Application for the CRG Networks Innovation Fund 2019

Instructions for inclusion and presentation of time-to-event outcomes in Cochrane Intervention Reviews – development of training resources
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Executive summary
Time-to-event outcomes are widely used in Cochrane systematic reviews of interventions. The analysis of time-to-event outcomes is methodologically complex and the results are prone to misinterpretation by review authors and editors. This project aims to improve the quality of Cochrane systematic reviews that include time-to-event outcomes by supporting authors and editors to avoid common mistakes in their inclusion and presentation. Detailed and concrete "hands on" instructions e.g. based on pictures will be created by pooling together important training materials for time-to-event meta-analyses and iterative discussions among Cochrane authors, editors and experts. Besides publication, the educational resources developed in this project will be distributed in workshops and webinars and might inform the next version of the Cochrane Handbook for Systematic Reviews of Interventions.

The CRG Networks involved
Cancer Network (Senior Editor Nicole Skoetz) will take the lead and will collaborate with the Musculoskeletal, Oral, Skin and Sensory (MOSS) network (Senior Editor Peter Tugwell) because this network also publishes some cancer reviews.

The CRG Network lead
Dr Nicole Skoetz
The Project Team
Short biographies of the project team are included in the appendix.

Project lead (principal investigator)
Nicole Skoetz (Senior Editor Cancer Network)
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Other members
Elvira van Dalen (Co-ordinating Editor Childhood Cancer)
Cochrane Childhood Cancer
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Project Plan

Purpose/organisational need

Background
Time-to-event outcomes are those which measure both the occurrence and the time to occurrence of a specific patient-related event. In trials of effectiveness, the time to event is usually measured from the point of randomisation. In oncology trials the common outcomes are time to death (overall survival) or time to disease recurrence (disease-free survival), but other outcomes such as progression-free survival and metastasis-free survival may also be of interest. Time-to-event outcomes are also relevant to trials in many other clinical contexts and include such varied measures as time to seizure recurrence, time to hospital discharge, length of prosthesis survival or time to complete ulcer healing.

If the time-to-event is relatively short and it is possible to obtain outcome information on all the trial participants (i.e. there is complete information on all participants up to a relevant time point) it would be possible to generate risk ratios for assessment of effectiveness. However, deriving binary risk ratios for time-to-event data may result in loss of information in the analyses and bias, when all participants cannot be observed for the same time period (1).

When trial recruitment and follow-up take place over a long duration of time and the events occur relatively slowly, it is commonly impossible to obtain complete information on all patients entered into the trial. In addition, there is a risk that some patients may be lost to follow-up or are withdrawn and it is not known whether they experienced the event of interest. Survival analysis techniques are characterised by the ability to address many of these issues and allow investigators to make best use of the available information in settings where study participants have different lengths of follow-up.

A common method to present these data is to construct Kaplan-Meier survival curves, which reflect the probability of events having occurred at various time points (2). Results may also be reported as median survival or percentage survival (event-free) at a given, clinically relevant time point, for the intervention arm in comparison to the standard arm. These outcomes are generally easy for health professionals and consumers to understand (3). Treatment effects are most commonly summarised using a Hazard Ratio (HR) which is a measure of how often the event occurs in one treatment group compared to how often the event occurs in the other group, across the timeframe of interest.

Common mistakes related to time-to-event outcomes in Cochrane Systematic Reviews of Interventions
Analyses of time-to-event outcomes are very widely used in cancer-related randomized controlled trials, but they are less intuitively or easy to understand than binary effect measures. As a result, they are also difficult to interpret and derive data from when it comes to systematic reviews and meta-analyses. As our study carried out in 2018 showed, 13% of Summary of Findings Tables in oncology Cochrane reviews published between 2011 and 2017 showed incorrectly calculated absolute effect size measures, and only one third reported results in a way easily understandable for the reader. This issue was mainly attributable to flawed interpretations of the HR including confusing as to the event of interest (4).
The findings of this paper led to the adaptation of the GRADEpro software so that now authors can choose between various options for presenting absolute effects for time-to-event outcomes to overcome these identified problems. To date, MAGICapp does not offer this added functionality which may result in the perpetuation of these type of errors. Therefore, we see a critical need for hands-on guidance for authors and editors on how to avoid common mistakes related to time-to-event outcomes.

Some guidance on time-to-event meta-analyses already exist (5-7). The Cochrane Handbook for Systematic Reviews of Interventions currently provides limited information with regard to the appropriate inclusion of time-to-event outcomes in Cochrane reviews (5). However, because of our findings as described above and personal experience with performing and editing Cochrane systematic reviews, we strongly believe that there is an urgent need for introductory guidance for authors and editors within Cochrane including the very basics of survival analysis. This will improve the quality of Cochrane systematic reviews including time-to-event data; not only cancer-related reviews, but also reviews within other fields and Networks. Furthermore, clear guidance will also improve both the author and editor experience.

Aims

The overall aim of this project is to improve the quality of Cochrane systematic reviews that include time-to-event outcomes by supporting authors and editors to avoid common mistakes in their analysis and presentation. The basic principles of time-to-event analysis may not be known to or may be poorly understood by many authors and editors of Cochrane systematic reviews, and so that detailed and concrete "hands on" educational materials are required.

Objectives

**Objective 1**: Provide introductory materials on time-to-event outcomes and guidance how to avoid mistakes (e.g. what are time-to-event outcomes, common methods to extract and meta-analyse data, underlying assumptions need to be considered, specific considerations when assessing risk of bias).

**Objective 2**: Provide guidance for communicating results of time-to-event outcomes in Cochrane systematic reviews (e.g. in terms of absolute effects or median survival).

Proposed methods, key milestones, timelines and planned deliverables

Both objectives will be achieved by pooling important training materials for time-to-event meta-analyses (6-9). The user-friendly format of the instructions will be developed by Cochrane authors, editors and methodological experts carrying out the project jointly. It will therefore reflect an “author/editor-perspective”.

Two webinars have already been given by the applicants: A comprehensive Cochrane Learning Live webinar held in July 2018 (https://training.cochrane.org/resource/meta-analysis-time-event-data) included introductory elements to time-to-event analyses, which may serve as a well-structured outline for this guidance. Another webinar was given by the applicants in December 2018 to guide Cochrane authors with the appropriate calculation of absolute effect estimates for time-to-event outcomes in Summary of Findings Tables. This may serve as the starting point for more guidance on communicating results of time-to-event outcomes (https://training.cochrane.org/resource/improving-grade-%E2%80%98summary-findings%E2%80%99-tables-cochrane-reviews-detailed-guidance-calculation).
Planned deliverables
We will develop short hands-on material and test this within a workshop we plan to deliver during the Colloquium in Chile. Thereafter we will implement this preliminary guidance by presenting this at the next Governance Meeting in Manchester, incorporating feedback from Coordinating Editors and Managing Editors into the final version of the guidance. We plan to disseminate further the created resources via webinars and to inform the next version of the Cochrane Handbook for Systematic Reviews of Interventions with our findings.

This project will not cover every single issue related to time-to-event outcomes, but will give answers to most common mistakes (e.g. how to extract time-to-event data from individual studies, how to calculate absolute effects, how to assess bias).

Methods, key milestones and timelines
Start of the project: June 2019

- Project plan development and search for interested experts/authors/editors (first two and a half months of the project, completed: Mid-August 2019)
  - Editor survey:
    - Coordinating and managing editors of review groups within the Cancer network to be surveyed on:
      - Common problems they face with time to event outcomes
      - Questions on time to event outcomes they receive from review authors
      - Challenges when review Cochrane reviews including time to event outcomes
  - Search for available resources for time to event meta-analysis
    - E.g. GRADE Handbook, Cochrane Handbook, ...
  - Search for available training resources for other issues that can serve as a road map for the training materials
    - E.g. Cochrane Interactive Learning Modules, Cochrane Webinars, ...

- Development of first guidance and training materials (1.5 months, completed: End of September 2019)
  - Evaluation of the survey and prioritization of issues that need to be tackled
  - Development of first guidance and training documents
    - Using the identified available resources and
    - In the style of existing training resources for other issues (from Cochrane)
  - Continuous teleconferences among all participants to develop materials and discuss progress

- Meeting at the Cochrane Colloquium in Santiago, Chile in October 2019: Workshop proposal submitted to present preliminary guidance how to avoid common mistakes
  - Present preliminary guidance and training materials to workshop participants (if accepted, otherwise will be presented at one of the Cancer Network conference calls)

- Adapt resources to the input gained from the discussion workshop at the Cochrane Colloquium in Santiago, Chile (1 months, completed: End of November 2019)
Continuous teleconferences among all participants to discuss materials and progress
Implement results and suggestions from workshop to final guidance

Implement guidance and training resources (November 2019 – April 2020)

Meeting at the Governance Meeting April 2020 in Manchester
Present guidance at Co-ordinating Editors Meeting and Managing Editors Executive Meeting
Implement final suggestions

Publication of guidance and development of long-term implementation strategy (completed: end of April 2020)

Responsibilities

Coordination
Nicole Skoetz

Draft and evaluate editor survey
Nicole Skoetz
Marius Goldkuhle

Search for available resources (both, time to event training and guiding materials for other issues)
Marius Goldkuhle

Discuss survey and prioritize issues
All members

Coordination of monthly teleconferences and assembly of guidance and training materials and drafts
Marius Goldkuhle

Participate at continuous teleconferences and discuss development of first guidance and materials
All members

Present workshop and first guidance at Cochrane Colloquium and Governance Meeting
All members

Participate at continuous teleconferences and implement suggestions to improve guidance and materials
All members

Actively support review authors and experts
All members
## Gantt chart

<table>
<thead>
<tr>
<th>Project steps/month</th>
<th>2019</th>
<th>2020</th>
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<tbody>
<tr>
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<td>J</td>
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<tr>
<td>Project plan development</td>
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<td>A</td>
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<tr>
<td>Survey development and distribution</td>
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<td></td>
<td>S</td>
<td>S</td>
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<tr>
<td>Search for existing resources and materials for orientation</td>
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<tr>
<td>Survey evaluation, prioritization, assembly of first guidance and training materials</td>
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<tr>
<td></td>
<td>N</td>
<td>N</td>
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<tr>
<td>Discussion and application of first guidance and training materials</td>
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<tr>
<td>Adaption of guidance and training materials</td>
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<td></td>
<td>J</td>
<td>J</td>
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<tr>
<td>Implementation</td>
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<tr>
<td>Publication and long-term implementation</td>
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</table>
Estimated budget

One member will
- To develop, distribute and evaluate the planned survey (MG)
- To identify and gather existing guidance (MG)
- Writing efforts for the designed guidance documents (MG)
- Organizational procedures, including teleconferences and the preparation of required materials (MG)

<table>
<thead>
<tr>
<th>Statement of costs for contributor (MG)</th>
<th>Units</th>
<th>Unit costs</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full time employee</td>
<td>10 months</td>
<td>6.000 GBP</td>
<td>5.500 GBP</td>
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<tr>
<td></td>
<td>0.076 FTE</td>
<td></td>
<td></td>
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<tr>
<td><strong>Total per contributor</strong></td>
<td></td>
<td></td>
<td><strong>5.500 GBP</strong></td>
</tr>
</tbody>
</table>

Several members will receive support to present guidance for various audiences at workshops (Cochrane Colloquium) and meetings (Governance Meeting) and to adapt guidance accordingly.

<table>
<thead>
<tr>
<th>Participation at the Cochrane Colloquium or the Governance meeting</th>
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<tbody>
<tr>
<td>Marius Goldkuhle</td>
<td>1.500 GBP</td>
</tr>
<tr>
<td>Elvira van Dalen</td>
<td>1.500 GBP</td>
</tr>
<tr>
<td>Philipp Dahm</td>
<td>1.500 GBP</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4.500 GBP</strong></td>
</tr>
</tbody>
</table>

All other applicants (FM, NO, CTS, NS) agreed to participate and contribute to the project without financial compensation.

Overall budget required: 10.000 GBP

References


8. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16-.

Appendix

Short biographies of the project team

Nicole Skoetz, MD

Present positions
Since 01/2018 Senior Editor Cochrane Cancer
Since 11/2015 Scientific Co-ordinator Working Group Standard Operating Procedures of the Comprehensive Cancer Centers, Center of Integrative Oncology Köln Bonn; University Hospital of Cologne, Germany

Previous positions
01/2011-12/2017 Co-ordinating Editor Cochrane Haematological Malignancies; Department I of Internal Medicine, University Hospital of Cologne, Germany
09/2012-08/2015 Assistant physician general medicine; Dres Rosenthal, Reinecke, Metternich. Cologne
01/2008 - 12/2011 Joint Co-ordinating Editor Cochrane Haematological Malignancies; Department I of Internal Medicine, University Hospital of Cologne
03/2007 - 12/2007 Deputy head of Clinical Trials Center Cologne, University Hospital of Cologne
01/2005 - 03/2007 Project manager; Clinical Trials Center Cologne, University Hospital of Cologne
08/2002 - 12/2004 Research associate; Cochrane Haematological Malignancies; Department I of Internal Medicine, University Hospital of Cologne
03/1992 - 08/1993 IT specialist; Bayer AG, Leverkusen

Personal statement
My principal interest is to be involved in new method developments and improvement of Cochrane Review quality. I have been active in Cochrane since 2002, first as a Consumer Co-ordinator and author, then as Managing Editor and since 2011 as Co-ordinating Editor of Cochrane Haematological Malignancies (CHM). I have always been actively involved in committees, like the Scientific Committee, Prognosis Implementation Strategy Group, Methods Application and Review Standards, and Co-Ed executive. By leading Cochrane Cancer right from the beginning in 2014, I try to bundle expertise from Cochrane Review Groups (CRGs) and Methods groups to identify gaps in the review production in the field of cancer, engage with stakeholders, collaborate with external international cancer organisations and apply collaboratively for funding.

As a guideline developer, I have a strong interest in interactive summary of finding tables and GRADE. As time-to-event outcomes are highly relevant for at least all cancer-related CRGs, I lead the GRADE Time-to-Event Project Group.
Within this proposed project we will solve recently identified shortcomings in Cochrane Reviews related to time-to-event outcomes and give hands-on guidance to improve Cochrane Review quality.

Selected peer-reviewed publications


Elvira van Dalen, MD, PhD

Present positions
2018-present  Postdoc/epidemiologist, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
2012-present  Co-ordinating Editor Cochrane Childhood Cancer

Previous positions
2007-2018  Postdoc / epidemiologist, Department of Pediatric Oncology, Emma Children’s Hospital / Academic Medical Center, Amsterdam, The Netherlands
2006-2011  Managing Editor Cochrane Childhood Cancer
2006-2009  Member Editorial Base Evidence-based Child Health, a Cochrane review journal
2002-2007  PhD student, Department of Pediatric Oncology, Emma Children’s Hospital / Academic Medical Center, Amsterdam, The Netherlands

Personal statement
My main research interests are systematic reviews and guidelines in the field of pediatric oncology, systematic review methodology and research on late adverse effects after treatment for childhood cancer. I have been active in Cochrane since 2002, first as an author (with different review groups), then as the managing editor and now Coordinating Editor of Cochrane Childhood Cancer. Furthermore, I’m a member of the international GRADE Network and the Dutch GRADE network and different Cochrane modalities like the Cochrane Trainers’ Network, Cochrane Cancer Network.

I have experience with time-to-event data both as an author and editor of systematic reviews and also from primary research and guidelines. As a member of the GRADE working group for time-to-event outcomes I’m involved with several projects aiming to improve the presentation of time-to-event outcomes in Summary of Findings tables and to provide guidance on the GRADE assessment of time-to-event outcomes. This has already led to the improvement of the GRADEpro software. During the 2018 Cochrane Colloquium I co-hosted a workshop on ‘Improving GRADE evidence profiles and 'Summary of Findings' tables: detailed guidance for time-to-event data’ and I co-presented a Cochrane training webinar on the same topic.

My experience with time-to-event outcomes and systematic reviews in different roles (e.g. author, editor, researcher) makes it possible to look at the problem from different perspectives. I love to be able to contribute as a member of the project team to an increased knowledge of time-to-event outcomes within the Cochrane community, thereby increasing the author and editor experience and the overall quality of Cochrane reviews.

Peer-reviewed publications


Dr. Fergus Macbeth MA DM FRCP FRCR

Previous positions, concluding with the present position: Director of Guidelines, NICE (2008-11), Hon Professor Cardiff University, Joint Coed Cochrane Lung Cancer Group. Co-Chair Cochrane Council (2017-9)

Personal statement

I have been involved with the Cochrane Lung Cancer Group since its inception 20 years ago and am currently joint Coordinating Editor. I am an author of several Cochrane reviews and have been involved with clinical guideline development in the UK since 1995 and in the past 6 years I have chaired three guideline committees for NICE. As a practising oncologist until retiring six years ago I was involved in clinical trials throughout my career and was Chief Investigator of one of the largest RCTs in lung cancer ever completed. I therefore have a good understanding of the problems of clinical outcome assessment and in particular of time-to-event outcomes. I think my experience as an author, editor, peer reviewer and user of Cochrane and other systematic reviews, and as a teacher of evidence-based healthcare means I can contribute significantly to this project.

Relevant awards and honors

British Thoracic Oncology Group Lifetime Achievement Award 2011

Selected peer-reviewed publications

1. Different knowledge, different styles of reasoning: a challenge for guideline development. Wieringa S; Dreesens D; Forland F; Hulshof C; Lukersmith S; Macbeth F; et al. BMJ Evidence-based Medicine. 2018 Apr 03.
6. Use of heparins in patients with cancer: individual participant data meta-analysis of randomised trials study protocol. Schunemann HJ; Ventresca M; Crowther M; Briel M; Zhou Q; Garcia D; Lyman G; Noble S; Macbeth F; Griffiths G; et al IPDMA heparin use in cancer patients research group. BMJ Open. 6(4):e010569, 2016 Apr 29.
Marius Goldkuhle

Present position
2018-present Research assistant, Cochrane Haematological Malignancies, University Hospital Cologne, Cologne, Germany

Previous positions
2015-2018 Student assistant, Cochrane Haematological Malignancies, University Hospital Cologne, Cologne, Germany

Personal statement
I am a research associate at Cochrane Haematological Malignancies at the University Hospital Cologne, Germany. My background is in health economics, where I received my bachelor’s and master’s degree in. Besides my active work in the conduction of Cochrane reviews and clinical guidelines; I am engaged in a variety of methodological projects aiming to improve the handling of time-to-event data in systematic reviews and meta-analyses. This includes the GRADE time-to-event group. There I am currently the lead author of a GRADE guidance paper on the consideration of censoring issues in a body of evidence. As member of this project, I will contribute based on my experience in time-to-event meta-analyses and coordinate the planned discussions among the other participants. In the past, I was a co-contributor to a variety of workshops (English and German) and a Cochran Live webinar, which aimed to assist authors in the appropriate calculation of absolute effect estimates for on time-to-event outcomes. With the experience gained there, I will a be engaged and able to make valuable contributions in the workshops, which are planned as part of this project.

Relevant awards and honors
Deutscher Akademischer Austauschdienst (DAAD) travel grant, GRADE Meeting, Hamilton, Canada 2019

Peer-reviewed publications
Newton Opiyo, PhD

**Present position**
2018 – Present: Associate Editor. Cochrane. London, UK

**Previous positions**
2013 – 2014: Post-doctoral Research Fellow. KEMRI-Wellcome Trust, Kenya
2005 – 2012: Research Scientist. KEMRI-Wellcome Trust, Kenya

**Personal statement**
I am the Associate Editor for the Public Health and Health Systems Network. I have been involved with Cochrane since 2007. My research experience are in the areas of evidence synthesis, pragmatic trials, knowledge translation and guideline development. I also have a strong interest in capacity building in evidence-to-policy processes and have been involved in training healthcare professionals and policymakers in systematic reviews and GRADE methodology. This experience, coupled with my training in epidemiology, will enable me to effectively contribute to the planned activities in this project (e.g training workshops, preparation of author resources, among others).

**Honorary appointments**

**Selected publications**