise strategy (busy searcher):
  - Using specific condition terms AND specific intervention terms
- A precise strategy:
  - Using just one specific term (usually for the named intervention)
- A sensitive strategy to maximise identification of relevant studies:
  - Condition terms (specific and generic) AND intervention terms (specific and generic)
- A highly sensitive strategy:
  - Usually intervention terms (specific and generic)



Example Strategy: Duan Review, Sensitive Strategy

	ClinicalTrials.gov	ICTRP
Basic interface	(tibia OR tibial) AND (pin OR nail OR screw OR plate OR fixator OR prostheses OR reamed OR unreamed)	tibia* AND nail* OR tibia* AND pin* OR tibia* AND screw* OR tibia* AND plate* OR tibia* AND fix* OR tibia* AND prosthes* OR tibia* AND ream* OR tibia* AND unreamed
Advanced interface	Conditions: tibia OR tibial Interventions: pin OR nail OR screw OR plate OR fixator OR prostheses OR reamed OR unreamed	Condition: tibia OR tibial Intervention: pin OR nail OR screw OR plate OR fixator OR prostheses OR reamed OR unreamed

YHEC: Results

Number of Included Studies Identified in the Trials Registers

	Number of included studies	included studies identified in ClinicalTrials.gov	included studies identified in ICTRP	Number of identified studies not found in either resource	Overlap between CT and ICTRP
Henry 1	252	4	8	244	4
Henry 2	14	1	1	13	1
Albaramki	28	5	6	22	5
Derry	7	0	0	7	0
Duan	11	1	1	10	1
Gluud	7	0	0	7	0
Jones	6	2	2	4	2
Langendam	22	8	12	10	8

YHEC: Identified Studies

- 2/8 reviews had **no** matching trial records in either ClinicalTrials.gov or ICTRP
- Between 0% and 54.5% of studies included in reviews had matching trial records
- Of 6 reviews with trial records, more unique trials were identified in ICTRP than ClinicalTrials.gov in 3/6 reviews
- However, the presence of records within databases does not mean strategies can find those records….
- How do different search strategies perform in finding the identified studies in the 6 reviews in the two resources?

Basic vs Advanced Search Interfaces

- Clinicaltrials.gov: using the advanced search interface tends to improve precision, without losing sensitivity
- ICTRP: Worrying trend for decreases in sensitivity when using the Advanced Search interface.
  - In those searches where sensitivity was maintained there was often no improvement in precision
- Ideally searches should be structured to search for
  - one concept
  - use a range of synonyms and related terms, to ensure sensitivity.

Which approach is best, 2?

- ICTRP
  - Searches of more than one concept should be constructed carefully with attention to the order of processing of the Boolean operators
  - Advanced interface offered no advantages
  - Has added value in form of unique trials
- ClinicalTrials.gov
  - Improve precision by using Advanced interface
  - Has added value in form of results
- Degree of variation in best approach suggests we should search **both** resources

Tai, Willson and Ghersi

- Presented at the 2012 Cochrane Colloquium, Auckland
- Implications of searching multiple trial registries: how should we search ClinicalTrials.gov and WHO ICTRP?
- http://2012.colloquium.cochrane.org/posters?title=trial+registries&tid=All

Conclusions of Tai et al

- Multiple basic and advanced searches in both CT.gov and ICTRP registries are necessary to detect all potential CT records
- ICTRP detected an additional 6-10% of CT.gov records
- Searchers should search both registers using “multiple basic and advanced searches” to detect all potential ClinicalTrials.gov records since searching ICTRP identified additional ClinicalTrials.gov records
- See also the poster by Chi also presented at the Colloquium
  - No single trial register encompasses all relevant trials

Hausner comment, 23 July 2014

- Comment on
  - Van Ernst W A et al. Identification of additional trials in prospective trial registers for Cochrane Systematic reviews. PLOSOne 2012 DOI: 10.1371/jounral.pone.0042812
  - Hausner states “It is inadequate to solely rely on the search results from…(ICTRP)”
  - Synonym searching seems inconsistent
  - Studies registered on CT.gov not found via ICTRP
  - Error messages after complex searches

Summary

- Clinicaltrials.gov and ICTRP
  - There are valuable major resources available to identify clinical trials
  - Current evidence suggests we need to search both
  - The interfaces operate in different ways
  - There will be overlap but also unique results
  - Different registers offer different added values e.g.
    - Results

Thank you

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