

Network meta-analysis for indirect treatment comparisons

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SUMMARY

I present methods for assessing the relative effectiveness of two treatments when they have not been compared directly in a randomized trial but have each been compared to other treatments. These network meta-analysis techniques allow estimation of both heterogeneity in the effect of any given treatment and inconsistency ('incoherence') in the evidence from different pairs of treatments. A simple estimation procedure using linear mixed models is given and used in a meta-analysis of treatments for acute myocardial infarction. Copyright © 2002 John Wiley & Sons, Ltd.

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1. INTRODUCTION

Direct randomized comparison is the most reliable way of comparing treatments. As the number of available treatments increases the number of possible pairwise comparisons increases quadratically, so it is common for only a small fraction of the possible comparisons to be performed. In the U.S.A. it is usual for new treatments to be compared to a placebo control, which means that direct comparisons with current standard treatment may be unavailable. On the other hand, in Europe it is relatively common to compare a new intervention to a standard treatment (active control), in which case it may be unclear whether it is better than placebo or better than some competing standard treatment.

There is at least one form of indirect comparison that is fairly commonly used. Suppose that treatment B is known to be superior to placebo. If A is better than B in a randomized trial then most people would believe that A is better than placebo. Similarly, if A is equivalent to B then A would still be better than placebo.

These examples are simple because there is no redundancy in the information and is thus no way to assess the reliability of the conclusions. Suppose that in the first example there is another treatment D that has also been compared to A and to placebo. We now have two separate sources of information about the difference between A and placebo. If these

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sources agree, we should be more confident about the result; if they disagree we should be less confident.

I present a methodology for using potentially very complex networks of treatment comparisons to detect inconsistency between randomized trials of different treatments, to estimate treatment differences and to assess the uncertainty in these estimates. Estimating treatment differences is straightforward; the main contribution of this paper is in methods for detecting and estimating the inconsistency among trials.

There are many possible reasons for inconsistency, with different implications for meta-analysis. The issue of comparability of trials and the implications of different possible control groups has been reviewed recently by the International Conference on Harmonization, in ICH Topic E10 [1].

Differences in patient population are perhaps the most obvious. A new treatment may be initially tested only in those for whom existing treatments are unsatisfactory. A new treatment may be superior for these patients but inferior in the general patient population where the existing treatment is effective. In the most extreme case, a new treatment may be equivalent to the existing treatment in patients for whom neither treatment works, but not in the general population. As the ICH E10 document says (Section 1.4.1):

A trial using any of the control types may demonstrate efficacy of the test treatment by showing it is superior to the control. ... An active control trial may, in addition, demonstrate efficacy in some cases by showing the new treatment to be similar in efficacy to a known effective treatment. This similarity establishes the efficacy of the test treatment, however, only if it can be assumed that the active control was effective under the conditions of the trial.

This cause of inconsistency is in addition to other imperfections in trial design or analysis. For example, in an open-label or ineffectively blinded trial there may be a tendency for a treatment to perform as expected by the researchers and subjects. This might cause the same treatment to perform better when it is new than when it is used as an active control.

This potential for inconsistency in comparisons leads the ICH E10 committee to state (Section 2.7.1.4, emphasis added):

Placebo-controlled trials lacking an active control give little useful information about comparative effectiveness, information that is of interest and importance in many circumstances. Such information *cannot reliably be obtained from cross-study comparisons*, as the conditions of the studies may have been quite different.

The methods I develop here provide a partial solution to this problem by making it possible in some situations to evaluate whether cross-study comparisons are reliable.

2. NETWORKS OF EVIDENCE

We can represent the available treatment comparisons using a simple graph. The graph does not show how evidence is combined from multiple trials of a single comparison, but this is the well-understood problem of a standard meta-analysis. In this section I will adopt the convention that we are interested in comparing treatments A and B, and that other letters denote treatments in which we have no direct interest. I will also assume that the result of

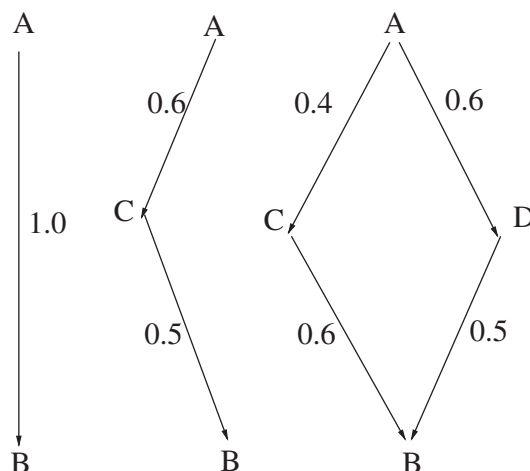


Figure 1. Simple networks of comparisons.

a single study can be summarized as a mean and standard error for a Normally distributed estimate of treatment difference. This could be a difference in means for a continuous outcome, a log-odds ratio for a binary outcome, or some other statistic.

Figure 1 shows some simple graphs. The points represent treatments and the arrows represent randomized comparisons. Numbers next to the lines represent treatment differences and the arrow indicates the direction of the comparison. A positive number indicates that the treatment at the head of the arrow has a higher outcome than that at the tail. A higher outcome may be beneficial (for example, mean quality of life) or harmful (for example, mortality). We write δ_{AB} for the difference when B is at the head of the arrow and A is at the tail. The leftmost figure, then, is a direct comparison between A and B, with $\delta_{AB} = 1$. The central figure shows that A is superior to C and C is superior to B in randomized trials. The obvious estimate of the difference between A and B is the sum of the differences between A and C, and C and B. That is

$$\delta_{AB} = \delta_{AC} + \delta_{CB}$$

$$\text{var}[\delta_{AB}] = \text{var}[\delta_{AC}] + \text{var}[\delta_{CB}]$$

The rightmost graph shows two treatments C and D, both of which have been compared to A and B. There are now two independent estimates of δ_{AB} corresponding to the two paths between A and B in the graph: $\delta_{AC} - \delta_{CB}$ and $\delta_{AD} - \delta_{DB}$. A sensible way to combine them would be to take an average of the two, weighted by the inverse of their respective variances. In this case the two estimates agree quite well, so they reinforce each other. If the two estimates disagreed strongly our confidence in the combined estimate would be impaired. We need to have some way of quantifying the degree of agreement of these independent estimates so that it can be translated into a confidence interval for the combined estimate.

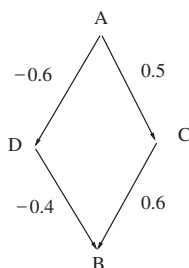


Figure 2. An incoherent network of comparisons.

Figure 2 demonstrates this problem. Combining δ_{AC} and δ_{CB} suggests that A is better than B, but combining δ_{AD} and δ_{DB} suggests that A is worse. There are now three possibilities. One is that the individual trials are sufficiently underpowered that the two estimates really are consistent. A second is that one or more of the treatments has a sufficiently heterogeneous effect that the two estimates really are consistent. Finally, it could be that each individual estimate of δ_{AB} is apparently reliable but they disagree. In the first two cases all the uncertainty about δ_{AB} is handled by standard meta-analytic methods. In the third case we have a qualitatively new form of uncertainty, which is not visible in a standard meta-analysis because it requires a closed loop involving at least three treatments.

I call this additional form of uncertainty ‘incoherence’ and I will present ways to estimate the incoherence of a network of evidence. A meta-analysis with large incoherence indicates that a single number summary is not a sensible way to approach the data. As in a standard meta-analysis where heterogeneity is large, it is important to look for possible causes of variation that might allow subsets of the studies to be combined appropriately. When incoherence is moderate, of the same order of magnitude as the other sources of uncertainty, it may still be useful to estimate a summary if we can construct a confidence interval that incorporates all the sources of uncertainty.

Figure 3 shows the final complication of a network meta-analysis. In this example there are multiple paths from A to B, some independent and some overlapping. A method is needed to determine weights for each path and to compute a confidence interval taking account of the overlap between paths. One solution to this problem is to write down a hierarchical model containing components for sampling variability, treatment heterogeneity, and incoherence and to apply maximum likelihood to this model.

DuMouchel and Harris [2] studied the somewhat similar problem of generalizing carcinogenicity studies from animals to humans. Rather than networks of linked trials they had a tabulation of the carcinogenicity of compounds by species tested and wished to impute the missing cells. Their method involved estimating the between-species agreement of tests on a given compound and the between-compound agreement of tests on a given species. The data consist entirely of comparisons within species between a potential carcinogen and control; all the comparisons between different species or different chemicals are indirect. In the context of clinical trials the problem considered by DuMouchel and Harris [2] is more closely analogous to the surrogate outcomes problem. Their methods have been extended by Daniels and Hughes [3] and Buyse and Molenberghs [4], attempting to generalize from efficacy on a surrogate

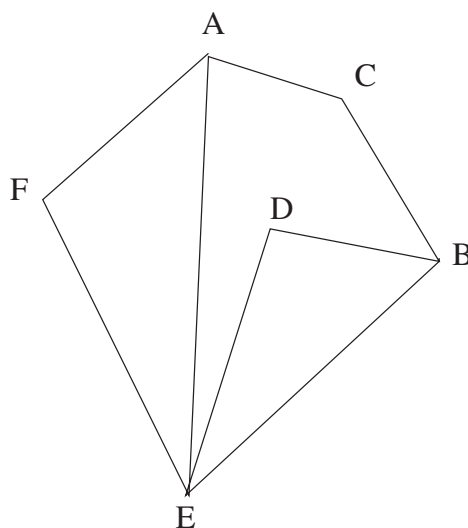


Figure 3. A realistically complex network of comparisons.

outcome to efficacy on a clinical outcome based on how these outcomes have been related for other drugs in the same class.

3. MODELS

I denote the treatment difference estimate from the k th randomized trial comparing treatments i and j by Y_{ijk} and its estimated standard error by σ_{ijk}^2 .

The model for the observed data Y_{ijk} has three components in addition to the sampling error within each study. The true average effects of treatments i and j are represented by μ_i and μ_j , so that $\delta_{ij} = \mu_i - \mu_j$. Random effects η_{ik} and η_{jk} with variance τ^2 represent the difference between the average effects of treatments i and j and their effects in this study; they capture the heterogeneity of treatment effect. Finally, a second random effect ξ_{ij} represents a change in the effect of treatment i when it is compared with treatment j . In order to combine different treatment comparisons we need the effect of treatment i to be the same no matter what it is compared against, that is, we need ξ_{ij} to be close to zero. Thus ξ_{ij} captures the inconsistency of this pair of treatments with the rest of the evidence. We call $\omega = \text{var}[\xi]$ the *incoherence* of the network. In principle we could allow ω and τ to vary with i, j or with covariates, but this would require substantially more data and would complicate estimation.

The formal model is thus

$$Y_{ijk} \sim N(\mu_i - \mu_j + \eta_{ik} + \eta_{jk} + \xi_{ij}, \sigma_{ijk}^2)$$

$$\eta_{ij} \sim N(0, \tau^2)$$

$$\xi_{ij} \sim N(0, \omega^2)$$

Maximum likelihood or restricted maximum likelihood (REML) estimation in this model is possible using software for linear mixed models. We describe estimation using the `lme()` function [5] in R and S-plus.

4. REML ESTIMATION

In order to use the `lme` function the data need to be structured so that the linear predictor includes the same term μ_i regardless of whether i is the ‘control’ or ‘new’ treatment in the trial.

Define variables X_i for each treatment and in a trial estimating $\mu_i - \mu_j$ we write $X_i = 1$, $X_j = -1$ and $X_{i'} = 0$ for all other treatments i' . There are two levels of random variation in the model: heterogeneity and sampling error ($\eta_{i(k)}$ and σ^2) at the level of the individual trial and incoherence (ξ_{ij}) at the level of the pair of treatments.

In fact the heterogeneity is modelled in a more flexible manner than this model would indicate, by specifying the variance in terms of a linear function of the standard error for the trial. That is

$$\text{var}[Y_{ijk}|\eta, \xi] = a(b + \sigma)^2 \quad (1)$$

The constant term b in this linear function corresponds approximately to the heterogeneity estimated by Dersimonian and Laird [6], in that it determines the extent to which the weight for a given trial depends on its size. When b is large trials of different sizes receive approximately the same weight; when b is small the weight is roughly proportional to the sample size. By also estimating the multiplicative overdispersion a we can allow the data to determine whether heterogeneity is equal in all trials or varies with the size of trial. It is certainly plausible that heterogeneity should vary with study size; large trials generally involve many centres and often many countries, so that heterogeneity due to differing patient populations could well be reduced.

As we have data only on differences between treatments the model is not identifiable as it stands; an arbitrary constant could be added to each μ_i . We constrain the parameters by setting one of the treatment means to zero.

It may be desirable to allow the heterogeneity τ^2 to vary between treatments. If there are sufficient trials involving each treatment the heterogeneity can be estimated separately for each trial using `lme()` (Figure 4). It would be also possible to model both τ^2 and ω^2 more flexibly by Bayesian methods, using software such as BUGS [7, 8], especially when expert opinion on their likely magnitude is available.

```
netmeta<-lme(effect~trt.B+trt.C+trt.D+trt.E,
             random=~1|trtpair,
             var=varConstPower(form=~sigma,fixed=list(power=1)))
```

Figure 4. `lme()` command to fit by maximum likelihood. `trt.A` is omitted from the formula for identifiability.

5. EXAMPLES

First I present two simple simulated examples, one with and one without significant incoherence, to show how the estimates behave in a simple case. I then present a real example comparing treatments for acute myocardial infarction.

5.1. Artificial example

The data are shown in Table I. The first set of data were constructed by taking $\mu_i = i$, and giving all of the trials an identical standard error ($\sigma^2 = 1/2$) and no heterogeneity ($\tau^2 = 0$). Thus

$$Y_{ijk} \sim N(i - j, 1/2)$$

In the second set we introduced incoherence by assuming that any treatment was 25 per cent less effective when used as a 'control', so that

$$Y_{ijk} = N(i - 0.75j, 1/2)$$

This might be due to a tendency to randomize precisely those patients for whom the current standard treatment is not ideal, or in the presence of imperfect blinding might be a bias resulting from the expectations of clinicians or patients.

We will use these data to estimate the difference between treatments 4 and 5. In the first case the incoherence is estimated as $\hat{\omega} < 0.0001$ and $\hat{\mu}_4 = 2.94$, $\hat{\mu}_5 = 4.06$ giving $\hat{\delta}_{24} = -1.12$. The standard error estimate for $\hat{\mu}_2 - \hat{\mu}_4$ is 0.623. This takes into account the incoherence of the observed network of information, but not the unobserved ξ_{24} . Thus the correct predictive error is

$$\sqrt{(0.623^2 + \hat{\omega}^2)}$$

which in this case is effectively identical. A 95 per cent confidence interval for δ_{45} is $[-0.101, 2.34]$. This is suggestive evidence ($p = 0.07$) of a difference.

In the second case the estimated incoherence is $\hat{\omega} = 0.381$. This immediately warns us that a meta-analysis is likely to be inappropriate. The estimated means are $\hat{\mu}_4 = 0.3.33$ and $\hat{\mu}_5 = 4.43$, giving $\hat{\delta}_{24} = -1.10$, and the standard error estimate is 0.677. Again, we must incorporate the variance of the unobserved ξ_{24} in this to get the predictive error

$$\sqrt{(0.677^2 + 0.381^2)} = 0.777$$

In this case the incoherence substantially increases the standard error and the predictive error. Our 95 per cent confidence interval for δ_{24} would be $[-2.62, 0.42]$, giving little or no evidence ($p = 0.16$) of a difference.

Assessing the consistency of the evidence allows us to reach different conclusions in these two cases, despite the fact that the standard errors for each individual trial and the heterogeneity of each pairwise comparison do not differ.

5.2. Treatments for acute myocardial infarction

Acute myocardial infarction ('heart attack') is caused by the formation of a clot in the coronary artery, blocking blood flow to part of the heart. One important mode of treatment is to remove

Table I. Artificial data. For Y_1 there is no incoherence; for Y_2 any treatment is less effective when it is the control, causing incoherence.

Active	Control	Y_1	Y_2
2	1	-2.428	-1.451
2	5	3.233	3.819
3	2	-0.493	-0.405
1	2	0.577	1.868
3	1	-2.06	-0.709
3	4	1.976	1.196
2	3	1.084	2.055
2	3	1.255	1.278
3	4	0.807	1.058
3	4	0.254	1.672
1	4	3.008	3.634
1	5	3.817	4.063
2	1	-0.755	-0.405
1	3	1.339	2.100

the clot, either by dissolving it with drugs (thrombolysis) or by physically breaking it up (angioplasty). The use of some reperfusion (clot-removing) treatment has been standard since the late 1980s. Since then, a number of trials have compared reperfusion techniques.

Our data comparing thrombolysis to angioplasty come from the Cochrane Library of Systematic Reviews [9]. Comparisons between thrombolytic regimens are taken from ISIS-3 [10], GISSI-2 [11] and its international extension [12], GUSTO [13], GUSTO 3 [14], INJECT [15] and RAPID-2 [16]. A number of outcomes are available for each of these trials; in this analysis we examine 30 or 35 day mortality.

As many of the possible treatment comparisons have been investigated, we can use this data to test the performance of network meta-analysis by comparing the actual results with those we would have estimated if the direct comparison had not been done. I present the calculations for two comparisons: accelerated t-PA versus reteplase and accelerated t-PA versus primary angioplasty. Finally, to give a real example of the technique I show how the direct and indirect evidence comparing accelerated t-PA to primary angioplasty can be combined to give a more precise comparison than either source of evidence alone.

The comparisons of accelerated t-PA to reteplase and to angioplasty were important from a health services viewpoint as well as for clinical reasons. Reteplase can be given by bolus injection rather than IV infusion, making it more convenient for out-of-hospital administration. It was important to know whether it is at least equivalent in effectiveness to accelerated t-PA, the current U.S. standard treatment. Angioplasty, on the other hand, is substantially more expensive than thrombolysis but was expected on theoretical grounds to be more effective. Figure 5 shows the network of comparisons. The dashed lines indicate the two treatment comparisons we will be examining. Table II gives the log-odds ratio and standard error for each trial.

First we consider estimating the relative effectiveness of reteplase and accelerated t-PA from indirect evidence, as if the direct comparisons (trials 16 and 17) had not been done. This allows us to evaluate the performance of network meta-analysis in a situation where the correct results from direct randomized comparison are known. The estimated incoherence $\hat{\omega}$ is a very

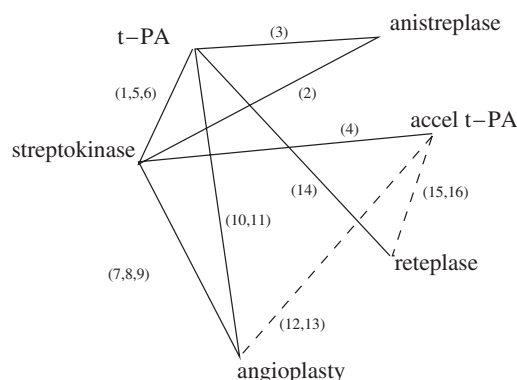


Figure 5. Network of comparisons for thrombolytics and angioplasty in acute myocardial infarction. The dashed lines are the two comparisons we will be estimating and the numbers beside each line refer to the trials in Table II that address each comparison.

Table II. Log-odds ratio and standard error for thrombolytic and angioplasty trials, and the source from which the data were obtained. A zero log-odds ratio indicates no difference, a positive one indicates a higher death rate with the second treatment.

	Treatments		log(OR)	Standard error	Source
1	streptokinase	t-PA	-0.0260	0.0394	ISIS-3
2	streptokinase	anistreplase	-0.0048	0.0392	ISIS-3
3	t-PA	anistreplase	0.0212	0.0395	ISIS-3
4	streptokinase	accelerated t-PA	-0.1727	0.0552	GUSTO
5	t-PA	streptokinase	-0.0684	0.0778	GISSI-2 Extension
6	t-PA	streptokinase	-0.0432	0.0634	GISSI-2
7	streptokinase	angioplasty	-0.122	0.6350	Grinfeld [17]
8	streptokinase	angioplasty	1.1403	1.1726	Ribeiro [18]
9	streptokinase	angioplasty	-1.3760	0.6620	Ziljstra [19]
10	t-PA	angioplasty	0.3819	0.9383	DeWood [20]
11	t-PA	angioplasty	0.1823	1.020	Gibbons [21]
12	accelerated t-PA	angioplasty	-0.2231	0.2450	GUSTO-2B [22]
13	accelerated t-PA	angioplasty	-1.2949	0.6754	Garcia [23]
14	reteplase	streptokinase	0.0588	0.0891	INJECT
15	reteplase	accelerated t-PA	-0.0337	0.0667	GUSTO III
16	reteplase	accelerated t-PA	0.7631	0.4857	RAPID-2

small 0.0085. The estimated treatment difference is $\hat{\delta}_{\text{ret,atPA}} = -0.112$, suggesting a modest advantage of accelerated t-PA. The standard error is 0.091, and after adding in the incoherence the predictive error is still 0.091. A 95 per cent confidence interval is thus $[-0.29, 0.07]$, suggesting that accelerated t-PA is more effective than reteplase. This is consistent with the actual results of GUSTO (RAPID-2 provides relatively little evidence, and mortality was not a primary outcome), which had a confidence interval of $[-0.164, -0.097]$.

We now consider the indirect comparison of accelerated t-PA and angioplasty, to compare our estimates with the direct comparisons available from trials 13 and 14. The estimated incoherence is again small: $\hat{\omega} = 0.001$. The estimated treatment difference is $\hat{\delta}_{\text{atPA,angio}} = 0.225$,

with standard error 0.377. The predictive error is also 0.377, giving a confidence interval of $[-0.96, 0.51]$.

Comparing accelerated t-PA and primary angioplasty also provides a good example of the practical use of network meta-analysis to combine direct and indirect evidence. While there are two trials comparing these treatments directly they are relatively small. On the other hand, the trials comparing different thrombolytics are very large. There is likely to be indirect evidence available from comparisons of other thrombolytics to primary angioplasty is likely to be substantial.

Combining all the trials gives $\hat{\delta}_{\text{atPA, angio}} = 0.313$, with a standard error of 0.202 and a confidence interval of $[-0.083, 0.709]$. The standard error, rather than the predictive error, is appropriate because our estimate from the direct randomized comparisons already includes $\xi_{\text{angio, atPA}}$. This estimate can be compared with the confidence interval $[-0.077, 0.799]$ from the Cochrane review, which is slightly wider because it does not include the indirect evidence. In fact, a fairer comparison would be to an analysis of the Cochrane review data using the heterogeneity model in equation (1), which gives $[-0.104, 0.799]$.

The Cochrane review also provides a narrower confidence interval $[0.062, 0.733]$ for all thrombolytics versus angioplasty. This narrower confidence interval combines the evidence from all the trials by assuming that the effects of different thrombolytics are the same. As we know from trials such as GUSTO that streptokinase and t-PA are not equivalent to accelerated t-PA this assumption cannot be strictly valid, particularly in a fixed-effects analysis. A random-effects analysis comparing all thrombolytics to angioplasty, and using the heterogeneity model in equation (1), gives a confidence interval of $[-0.108, 0.768]$, wider than the confidence interval from network meta-analysis. The network meta-analysis allows all the available information to be used without assuming that different thrombolytics are equivalent.

The reperfusion data also illustrate a minor difficulty with the structure we have presented for network meta-analysis. ISIS-3 compared three different thrombolytics: t-PA; anistreplase, and streptokinase. This means that data from ISIS-3 shows up in three lines in the network. In estimating the incoherence of network we included the incoherence between the three ISIS-3 comparisons. However, we know that the three treatment comparisons within ISIS-3 show no incoherence, since they are based on the same data. Thus the overall estimate of incoherence will be biased slightly downwards. We could have easily handled this by removing anistreplase from the meta-analysis, which does not alter the results noticeably. In some circumstances, however, a more sophisticated analysis would be necessary. This would be particularly important if one or more multi-arm trials contributed a large fraction of the evidence about a particular indirect comparison.

6. DISCUSSION

I have presented methods of estimating treatment differences between treatments that have not been directly compared in a randomized trial, and, more importantly, methods of estimating the uncertainty in these differences. These methods require information from a large number of different treatment comparisons. The resulting estimates will be less reliable than those from direct randomized comparisons, but may be useful in planning such comparisons or in cases where these direct comparisons are no longer ethically possible. To some extent this lesser reliability will already be incorporated in our error estimates via the estimated incoherence.

Coherence of the network does not of itself guarantee that the conclusions are reliable and generalizable, but it provides a useful test for some important sources of bias and allows all the available information to be integrated.

Estimating incoherence is possible only when there are closed loops in the network of comparisons, and will be reliable to the extent that the trials in these closed loops are similar to other trials. This assumption can be weakened by modelling the incoherence more flexibly, though this would require different computational methods.

Meta-analyses with large numbers of multi-armed trials present difficulties for network meta-analysis, and extensions to handle multi-armed trials correctly should be investigated.

REFERENCES

1. The European Agency for the Evaluation of Medical Products. ICH Topic E10: Choice of Control Group in Clinical Trials. 2000. Available from www.eudra.org/emea.html.
2. DuMouchel WH, Harris JE. Bayes methods for combining the results of cancer studies in humans and other species (c/r: P308-315). *Journal of the American Statistical Association* 1983; **78**:293–308.
3. Daniels MJ, Hughes MD. Meta-analysis for the evaluation of potential surrogate markers. *Statistics in Medicine* 1997; **16**:1965–1982.
4. Buyse M, Molenberghs G. The validation of surrogate endpoints in randomized experiments. *Biometrics* 1998; **54**:1014–1029.
5. Pinheiro JC, Bates DM. *Mixed Models in S and S-PLUS*. Springer: New York, 2000.
6. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986; **7**:177–188.
7. Gilks WR, Thomas A, Spiegelhalter DJ. A language and program for complex Bayesian modelling. *Statistician* 1994; **43**:169–178.
8. Spiegelhalter DJ, Thomas A, Best NG. *WinBUGS Version 1.2 User Manual*. MRC Biostatistics Unit: Cambridge, 1999.
9. Cucherat M, Bonnefoy E, Tremeau G. Primary angioplasty versus intravenous thrombolysis for acute myocardial infarction (Cochrane Review). In *The Cochrane Library*. Update Software: Oxford, 2000.
10. ISIS-3 Collaborative Group. A randomized comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992; **339**:753–770.
11. GISSI-2. A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 1990; **336**:65–71.
12. The International Study Group. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with and without heparin. *Lancet* 1990; **336**:71–75.
13. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *New England Journal of Medicine* 1993; **329**:673–682.
14. The GUSTO III Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *New England Journal of Medicine* 1997; **337**:1118–1123.
15. International Joint Efficacy Comparison Thrombolytics. Randomized, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. *Lancet* 1995; **346**:329–336.
16. The RAPID II Investigators. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. *Circulation* 1996; **94**:891–898.
17. Grinfeld L, Berrocal D, Belardi J, Spinetta A, Rojas Matas C, Oberti P, Doval H, Bazzino O, Cagide A. Fibrinolytics vs primary angioplasty in acute myocardial infarction (fap): A randomized trial in a community hospital in Argentina. *Journal of the American College of Cardiology* 1996; **27**:222A.
18. Ribeiro EE, Silve LA, Carneiro R, D'Oliviera LG, Gasquez A, Amino JG, Tavares JR, Petrizzo A, Torossian S, Duprat Filho R. Randomized trial of direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction. *Journal of the American College of Cardiology* 1993; **22**:376–380.
19. Zijlstra F, Beukema WP, van't Hof AWJ, Liem A, Rieffers S, Hoortnne JCA, Suryapranata H, de Boer, MJ. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. *Journal of the American College of Cardiology* 1997; **29**:908–A912.
20. DeWood MA, Fisher MJ. Direct PTCA versus intravenous rt-PA in acute myocardial infarction: Preliminary results from a prospective randomized trial. *Circulation* 1989; **80**(S2):418.

21. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. *New England Journal of Medicine* 1993; **328**:685–691.
22. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) angioplasty substudy investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *New England Journal of Medicine* 1997; **336**: 1621–1628.
23. Garcia E, Elizaga J, Soriano J *et al.* Primary angioplasty versus thrombolysis with t-PA in the anterior myocardial infarction. *Journal of the American College of Cardiology* 1997; **29**:A235–A236.