

*Canadian Agency for
Drugs and Technologies
in Health*

*Agence canadienne
des médicaments et des
technologies de la santé*

HTA

**USER GUIDE —
Indirect Treatment Comparison**

MARCH 2009

Supporting Informed Decisions

Canadian Agency for Drugs and Technologies in Health

Indirect Treatment Comparison

USER GUIDE

March 2009

The software described in this user manual was developed by George Wells, Shagufta A. Sultan, Li Chen, Maryam Khan, and Doug Coyle.

References to the software can be cited as: Wells GA, Sultan SA, Chen L, Khan M, Coyle D. Indirect treatment comparison [computer program]. Version 1.0. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

Further reference to the appropriate use of this software can be found in the CADTH Report Wells GA, Sultan SA, Chen L, Khan M, Coyle D. *Indirect evidence: indirect treatment comparisons in meta-analysis*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

We would like to thank Jenny Mehan for writing the user manual.

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ABOUT THIS GUIDE

Introduction

The ITC User Guide has been prepared to assist in the use of the ITC application. It describes:

- The theory behind the development of the ITC application
- The components of the ITC application
- A detailed example of use.

Audience

This user guide assumes that the user is familiar with the theory and methodology surrounding indirect treatment comparisons.

Conventions

The conventions used in this document are:

NOTE

Means “Reader, take note.” Notes contain helpful suggestions or background information.



CAUTION

Means “Reader, be careful. Loss of data can result from your actions.”



HINT

Alerts the reader to a helpful tip, suggestion, or example.

Related Documentation

Wells GA, Sultan SA, Chen L, Khan M, Coyle D. *Indirect evidence: indirect treatment comparisons in meta-analysis*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

Technical Support

For assistance with the ITC application, please contact your designated support person.

1 INTRODUCTION

1.1 Overview

1.1.1 Introduction

This chapter provides background information about indirect treatment comparisons and an introduction to the methodology behind the ITC application.

1.1.2 In this chapter

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1.2 Indirect Treatment Comparison

1.2.1 Background

When comparing treatment interventions, the need for indirect approaches is increasing. A direct assessment of interventions A and B is available if a randomized controlled trial of A versus B has been conducted. However, many competing interventions have not been compared directly and/or such direct evidence is limited and insufficient. The reasons for lack of a direct comparison vary.

More complex indirect evidence settings can arise. In the next simplest setting, we may have direct evidence from A versus C, B versus D, and C versus D. Using this evidence, we can attempt an indirect comparison of A versus B using, in particular, the direct evidence of C versus D. Even in the situation of A versus C, B versus C, D versus C, and D versus F, treatment F can be an important contributor to the indirect comparison of A versus B. The web of direct and indirect evidence can be complex.

Within this web of evidence, there is often a need to synthesize evidence from randomized controlled trials, and methods for deriving indirect treatment comparisons using meta-analysis are of prime interest.

1.2.2 Methodology

The Bucher et al. (1997) method has been widely used for making indirect comparisons. The approach is pragmatic, and the assumption of independence among trials often holds in settings where the direct comparison between treatments is not available and one needs to use results (possibly from meta-analysis) from non-overlapping treatment pairs. These indirect approaches have recently been applied in published meta-analyses by Yazdanpanah et al. (2004) and Lim et al. (2003).

For discrete outcomes, expanding the indirect odds ratio approach by Bucher et al. (1997) for more complex webs of evidence involving any number of direct comparisons was considered. This generalized approach was then considered for the relative risk (RR), hazard ratio, risk difference, and mean difference. The ITC software application has been developed to assist analysts in applying this expanded approach.

2 USING THE ITC APPLICATION

2.1 Overview

2.1.1 Introduction

This chapter introduces the user interface and basic functionality of the ITC application.

2.1.2 In this chapter

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2.2 Starting the ITC Application

2.2.1 Introduction

The ITC application is launched either from the disk or from your desktop.

- Locate and double-click the ITC application icon.



2.3 User Interface

2.3.1 Introduction

The ITC application has been developed in Visual Basic to assist with various calculations associated with indirect comparisons.



When entering data, you can tab from one cell to the next.

2.3.2 Screen 1: Main window

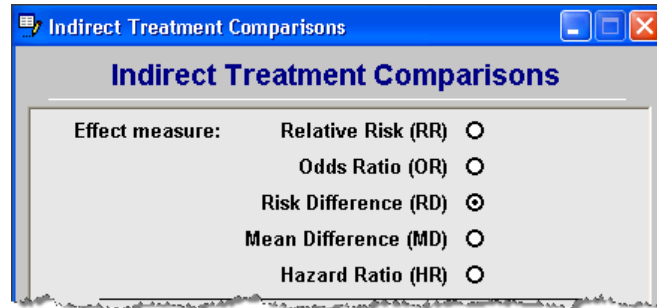
The ITC application consists of two windows. On the first window, the effect measure of interest is identified. Information for each consecutive pair of treatments is entered in terms of the point estimate and 95% confidence interval (CI) of the effect measure for each direct comparison involved in the indirect comparison. The resulting indirect comparison estimates for the effect measure and the 95% CI as well as the P value for the test of association corresponding to this effect measure are provided.

Figure 1: Main Window

	Estimate	95% LCL	95% UCL	Reverse
(1,2)				<input type="checkbox"/>
(2,3)				<input type="checkbox"/>
(3,4)				<input type="checkbox"/>
(4,5)				<input type="checkbox"/>
(5,6)				<input type="checkbox"/>
(6,7)				<input type="checkbox"/>
(7,8)				<input type="checkbox"/>
(8,9)				<input type="checkbox"/>
(9,10)				<input type="checkbox"/>

2.3.3 Effect measure

- The desired **Effect measure** is chosen by selecting the corresponding option button.



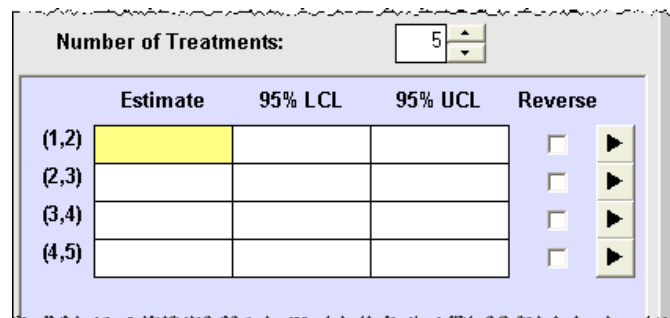
2.3.4 Number of treatments

- The **Number of Treatments** (k) is entered by typing directly in the appropriate field or by using the arrows to scroll to the desired value. The highest number you may enter is 10.
- For each consecutive pair of treatments, provide the direct estimates of the measure of association and the 95% lower confidence limit (95% LCL) and 95% upper confidence limit (95% UCL).

The order of entry of the treatment pairs must follow the exact sequence indicated with the bridging comparison groups linking the treatment pairs.

- To reverse the order of a treatment comparison, select the appropriate checkbox.

For example, if 1 = Treatment A, 2 = Treatment B, and 3 = Treatment C, then (1,2) is (A,B), and for (2,3) we can enter (C,B) and use the reverse option to switch it to (B,C). This option can be useful when B is a placebo and the results are given as the active treatment versus placebo (i.e., A versus Placebo[B] and C versus Placebo[B]).



2.3.5 Toolbars

The toolbars on the main window allow you to calculate, clear, import, and save your data as well as exit the application.

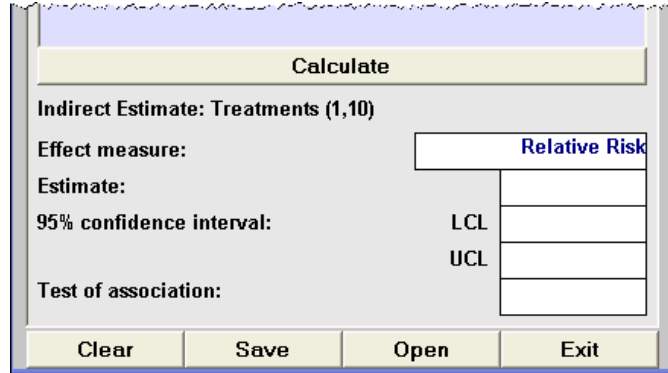
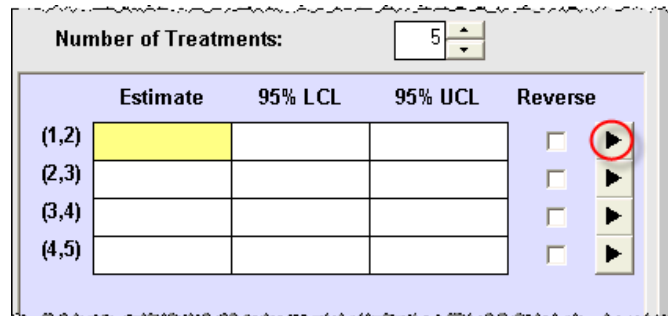


Table 1: Main Window Toolbars	
Button	Description
Calculate	When all data has been entered, returns the desired calculations.
Clear	Clears all data from the main window.
Save	Allows the user to save the data (*.txt file).
Open	Allows the user to import previously saved data.
Exit	Closes the application without saving the data.

2.3.6 Screen 2: Requested weights window

If the test of association is needed, the weights used for the calculation of each weighted average estimate from the main window are required for its calculation. The requested weights window is accessed by clicking the arrow to the right of the corresponding information for each consecutive pair of treatments.



The requested weights window calculates the weighted effect measure for the direct comparison on the main window. These weights are needed to calculate the test statistic for the test of association. There are various formats in which the information to calculate these weights can be provided, and these formats are identified through the weight selections (direct versus derived; fixed versus random), and the specific information for each study involved in the direct comparison is then identified and requested.

- For a direct treatment (i, i + 1), enter the number of studies on which the estimate is based by typing directly in the corresponding field or by using the arrows to scroll to the desired value. The highest number you may enter is 20.
- The desired **Weight** is chosen by selecting the corresponding option button.
 - The option is available to enter the weights directly. In particular, if the effect estimate is based on one study, then a single weight of 1 can be entered.
 - The weights can also be computed from first principles, based on the frequencies (for RR, odds ratio, and risk difference) or the standard errors (for mean difference), using either the fixed or random effects model, or the general inverse method.

Figure 2: Requested Weights Window

2.3.7 Toolbar

The toolbar on the requested weights window allows you to save your data and close the window, or clear your data.

Table 2: Requested Weights Window Toolbar	
Button	Description
Close	Saves data and closes the window.
Clear	Clears all data from the window.

3 EXAMPLE

3.1 Overview

3.1.1 Introduction

This chapter provides an in-depth walk-through of a worked example detailing the clinical-effectiveness of pharmacological interventions for preventing fractures.

3.1.2 In this chapter

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3.2 Overview

Osteoporosis is associated with important medical, social, and financial implications, and its incidence is expected to increase significantly as the Canadian population ages. Many of the consequences of osteoporosis are potentially lessened through the use of a number of non-pharmacological and pharmacological interventions. The oral bisphosphonate drugs etidronate, alendronate, and risedronate have been introduced as pharmacological options for the primary and secondary prevention of osteoporotic fractures.

We have conducted a systematic review assessing the clinical-effectiveness of etidronate, alendronate, and risedronate in the primary and secondary prevention of osteoporotic fractures in postmenopausal women receiving these agents compared with untreated women over a follow-up period of at least one year. A systematic literature search of the evidence from randomized placebo-controlled trials of each of the three drugs was conducted using a standardized Cochrane Collaboration approach to literature search, article selection, data extraction, and quality assessment. Clinical data analysis was conducted according to the methodology of the Cochrane Collaboration for systematic reviews and meta-analyses.

Considering the data available for the longest treatment duration in the trials and using the follow-up denominators for the number of patients in the trial, a detailed worked example will be considered. For this detailed worked example, the weighted RR effect estimates of fracture after treatment with the bisphosphonates alendronate and etidronate compared with placebo will be used to derive an indirect estimate. The indirect treatment comparison method will be used to evaluate the head-to-head comparison of alendronate to etidronate, using the placebo as the bridging group in the one-step comparison (i.e., $k = 3$).

3.3 Step 1: Effect Measure and Number of Treatments

In the main window, the effect measure of interest is identified, and information for each consecutive pair of treatments of interest is requested in terms of the point estimate and 95% CI of the effect measure for each direct comparison involved in the indirect comparison.

The effect measure of interest is the **Relative Risk (RR)**, which is chosen by selecting the corresponding option button.

There are three treatments involved in this indirect comparison — alendronate, etidronate, and placebo — and the number 3 is entered in the **Number of Treatments** field.

For each consecutive pair of treatments, the direct estimates of the measure of association and the 95% LCL and UCL must be provided. The order of entry of the treatment pairs must follow the exact sequence indicated with the bridging comparison groups linking the treatment pairs. The interest here is to compare alendronate with placebo and then placebo with etidronate and, in so doing, use placebo as the bridging comparison group.

Indirect Treatment Comparisons

Indirect Treatment Comparisons

Effect measure: **Relative Risk (RR)**
Odds Ratio (OR)
Risk Difference (RD)
Mean Difference (MD)
Hazard Ratio (HR)

Number of Treatments:

	Estimate	95% LCL	95% UCL	Reverse
(1,2)				<input type="checkbox"/> ▶
(2,3)				<input type="checkbox"/> ▶

Calculate

Indirect Estimate: Treatments (1,10)

Effect measure: **Relative Risk**

Estimate:

95% confidence interval: LCL
UCL

Test of association:

Clear Save Open Exit

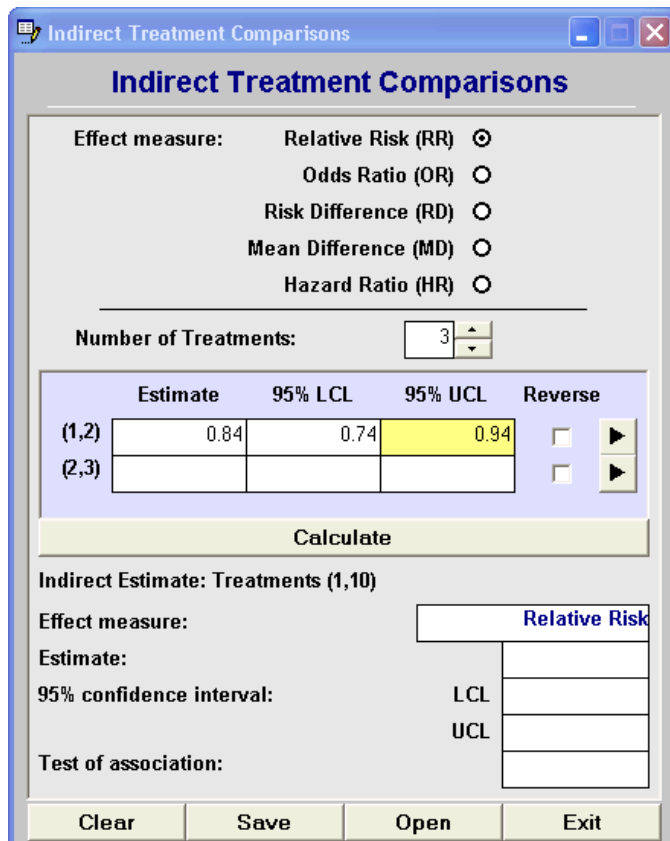
3.4 Step 2: Comparing Alendronate with Placebo

A systematic review was conducted for trials that compared alendronate with placebo for primary or secondary prevention. Non-vertebral fractures were reported in eight trials. One trial did not report fractures separately by treatment groups, and one trial reported that no fractures occurred in either treatment group.

The pooled estimate of the RR of non-vertebral fractures from the five trials that could be analyzed demonstrated a significant reduction (16%) in non-vertebral fractures (RR: 0.84 [95% CI 0.74 to 0.94]).

The direct estimate from this meta-analysis for the RR (0.84) and the 95% lower confidence limit (0.74) and 95% upper confidence limit (0.94) are entered on the first direct comparison line (1 = alendronate, 2 = placebo).

To request the weights used for calculating the weighted effect measure for the direct comparison, the arrow to the right of the (1,2) line is clicked. If the test of association is not of interest, this step can be skipped.



3.5 Step 2a: Weighted Effect Measure (1,2)

The pooled estimate of the RR of non-vertebral fractures (RR 0.84, 95% CI 0.74 to 0.94) was based on five trials. To calculate the weights that were used for this weighted RR risk, the **Derived** option and the **Fixed effect** option are selected because heterogeneity was not an issue.

Rates for the treatment and control groups for each study are requested in the form of numerator (number of events) / denominator (number of subjects). From the systematic review:

Treatment (n/N)	Control (n/N)
122/1022	148/1005
261/2214	294/2218
3/46	1/45
45/500	38/332
19/792	37/841

These results are entered in the corresponding lines provided. Click **Close** to save the entries and close the window.

Number of Studies: 5

Weights: Direct Fixed effect
 Derived Random effect
 General inverse method

	Treatment		Control	
	Events	Subjects	Events	Subjects
1	122	1022	148	1005
2	261	2214	294	2218
3	3	46	1	45
4	45	500	38	332
5	19	792	37	841

Close Clear

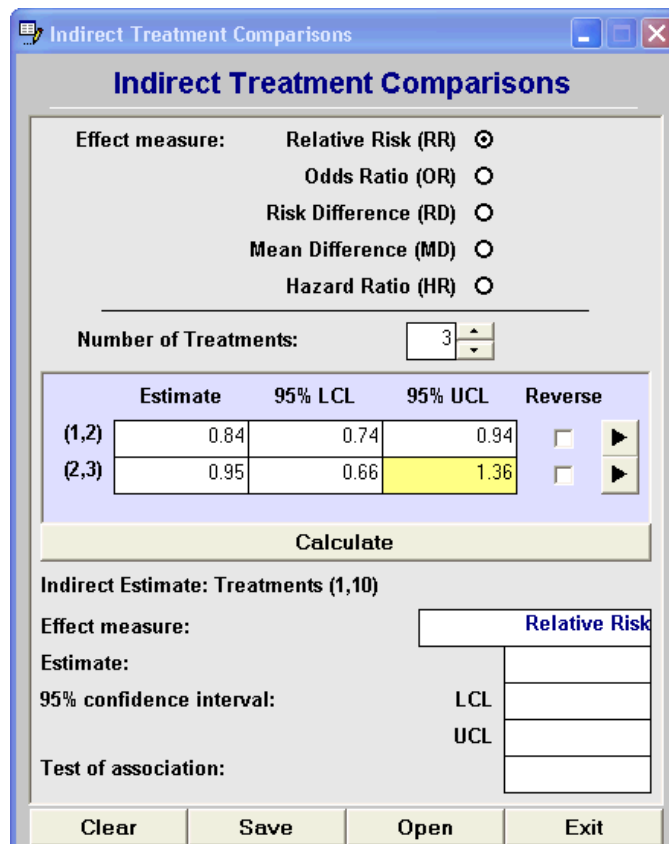
3.6 Step 3: Comparing Etidronate with Placebo

A systematic review was conducted for trials that compared etidronate with placebo for primary or secondary prevention. Non-vertebral fractures were reported in seven trials.

The pooled estimate of the RR of non-vertebral fractures from the seven trials indicated a lack of effect of etidronate on non-vertebral fractures. The 95% CI around the RR estimate for all non-vertebral fractures was wide with a relative risk reduction of approximately 32% and a relative risk reduction increase of 42% (RR 0.95, 95% CI 0.66 to 1.36). Results were consistent across the seven trials.

The direct estimate from this meta-analysis for the RR (0.95) and the 95% lower confidence limit (0.66) and 95% upper confidence limit (1.36) are entered on the second direct comparison. The results entered compare etidronate with placebo. By selecting **Reverse**, the results will be reversed so placebo is compared with etidronate and the (2,3) will correspond to (2 = placebo, 3 = etidronate).

To request the weights used for calculating the weighted effect measure for the direct comparison, the arrow to the right of the (2,3) line is clicked. If the test of association is not of interest, this step can be skipped.



3.7 Step 3a: Weighted Effect Measure (2,3)

The pooled estimate of the RR of non-vertebral fractures (RR 0.95, 95% CI 0.66 to 1.36) was based on seven trials. To calculate the weights that were used for this weighted RR, the **Derived** option and the **Fixed effect** option are selected because heterogeneity was not an issue.

Rates for the treatment and control groups for each study are requested in the form of numerator (number of events) / denominator (number of subjects). From the systematic review:

Treatment (n/N)	Control (n/N)
3/39	5/35
2/25	3/24
3/45	6/46
5/20	6/20
20/92	16/89
14/93	12/89
1/14	1/14

These results are entered in the corresponding lines provided. Click **Close** to save the entries and close the window.

Number of Studies:

Weights: Direct Fixed effect
 Derived Random effect
 General inverse method

	Treatment		Control	
	Events	Subjects	Events	Subjects
1	3	39	5	35
2	2	25	3	24
3	3	45	6	46
4	5	20	6	20
5	20	92	16	89
6	14	93	12	89
7	1	14	1	14

Close Clear

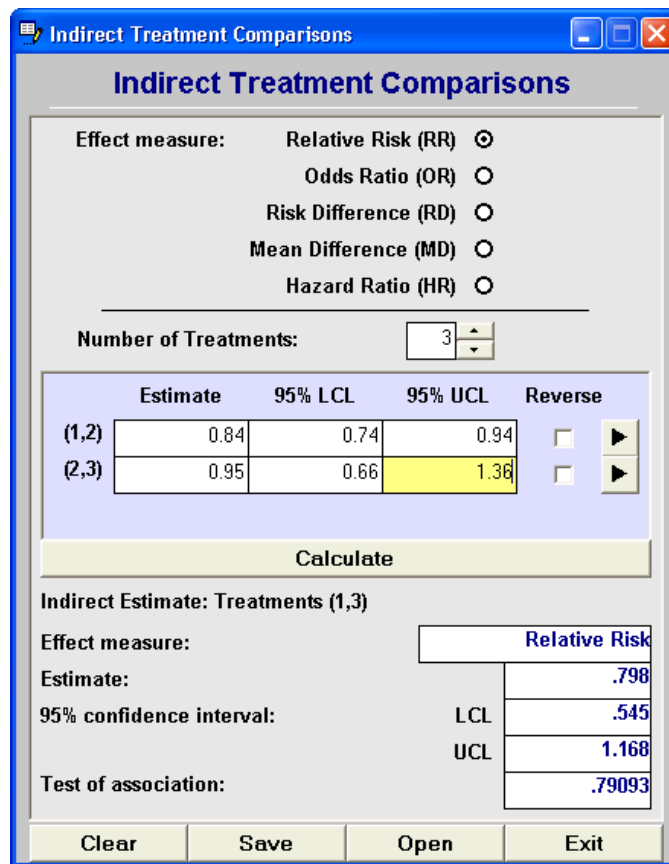
3.8 Step 4: Calculating Results

Once all the data are entered, the resulting indirect comparison estimates for the effect measure and the 95% CI as well as the P value for the test of association corresponding to this effect measure are provided in the main window for the comparison of treatments (1,3) using treatment 2 as the bridging comparison.

When all data is entered, click **Calculate**.

The indirect treatment effect estimate for the RR of alendronate compared with etidronate was 0.88 with the 95% CI (0.60 to 1.29). The result indicates that alendronate and etidronate are not significantly different. This is confirmed with the P value for the test of association of 0.79.

To save these results to a .txt file, click **Save**.



4 GLOSSARY

CI	confidence interval
ITC	Indirect Treatment Comparison
LCL	lower confidence limit
OR	odds ratio
RR	relative risk
UCL	upper confidence limit