Cochrane Methods

Using Clinical Study Reports

Cochrane Review Group Starter Pack

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Document developed by Ella Flemyng (Methods Implementation Manager, Cochrane) with feedback from the Cochrane Clinical Study Report Working Group

If you have suggestions for updating this document, including recommendations of new resources to include, please contact methods@cochrane.org.

Background

The latest recommendation from the Cochrane Scientific Committee on using clinical study reports and other regulatory documents can be found via the Cochrane Methods website.

In May 2019, Cochrane held a consultation meeting to discuss and agree next steps on using clinical study reports as a data source in Cochrane Reviews – see summary news post and links to the full minutes here.

Given the additional resources and time required to use clinical study reports and because there are certain criteria that should be met when deciding whether or not to use them, review teams must ensure the Managing Editor of their Cochrane Review Group and Associate Editor are aware of the intention to use clinical study reports before the protocol is developed.

What guidance is available?

Cochrane Handbook

The *Cochrane Handbook for Systematic Reviews of Interventions* (Version 6) mentions clinical study reports in the following chapters:

- Chapter 4: Searching for and selecting studies, inc. Section 4.3.2. and Section 4.3.4., as well as the Technical Supplement available here.
- Chapter 5: Collecting data, inc. Section 5.2., Section 5.2.2., and Section 5.5.6.
- Chapter 7: Considering bias and conflicts of interest among the included studies, inc. Section 7.3.1. and Section 7.8.5.
- Chapter 13: Assessing risk of bias due to missing results in a synthesis, inc. Section 13.2.1.2.
- Chapter 19: Adverse effects, inc. Section 19.1.2.2. and Section 19.3.4.

MECIR

The Methodological Expectations for Cochrane Intervention Reviews (MECIR) does not explicitly mention clinical study reports; however, C28 (Searching for grey literature) is highly desirable.

When to use clinical study reports

As a rule of thumb, clinical study reports are created for the purpose of regulatory submissions, so clinical studies submitted to regulators generally have clinical study reports. In addition, clinical study reports may be developed for other reasons, such as post-marketing, new indications not yet approved, etc.

Therefore, industry trials generally have clinical study reports whereas non-industry trials do not. Non-industry trials do produce a final report of some kind, which could be useful for reviews, but these are not formal clinical study reports (and not currently within the remit of this document).

Clinical study reports are created for drug (small and large molecule) trials as well as vaccines and many medical device trials.

A paper in *BMJ Evidence-Based Medicine* titled 'When to include clinical study reports and regulatory documents in systematic reviews' was published in 2018, which was funded by the Cochrane Methods Innovation Fund.

How to access clinical study reports

The Restoring Invisible and Abandoned Trials (RIAT) website provide guidance on getting started, types of data, the right party from which to request the data and requesting data – see here. Their advice highlights the review teams should follow this process:

1. **Consider searching for study metadata in the CRS/CENTRAL or on the web** with a Google search for the trial ID (if that's all you have) to see if there's a pre-existing record (also consider searching CT.gov and ICTRP).
2. **Consider whether regulators hold the data you seek** – details on the policies and how to access clinical study reports and other data (if available) can be found via the RIAT Regulatory Resources page.
3. **Approach the pharmaceutical companies** - details on the policies and how to access clinical study reports and other data (if available) can be found via the RIAT Institutions offering data access page.
4. **Consider data sharing platforms** – some sharing platforms aim to facilitate access to clinical study reports and other data, such as vivli.org, the YODA Project or clinicalstudydatarequest.com.
5. **Still struggling to find or access clinical study reports for trials**? The RIAT Support Center offers free-of-charge support to researchers. Their website offers practical how-to advice on obtaining clinical study reports but when their website doesn't answer your questions, you can contact them directly.

Data sharing agreements

This chapter in 'Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk' includes details on understanding data sharing agreements.

Navigating clinical study reports

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has detailed guidance on the structure and content of clinical study reports.

What training is available?

Navigating clinical study reports

N Fusco, T Li, K Dickersin. Navigating the clinical study report (CSR): a road map to the data abstraction of CSRs for systematic reviews [abstract]. In: Cochrane Colloquium 2016; 23-27 October 2016; Seoul, Korea: http://2016.colloquium.cochrane.org/workshops/navigating-clinical-study-report-csr-road-map-data-abstraction-csrs-systematic-reviews - Nicole Cameron Fusco and the others involved in this workshop have kindly provided access to the **slides** (Navigating the clinical study report: a road map to the data abstraction of CSRs for systematic reviews) and **handout** (One pager – recommendations from our experiences in navigating clinical study reports).

Outcome specification

Protocols need to address issues around planning for multiplicity. We recommend this talk on the problem of multiplicity and the use of hierarchical selection rules from Matthew Page as part of the 2019 Methods Symposium.

What tools are available?

No information yet.

What support is available?

Cochrane Clinical Study Report Working Group

Members of the Cochrane community with experience or an interest in using clinical study reports have signed up as members of the Clinical Study Report Working Group. If you have any questions while conducting a Review using clinical study reports, we can send this to the Working Group. If you have a

question, send it to Ella Flemyng (eflemyng@cochrane.org, Methods Implementation Manager) or methods@cochrane.org.

Methods Support Unit

Cochrane's Methods Support Unit aims to improve the consistency and methodological quality of Cochrane Reviews through support, peer review and training, and to support implementation of new methods in Cochrane Reviews. Details on the process for requesting support or feedback can be found via the Cochrane Methods website.

RIAT Support Center

The RIAT Support Center offers free-of-charge support to researchers accessing and using clinical study reports. Their website offers practical how-to advice on clinical study reports but when their website doesn't answer your questions, you can contact them directly.

Considerations for protocol development

This section is being developed with feedback from review authors and editorial teams.
For review groups who plan to use clinical study reports, here is a list of considerations for the protocol:

- Specify which trial document will be the primary document if documents disagree, ensuring you check the dates of the different document to understand the chronological order.
- Specify what you will do if you cannot access clinical study reports for all studies, including limitations on how long you can wait before proceeding with the review.
- Protocols need to address issues around planning for multiplicity.

Other useful resources

- Section 3.4 'Further information sources and search techniques' of: The EUnetHTA JA3WP6B2-2 Authoring Team. Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness. Methodological Guidelines. Diemen (The Netherlands): EUnetHTA; 2019. Available from https://www.eunethta.eu/
- Clinical trials in the European Union: A roadmap to greater transparency – Report from Health Action International and TranspariMED published in February 2019 (as well as a supplementary bibliography 'Access to clinical study reports: mechanisms, barriers and benefits').

We would like to know how you found using clinical study reports

In order to develop processes and support for clinical study report use in Cochrane Reviews, we welcome any and all feedback review groups that have in used them. We are particularly interested in the following:

1. How did clinical study report access impact your knowledge and assessment of adverse events (both for systematically collected adverse events and non-systematically collected adverse events) compared to journal publications and other data sources?
2. How did clinical study report access impact the reliability and consistency of risk of bias assessments in compared to journal publications and other data sources?
3. Do you have any practical advice on how review groups should navigate clinical study reports, including implications for searching stages and data extraction?

4. Feedback from the previous consultation meeting highlighted the potential for a hierarchical approach to using clinical study reports and other data sources, with CSR appendices at the top of the hierarchy, followed by the CSR report, CSR synopsis, journal publications, and finally registry records. How do you think this approach worked in practice, what are the strengths and limitations, and where do other data sources fit within the hierarchy?
5. Did you use any of the guidance or resources listed in this document? If so, how were they useful or not?
6. Were there any implications for using RevMan or any other tools/systems (Covidence, EPPI-Reviewer, GRADEPro, etc.) that we need to be aware of?
7. How did you find this Starter Pack and do you think there are any important guidance, tools, software or other information missing that should be added?
8. On reflection, was there anything you would have done differently at the protocol stage to facilitate using clinical study reports?
9. Any final comments or recommendations to review groups that are considering using clinical study reports?

FAQs

The section will continue to develop following feedback from review teams.

Are there any published examples of Cochrane Reviews that have used clinical study reports?
We are aware of only a few Cochrane Reviews that have used clinical study reports, as well as a few others published in *The BMJ*:

- **(Ultra-)long-acting insulin analogues for people with type 1 diabetes mellitus** (Cochrane Review - 2021)
- Blood pressure lowering efficacy of renin inhibitors for primary hypertension (Cochrane Review - 2017)
- Neuraminidase inhibitors for preventing and treating influenza in adults and children (Cochrane Review - 2014)
- Blood pressure targets for the treatment of people with hypertension and cardiovascular disease (Cochrane Review - 2018)
- Interventions for cutaneous molluscum contagiosum (Cochrane Review – 2017)
- Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports (The BMJ - 2016)
- Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials (The BMJ - 2010)

Contact

If you have any questions about this Starter Pack or using clinical study reports in Cochrane Reviews, please contact Ella Flemyng (eflemyng@cochrane.org; Methods Implementation Manager) or methods@cochrane.org.