

# A computational way station for reporting network meta-analyses

Charles T. Gray, Gavin Stewart, Matthew Grainger

January 20, 2021

## 1 Network meta-analysis reporting

Pairwise analyses between treatment and control, exposed and unexposed, intervention and no intervention, are conventionally undertaken with meta-analysis in fields such as ecology, medicine, and the social sciences [1]. Network meta-analysis provides a means of comparing three or more treatments or interventions, including control or placebo [5]. The question answered by a network meta-analysis is not *if* a treatment works, but *which* treatments perform better, comparatively [4]. A particularly useful aspect of network meta-analysis is combining the results of more than one pairwise analysis and constructing indirect comparisons, where pairwise evidence is unavailable, from a network of direct comparisons. An example of direct comparisons provided by existing evidence is shown in Figure 1. Network meta-analysis

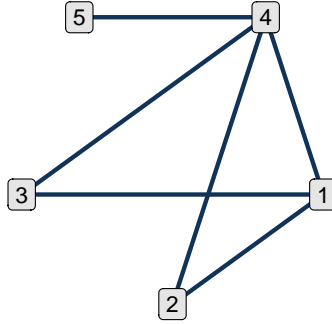


Figure 1: This network shows the direct evidence provided by pairwise comparisons in seven studies on treatments for Parkinson’s disease [10]. Each node represents a treatment, including one placebo, represented by the fourth node. Where there is an edge connecting two treatment nodes, there exists a pairwise comparison in the literature between these two treatments. Where there is no edge connecting the nodes of the network, there is no direct evidence.

17 converts the network to a complete graph, where all treatments are compared  
 18 with all other treatments, that is, every node connects to every other node  
 19 via direct or indirect comparison.

20 Software to implement network meta-analyses are relatively new and do  
 21 not provide complete toolchains for specific protocols, such as reporting re-  
 22 sults according to Cochrane’s handbook [5]. For example, the handbook  
 23 recommends reporting the network of direct evidence, for which the R pack-  
 24 age `multinma::` includes a tool [10], an example of which is shown in Figure  
 25 1. However, the handbook also recommends reporting a **contribution ma-**  
 26 **trix** of the percentage of each study’s contribution to the estimated overall

27 effect, and this is not provided as a visualisation tool with `multinma::`.

28 Furthermore, open source scientific software is shifting from all-purpose  
29 packages for an entire analysis, such as `metafor::`, to smaller task-specific  
30 software packages. One method of aggregation of tools is a **metapackage**,  
31 such as `tidyverse::` [14], for data engineering, which comprises a number of  
32 packages that each pertain to different problems, such as `ggplot2::` for data  
33 visualisation, and `dplyr::` for Boolean data manipulation. Here we explore  
34 another way of aggregating resources, for the specific purpose of network  
35 meta-analysis reporting: a computational **way station**, a temporary resting  
36 place between two points of travel, of toolchains and tool development.

## 37 1.1 A snapshot of a living resource

38 In this manuscript, we next describe the gaps in the toolchain for implement-  
39 ing network meta-analysis via R according to Cochrane’s reporting standards.  
40 Standards for network meta-analysis are not, however, fixed, but in devel-  
41 opment, and Cochrane’s reporting standards may not be appropriate for,  
42 say, ecological network meta-analyses. Thus, instead of aiming to provide  
43 a complete toolchain for network meta-analysis, we instead propose a com-  
44 putational way station as a meeting place for stakeholders with different  
45 priorities to provide perspective and collaborate. This way station is a **liv-**  
46 **ing resource**, in anticipation of future updates following stakeholder input  
47 and computational development, comprising multiple points of access:

48 **website** A website with vignettes of toolchains. Currently the existing solu-  
49 tions for Cochrane’s reporting standards are provided, however there is  
50 scope for future vignettes for network meta-analyses according to other  
51 discipline or organisational protocols.

52 **open source code repository** Source code is provided for toolchains and  
53 software extensions.

54 **contributing** Detailed instructions for different stakeholders with varying  
55 levels of mathematical and computational training to contribute.

56 **issues** In addition to the source code, the issues associated with the code  
57 repository provide a public record for discussions.

58 Living resources provide a solution to the problem of overabundance of  
59 systematic reviews, flooding literature to the point that decision makers are  
60 unsure of where to look [3, 6, 7, 11]. Consider Covid-19, where in the first 88  
61 days after naming the disease, there already existed 88 systematic reviews,  
62 one for every day since the disease was named [9]. Cochrane’s COVID-NMA  
63 initiative (<https://covid-nma.com/>) is a living synthesis solution to this prob-  
64 lem, via network meta-analysis of regularly updated Covid-19 research [2].

## 65 2 Toolchain gaps in Cochrane reporting stan- 66 dards

67 There exist several software packages for conduction network meta-analysis in  
68 R; for example, `gemtc::` [13], `multinma::` [10], and `netmeta::` [12]. Different  
69 tools will no doubt have unique advantages and disadvantages, however, there  
70 is no one tool for all reporting standards for a Cochrane network meta-  
71 analysis. Furthermore, visualisations and reporting for meta-analysis are  
72 still being developed.

### 73 2.1 Missing tables and improved visualisations

74 Cochrane recommends reporting the percentage each study contributes to  
75 the overall estimated effect via a **contribution matrix**, shown in Figure 2.

76 The `netmeta::` package has tools for contribution matrices, but if one  
77 is performing the analysis with, say, `multinma::`, it is unclear how to piece  
78 together the tools to produce a complete set of Cochrane reporting.

79 *Gav, is the contribution matrix only for frequentist analysis?*

80 Visualisations, too, are still in development. A recent improvement on  
81 standard forest plots are orchard plots which contain not only credible in-  
82 tervals, but prediction intervals, and group studies categorically, particularly  
83 useful for large meta-analyses [8].

**Figure 11.6.b** Contribution matrix for the network on interventions for heavy menstrual bleeding presented in Figure 11.4.a. Four direct comparisons in the network are presented in the columns, and their contributions to the combined treatment effect are presented in the rows. The entries of the matrix are the percentage weights attributed to each direct comparison. The intervention labels are: A, first generation hysteroscopic techniques; B, hysterectomy; C, second generation non-hysteroscopic techniques; D, Mirena

		Direct comparisons in the network (% contribution)			
		A-B	A-C	A-D	C-D
Network meta-analysis estimates	Mixed estimates				
	A-B	100.0			
	A-C		97.8	1.1	1.1
	A-D		34.5	34.1	34.5
	C-D		14.4	14.4	71.2
	Indirect estimates				
	B-C	49.6	48.9	0.7	0.7
	B-D	38.5	28.0	15.5	28.0
Entire network		34.4	36.4	10.5	21.7
Included studies		5	11	1	3

Figure 2: A contribution matrix shows what percentage each study contributes to the overall estimated effect in a network meta-analysis. This is the example given in the Cochrane Handbook [5].

## 2.2 Sensitivity analyses

## 3 Computational way station for open and inclusive scientific method development

Stakeholders engage with meta-analyses in multiple ways. A lead researcher may not be interested in interacting with code repositories, but may well have thoughts about how to improve reporting for inference. A computational collaborator may wish to contribute tools for related analyses, even if not directly involved in the project.

In this section, we consider developing a toolchain for reporting a Cochrane network meta-analysis, considering how different researchers may wish to

94 provide feedback on the implemented protocol. With increasing levels of  
95 computational complexity, we step through how researchers in various roles  
96 might contribute.

### 97 **3.1 Domain-specific principal investigator**

98 Consider a study where the principal investigator (PI) is a psychologist who  
99 delegates statistical analysis to other members of the team: a lead statis-  
100 tician, and a postdoctoral scholar under their supervision. The PI will in-  
101 terpret the meta-analytic findings, but will not wish to interact with code  
102 repositories. In this case, an email address of the primary maintainer (the  
103 postdoctoral scholar) of the living resource is provided for comments that can  
104 then be converted to issues by the maintainer on the repository for discussion  
105 amongst the community.

### 106 **3.2 Lead statistician**

107 The lead statistician will be comfortable with code, but will be time poor in  
108 comparison to the maintainer of the living resource, the postdoctoral scholar  
109 under their supervision. Whilst they may not have time to contribute they  
110 will likely have comments for the maintainer. They will likely have a GitHub  
111 account, and thus can contribute to the discussion via issues, where not  
112 only the maintainer, but any interested party can consider and add to the  
113 suggestions.

### 114 3.3 Computational collaborators

115 Now consider a computational ecologist, interested in developing tools and  
116 protocols for their own network meta-analyses. In this case, they may wish  
117 to contribute new vignettes to the website, with new toolchains, as well as  
118 develop new tools to fill the toolchain gaps.

119 The R package `usethis::` includes a workflow for contributing to some-  
120 one else's package<sup>1</sup> [15].

121 In Figure 3 is a sketch of the workflow for contributing to `nmareporting::`,  
122 the underlying code base of the site and development. Let us suppose  
123 the ecologist is contributing an ecology-specific vignette for network meta-  
124 analysis.

## 125 4 Conclusion

## 126 References

- 127 [1] Michael Borenstein, Larry V. Hedges, Julian P. T. Higgins, and Han-  
128 nah R. Rothstein. *Introduction to Meta-Analysis*. John Wiley & Sons.  
129 Google-Books-ID: JQg9jdrq26wC.
- 130 [2] Isabelle Boutron, Anna Chaimani, Joerg J. Meerpohl, Asbjørn  
131 Hróbjartsson, Declan Devane, Gabriel Rada, David Tovey, Giacomo

---

<sup>1</sup>Workflow documentation available here: <https://usethis.r-lib.org/articles/articles/pr-functions.html>



```

library(usethis)
# create a fork and clone
create_from_github("softloud/nmareporting")
# create a branch for the specific contribution
pr_init("ecovignette")
#
# ecologist then writes vignette
#
# contribute the vignette to the code repository
pr_push()
#
# waits for maintainer to merge
#
# once the maintainer has merged
pr_finish()

```

Figure 3: A workflow for contributing to the `nmareporting::` computational way station.

- 132      Grasselli, and Philippe Ravaud. The COVID-NMA project: Building an  
133      evidence ecosystem for the COVID-19 pandemic. 173(12):1015–1017.
- 134    [3] S. Gopalakrishnan and P. Ganeshkumar. Systematic reviews and  
135      meta-analysis: Understanding the best evidence in primary healthcare.  
136      2(1):9–14.
- 137    [4] Mathias Harrer, Prof Dr Pim Cuijpers<sup>2</sup>, Prof Dr Toshi A. Furukawa<sup>3</sup>,  
138      and Assoc Prof Dr David D. Ebert<sup>2</sup>. *Doing Meta-Analysis in R*.
- 139    [5] Julian PT Higgins, James Thomas, Jacqueline Chandler, Miranda  
140      Cumpston, Tianjing Li, Matthew J Page, and Vivian A Welch. *Cochrane*  
141      *handbook for systematic reviews of interventions*. John Wiley & Sons.

- 142 [6] David Moher. The problem of duplicate systematic reviews. 347:f5040.  
143 Publisher: British Medical Journal Publishing Group Section: Editorial.
- 144 [7] Morten Hylander Møller, John P. A. Ioannidis, and Michael Darmon.  
145 Are systematic reviews and meta-analyses still useful research? we are  
146 not sure. 44(4):518–520.
- 147 [8] Shinichi Nakagawa, Malgorzata Lagisz, Rose E. O’Dea, Joanna  
148 Rutkowska, Yefeng Yang, Daniel W. A. Noble, and Alistair M.  
149 Senior. The orchard plot: Cultivating a forest plot for  
150 use in ecology, evolution, and beyond. 12(1):4–12. \_eprint:  
151 <https://onlinelibrary.wiley.com/doi/pdf/10.1002/jrsm.1424>.
- 152 [9] David Naumann. Too many systematic reviews for a disease that has  
153 existed for a few months.
- 154 [10] David M. Phillippo. multinma: Network meta-analysis of individual and  
155 aggregate data in stan.
- 156 [11] Derek Richards. Too many reviews too few trials. 19(1):2–2. Number:  
157 1 Publisher: Nature Publishing Group.
- 158 [12] Gerta Rücker, Ulrike Krahn, Jochem König, Orestis Efthimiou, and  
159 Guido Schwarzer. netmeta: Network meta-analysis using frequentist  
160 methods.
- 161 [13] Gert van Valkenhoef and Joel Kuiper. gementc: Network meta-analysis  
162 using bayesian methods.

- 163 [14] Hadley Wickham. tidyverse: Easily install and load the 'tidyverse'.
- 164 [15] Hadley Wickham and Jennifer Bryan. usethis: Automate package and
- 165 project setup.