Acknowledgements

- Julian Elliott and Tari Turner, Cochrane Australia, Monash University
- Harriet MacLehose, Cochrane Editorial Unit
- The Living Systematic Review Network
Outline

1. Background
2. What is a Living Systematic Review (LSR)?
3. When an LSR is appropriate
4. LSR methods
5. Production and publication implications of LSRs
6. LSRs in practice: Cochrane and beyond
1. Background
Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will We Ever Keep Up?

Hilda Bastian¹, Paul Glasziou², Iain Chalmers³

75 Trials per day

Number of Clinical Trials / Year

Artefactual plateau due to processing

MEDLARs established

FDA regulations

Year

1950 1970 1990 2010

CCTR
Controlled Trials
Haynes filter
Time from study to systematic review

Median time from study published to included in systematic review is 2.5 to 6.5 years.

Elliott 2014 PLoS Med 11(2)
Survival of systematic review accuracy

Shojania 2007 Ann Intern Med. 147(4)
Currency versus quality trade-off
Living Systematic Reviews: An Emerging Opportunity to Narrow the Evidence-Practice Gap

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The Bridge from Evidence to Practice

Summary

Elliott 2014 PLoS Med 11(2)
2. What is a Living Systematic Review?
What is a Living Systematic Review?

A systematic review that is continually updated, incorporating new evidence as it becomes available.

Adapted from Elliott 2014 *PloS Med* 11(2)

Key elements:
- “Systematic review” (retains core methods)
- “Continually” (frequency?)
- “Updated” (where?)
- “Incorporating new evidence” (how?)
Other related definitions

Live cumulative network meta-analysis
“A single systematic review and evidence synthesis encompassing the whole randomised evidence for all available treatments in a specific condition and continuously updated.”

Créquit 2016 BMJ Open 6

Living meta-analysis
“Data are maintained and publicly available online; other investigators are invited to make use of the data and to make online additions to the analysis when new data are available.”

Simpson 2016 J Crit Care 36
## LSR vs SR: Key differences

<table>
<thead>
<tr>
<th>Category</th>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production</td>
<td>Work processes</td>
<td>Search strategy maintained and fed continuously into SR workflow</td>
</tr>
<tr>
<td></td>
<td>Author team management</td>
<td>Coordinated and continuous effort</td>
</tr>
<tr>
<td></td>
<td>Methods</td>
<td>LSR-specific approach to search and study incorporation is pre-specified; Potential statistical adjustments to allow for frequent updating of meta-analysis</td>
</tr>
<tr>
<td>Publication</td>
<td>Publication format</td>
<td>Persistent, dynamic, online-only publication</td>
</tr>
</tbody>
</table>

Adapted from Elliott 2014 *PloS Med* 11(2)
Features of Cochrane LSR approach

- A new review or an update can be living
- Applies to any type of review (e.g. qualitative, network meta-analysis)
- Core review methods remain; some additional LSR-specific methods apply
- LSR-specific methods must be pre-specified in protocol
- Evidence surveillance (searching) is continual
- Reader *alerts* are continual, but not necessarily *full re-publication* of review with new evidence
3. When an LSR is appropriate
When should you do an LSR?

- High priority (or emerging) question for policy and practice
- Important uncertainty in the existing evidence
- Emerging evidence (e.g. in trial registers) that is likely to impact on what we currently know

- You and your network of contributors have capacity and resources to sustain an ongoing SR commitment
LSRs as part of something bigger

Elliott 2014 PloS Med 11(2) Fig 2
4. LSR methods
## Protocol template: Cochrane Living Systematic Reviews

<table>
<thead>
<tr>
<th>Methods considerations specific to LSRs</th>
<th>LSR protocol suggested text and/or examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Description of the condition; Description of the intervention; How the intervention might work</strong></td>
<td></td>
</tr>
<tr>
<td>No changes proposed</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Why it is important to do this review</strong></td>
<td></td>
</tr>
<tr>
<td>It should be clear to the reader why a Living Systematic Review approach is appropriate for your Cochrane Review.</td>
<td><strong>Suggested text</strong></td>
</tr>
</tbody>
</table>

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*Note: The above table is a draft version and may be subject to change.*
LSR methods: Searching

- Search frequency should be explicit
  - Electronic databases, and trial registers, searched monthly (via auto-alerts)
  - Other sources (websites, conference proceedings) on a case-by-case basis

- Search strategies should be re-run in full

- Search sources and strategies reviewed over time
LSR methods: Screening

• Screening frequency should be made explicit
  o (Need to screen monthly if searching monthly)

• LSR’s may use technological tools to support screening, if so, should be described, e.g.
  • Machine learning / RCT Classifiers
  • Citizen science
LSR methods: Data extraction and risk of bias assessment

- No changes to review methods

- LSRs may use technological tools to support data extraction and risk of bias assessment, if so, should be described
LSR methods: Data synthesis

- Deciding *when* to incorporate new evidence
  - Default position: immediate incorporation of new evidence (studies, data, information)
  - BUT, may be instances (e.g. very small study) where it doesn’t change review findings / credibility in meaningful way.
  - Decision rules can be devised about *when* new evidence will be incorporated.
LSR methods: Data synthesis

- Adjustments for frequent meta-analyses
  - Frequently updated meta-analyses can lead to inflated false-positive rate
  - Issue applies to all SR updates (not just LSRs)
  - Current work underway in Cochrane, and elsewhere
  - No clear consensus yet on the best approach to manage this
LSR methods: Other

• Occasional review of scope and methods should be pre-specified
  - Methods and the topic area may change over time

• Some thought to when the review will no longer be kept living
  - Unlikely to need an LSR forever (!)
5. Production and publication implications of LSRs
Basic LSR process

Run searches and screen

NO new evidence found

NEW evidence found

Integrate LATER

Integrate NOW

Data extraction, risk of bias, synthesis

Update review
Author / team implications

• Planning for ongoing contribution (do and maintain!)
  o Frequent, small commitment from authors
  o Needs clear project management

• Size of author team
  o Larger teams may be needed

• Evolving author team
  o Maintaining institutional memory and consistent approach critical
Author / team implications

- Academic credits
  - Existing and new authors need appropriate acknowledgement via new citations

- Funding
  - Funding tends to be time-limited, may need creative ways to fund an ongoing commitment
## (Living) systematic review enablers

<table>
<thead>
<tr>
<th>Category</th>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production</td>
<td>Workflow and collaboration tools</td>
<td>Tools and platforms for SR authoring (e.g. Covidence, EPPI-Reviewer)</td>
</tr>
<tr>
<td></td>
<td>Semi-automation</td>
<td>Machine assisted SR production processes (e.g. machine learning, Evidence Pipeline)</td>
</tr>
<tr>
<td></td>
<td>Data repositories and linked data</td>
<td>Repositories of structured SR data (e.g. Cochrane linked data project)</td>
</tr>
<tr>
<td></td>
<td>Participation and the crowd</td>
<td>Large and diverse author groups, citizen and crowd participation (e.g. TaskExchange, Cochrane Crowd)</td>
</tr>
</tbody>
</table>

Adapted from Elliott 2014 *PloS Med* 11(2)
LSR publishing challenge

- Each systematic review (and update) is a new article
- Each article has a unique identifier (Digital Object Identifier = DOI)
- DOI = new citation
- New citation = new entry in PubMed
- So if re-publish LSR each month = ++new citations

- Confusing for readers, more work for authors / publishers and low citations per article
LSR publishing options

- Publish elsewhere (i.e. project website)
- Publish less frequently (e.g. yearly)
- Allow post-publication revisions to article

- Or split the *process* from the *publication*: What’s happening? versus What’s new?
What’s happening?

**What?**
- Review being updated
- Another ongoing study No new trials

**How?**
- Information around the article

**Where?**
- Journal website

What’s new?

**New studies incl/excl Findings have changed New protocol**

**Article update type?**

**Journal website PubMed**
5. Example LSRs: Cochrane and beyond
Cochrane LSR pilots

- 4 x author groups, each piloting ≥1 Cochrane Review
- LSR methods / model devised by LSR Network
- Support and evaluation provided by Project Transform
- First Cochrane Reviews transitioning to LSRs on the Cochrane Library in coming months
- Using Update Status Classification to communicate ‘What’s happening’
- Re-publishing the review to communicate ‘What’s new’
What’s happening (Update Status)

<table>
<thead>
<tr>
<th>Status</th>
<th>Up to date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rationale</td>
<td>New information identified but unlikely to change conclusions</td>
</tr>
<tr>
<td>Explanation</td>
<td>This is a Living Systematic Review. Searches are run and screened monthly. Last search date XX. A new stud(ies) has(ve) been identified in a recent search [hyperlink to DoI] but the new information is unlikely to change the review findings (as assessed by the authors and editorial team). The conclusions of this Cochrane Review are therefore considered up to date.</td>
</tr>
</tbody>
</table>
Other LSR examples

- Brazinova 2015 *J Neurotrauma* Nov 2015
- Simpson 2016 *J Crit Care* 36
- Crequit 2016 *BMJ Open* 6
Involving a community

Charidimou 2016 Lancet Neurol 15(9)

Correspondence

A call for researchers to join the META-MICROBLEEDS Consortium

During the last decade, cerebral microbleeds, a common neuroimaging finding in patients with cerebral small-vessel disease, have been increasingly recognized as important contributors to neurological disability. International collaborations, including group-level and individual patient data meta-analyses of cerebral microbleeds, and other information sources, and we plan to invite these people to join the Consortium. Our initiative...

Contribute

We're currently developing live cumulative network meta-analysis as a new approach to evidence synthesis. At the same time, we need your help to expand the cumulative network meta-analysis project as widely as possible.

You can contribute in several ways, either by getting directly involved in a live cumulative network meta-analysis, or by spreading the word.

- If you'd like to contribute to the ongoing live cumulative network meta-analysis on second-line treatments of advanced lung cancer or other diseases...

- Share on Facebook
- Send a Tweet

Here are a few examples that you can use:

- *Embrace live cumulative network meta-analysis for evidence synthesis* http://livenetworkmetaanalysis.com
- *A single synthesis covering all treatments for the same disease, systematically updated when new trial results become available*
- Send us feedback at livenetworkmetaanalysis.com

crequit 2016 BMJ Open 6
livenetworkmetaanalysis.com
Results on websites

Prostate cancer screening with prostate specific antigen
A living systematic review

View the Project on GitHub

- PRisma documentation
- Reconciliation of studies included with other meta-analyses
- PICo table
- Risk of bias table
- Calculations and plots of years of monitoring added by screening in each trial
- Forest plots (source data)
- Prostate Facts (patient information handout)

The forest plot for the primary outcome is below. Additional forest plots of secondary analyses may be available.

Rahal 2016 *PLOS One* 11(4)

http://openmetaanalysis.github.io/Prostate-cancer-screening-with-prostate-specific-antigen/
Adherence to Guidelines in Adult Patients with Traumatic Brain Injury: A Living Systematic Review


This article is published as a Living Systematic Review. All Living Systematic Reviews will be updated at approximately three month intervals, with these updates published as supplementary material in the online version of the Journal of Neurotrauma. (To review original article click here.)

**Table 1. Living Systematic Review History**

<table>
<thead>
<tr>
<th>Version</th>
<th>Search date</th>
<th>Number of new included studies</th>
<th>Implications for conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>October 2014</td>
<td>22</td>
<td>n/a</td>
</tr>
<tr>
<td>Update 1</td>
<td>September 2016</td>
<td>22 This update: 7 Cumulative for updates: 7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adherence to ICP monitoring guidelines was higher in studies published in 2015 and 2016 than reported in the original review. The association between guideline adherence and clinical outcome became more uncertain due to the inclusion of a high-quality study that did not find an association between adherence and outcome.</td>
</tr>
<tr>
<td>Update 2</td>
<td>January 2017</td>
<td>1 This update: 1 Cumulative for updates: 8</td>
<td>As update 1</td>
</tr>
</tbody>
</table>