TRAINING MANUAL FOR HANDSEARCHERS

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Training Manual for Handsearchers
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PDF Version

FOREWORD

The aims of the Cochrane Collaboration are "preparing, maintaining and promoting the accessibility of the effects of health care." Before one can prepare a systematic review, one has to find the relevant research reports; in the case of the Cochrane Collaboration, this usually means reports of randomized and possibly randomized clinical trials.[1] This is never an easy task.[2,3] Cochrane reviewers rely on several means of searching for relevant reports, including both electronic and manual methods. For complete identification of published reports, there appears to be no alternative to a page-by-page search of the healthcare literature ("handsearching"). This Manual is designed to provide written training materials for those planning to engage in handsearching.

The Manual sections are written primarily with members of Cochrane Centers, Collaborative Review Groups, Fields, and Networks in mind, but we hope that the information presented will be helpful to all involved with searching for trials. The Manual is divided into the following sections:

- **Section 1: Introduction**
  Describes the rationale for the creation of the Cochrane Collaboration and the development of the Cochrane CENTRAL Register of Controlled Trials ("CENTRAL" for short), the Cochrane Collaboration's source of trial reports, and introduces the Cochrane Collaboration classifications of trials eligible for inclusion in CENTRAL;

- **Section 2: Identifying and Classifying Trial Reports Eligible for CENTRAL**
  Describes where in journal articles the information needed for identification and classification of trial reports may be found, and outlines the step-by-step decision making necessary in identification and classification for trial reports eligible for CENTRAL;

- **Sections 3: Self-Assessment Exercise with Abstract Examples**
  Provides a self-assessment exercise in identifying and classifying trial reports eligible for CENTRAL from abstracts;

- **Section 4: Self-Assessment Exercise with Full-Text Article Examples**
  Provides a self-assessment exercise in identifying and classifying trial reports eligible for CENTRAL from full-text examples;

- **Section 5: Handsearching Test**
  Tests the trainees ability to identify and classify trial reports eligible for CENTRAL by handsearching a full issue of a journal and a sample of conference abstracts;

- **Appendix A: Cochrane Collaboration Criteria for Classification of Reports of Randomized Controlled Trials (RCTs) and Controlled Clinical Trials (CCTs)**
  A detailed description of rules for classification of trial reports for inclusion in CENTRAL;

- **Appendix B: Glossary**
  A glossary of terms relevant to study design and report classification;

- **Appendix C: Handsearcher Training Manual Evaluation**
  An assessment of the strengths and weaknesses of this training manual, to be completed by the trainee after training is completed.

A training manual for handsearchers called the Cochrane Handsearch Manual: Overview of Searching Activities was originally written by Kay Dickersin and Kristen Larson in 1994. Suzanne Brodney and Susan Wieland coordinated this version of the Training Manual for Handsearchers (2002), which has been largely rewritten, incorporating some material from the original Cochrane Handsearch Manual and other material presented at Cochrane Colloquia (2000 and 2001) handsearcher training workshops facilitated by Susan Wieland and Eric Manheimer. Pam Sieving provided many useful suggestions to this version of the Training Manual for Handsearchers.

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OBJECTIVES

After completing the Training Manual for Handsearchers, the participant will:

1. Understand the rationale for the development of the Cochrane CENTRAL Register of Controlled Trials;

2. Understand the difference between a randomized controlled trial and a controlled clinical trial;

3. Be able to handsearch a print journal, or review report abstracts, to identify and classify reports of controlled trials;

4. Be able to correctly distinguish between eligible and ineligible reports of studies for the Cochrane CENTRAL Register of Controlled Trials, and to classify these reports as RCT or CCT or neither.

1. INTRODUCTION

"Progress, far from consisting of change, depends on retentiveness... Those who cannot remember the past are condemned to repeat it." George Santayana (1905)

1.1 The importance of systematic reviews

Over the past twenty years we have witnessed a rapid growth in health care information. There are over 20,000 journals catering to the health care community. Every month, clinicians, policy makers and patients face a deluge of evidence from published reports of new trials. These reports have become so numerous and are so widely dispersed that it is unreasonable to expect people to have read them all and retained the information they contain. Most health care providers report that they rely on reviews of primary research, and the summary recommendations they offer.

Although reviews occupy a key position in the chain which links the results of primary research to improved outcomes in health care, the quality of many reviews leaves much to be desired. Many reviewers do not approach their task systematically, with a respect for scientific principles, in particular the control of bias and random error. Because of the poor quality of some reviews, advice on some highly effective forms of health care has been delayed for years, while other forms of care have continued to be recommended long after controlled research has shown them to be either ineffective or actually harmful.[4] With the growing demand that clinical practice should be evidence-based, the adoption of *systematic reviews* - research summaries that use objective, reproducible methods to identify eligible studies and to abstract and analyze relevant data - should provide the most useful mechanism for assessing the value of the evidence derived from research.

1.2 The Cochrane Collaboration

The Cochrane Collaboration was established in 1993 in response to the need for systematic, up-to-date reviews of health care interventions.[5,6] This worldwide partnership currently includes over 5,000 individuals, many or most of whom are volunteers, and counts among its supporters public and private, large and small, local, regional, national, and international organizations.

The Cochrane Collaboration is composed of several different types of organizational entities: the Collaborative Review Groups (CRGs), the Fields, the Consumer Network, the Methods Groups, and the Centers. Preparing and maintaining systematic reviews is coordinated by 49 CRGs, each focusing on a specific area of health and health care. Members of Fields may also contribute to systematic reviews; their main role is to ensure coverage of the many health topics that should be covered by multiple CRGs, such as Complementary Medicine, Health Care

of Older Persons, and Primary Care. The Consumer Network ensures the involvement of consumers in all aspects of the Collaboration, including the preparation and maintenance of reviews. The Methods Groups (e.g, Diagnostic Testing, Statistical Methods) develop the methods used for the systematic reviews. The main regional organizational units of the Collaboration are the 14 international Cochrane Centers. The general functions of the Centers are to train contributors, maintain a directory of people contributing to or interested in the Collaboration, to help to establish review groups, to coordinate contributions to the creation and maintenance of a comprehensive register of controlled trials, and to foster research to improve the quality of systematic reviews. Additional information about the Cochrane Collaboration is available at the Collaboration website at www.cochrane.org.

1.3 The Need for a Centralized Register of Clinical Trials

A necessary starting point for performing systematic reviews of health care interventions is identification of the maximum possible number of potentially relevant clinical trials, research studies that assess an intervention's efficacy. The *randomized controlled trial* (RCT), where patients are assigned to an intervention based on a formal method that relies on "chance" and is similar to flipping a coin, has emerged as the mostly highly regarded tool for critical evaluation of the effects of health care. Thus RCTs are the preferred source of data for systematic reviews of health care interventions.

Complete identification of trials for a systematic review, even when fully published reports are available, continues to be remarkably difficult. The process is time consuming and inefficient, and no single database has contained reports of trials for all languages and from all print sources.[7,8] At the time the Cochrane Collaboration was formed, it was recognized that a centralized trials register was needed to ensure that Cochrane CRGs had access to all possibly relevant trials.

1.4 The Cochrane Collaboration's CENTRAL Register of Controlled Trials

The Collaboration's approach is to assure that all trials identified by the CRGs and other entities, whether relevant to the Group's particular area of study or not, are contributed to a centralized trials register for general dissemination. This register is called the Cochrane Collaboration's CENTRAL Register of Controlled Trials, or "CENTRAL."

1.5 Cochrane Criteria for Inclusion of a Report in CENTRAL

To ensure comprehensive coverage of all trials in CENTRAL, the Collaboration's goal is to be as "sensitive" as possible, that is, to include all trials that are definitely or possibly randomized or quasi-randomized. The Cochrane Collaboration eligibility criteria were devised and agreed upon in November 1992,[9] and were first published, in 1994, in Section 5 of the Cochrane Handbook. These criteria are now included as Appendix 5b.1 of the Cochrane Reviewer's Handbook. According to these eligibility criteria:

> A trial is eligible if, on the basis of the best available information (usually from one or more published reports), it is judged that:
>
> The individuals (or other units) followed in the trial were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using:
>
> - random allocation; or
> - some quasi-random method of allocation (such as alternation, date of birth, or case record number).

In addition, at this meeting it was decided that reports of trials dealing only with animals should not be included in CENTRAL.

1.6 Classification of Eligible Trial Reports

Trial reports included in CENTRAL are classified according to the degree of certainty that random allocation was used to form the comparison groups in the trial. If the author(s) state explicitly (usually by using some variant of the term "random" to describe the allocation procedure used) that the groups compared in the trial were established by random allocation, then the trial is classified as "RCT" (randomized controlled trial). All other eligible trial reports are classified as "CCT" (controlled clinical trial).

Trial reports classified as CCTs belong to one of two categories. The first category consists of trial reports in which the method of allocation is known but is considered to be quasi-random (e.g., use of alternation) rather than strictly random. The second category includes trial reports in which the method of allocation cannot be clearly understood from the report but may possibly be either random or quasi-random. Note that the term "controlled clinical trial" is generally used to refer to a clinical trial with a comparison group for whom the intervention is administered and data are collected concurrently with the intervention group. This term is used more specifically, however, when reports included in CENTRAL are at issue, as described

above.

1.7 How Trials are Identified for CENTRAL

Trial reports are identified for CENTRAL in two major ways. First, the Collaboration relies on identifying trial reports the US National Library of Medicine (NLM) has classified as RCTs and CCTs in MEDLINE. (Note that MEDLINE definitions of RCT and CCT are slightly different from Cochrane definitions, but they are similar enough for our purposes.)

The Cochrane Collaboration, in turn, works with the NLM to identify and help index articles in MEDLINE with the terms RANDOMIZED CLINICAL TRIAL (PT) [RCT] and CONTROLLED CLINICAL TRIAL (PT) [CCT], through the efforts of the New England Cochrane Center Providence Office. The Cochrane Collaboration then searches MEDLINE periodically for RCTS and CCTs and updates CENTRAL with newly identified RCTs and CCTs.

The second major way in which trial reports are identified for CENTRAL is that Cochrane contributors, volunteers and journal editors search individual journals and other publications, using both electronic (MEDLINE, EMBASE and other bibliographic databases) and handsearching methods. CRGs, Fields and Networks are responsible for searching the specialist literature in their particular area of interest, while Cochrane Centers are responsible for searching the general medical literature published in their country or region. The New England Cochrane Center Providence Office is responsible for overall coordination of Cochrane search efforts.

2. IDENTIFYING AND CLASSIFYING TRIAL REPORTS ELIGIBLE FOR CENTRAL

The purpose of this chapter is to provide a Training Manual for handsearchers and to provide a resource for future use. It describes briefly how to read an article to identify key terms and concepts that will allow classifying the design of the research it describes. A glossary of the terms used in this section is attached as Appendix B, and should be referred to when an unfamiliar term is encountered.

Generally speaking, healthcare journals require their authors to present original research findings in articles having the following sections in the following sequence: Title - Summary or Abstract - Introduction - Methods - Results - Discussion - References. However, this has not always been the case, and editorial practices have varied widely over the years and from journal to journal. **As a searcher, you will rarely need to read an entire article all the way through.** Often, reading through the Title, Summary/Abstract and Methods sections will be sufficient to tell you whether or not a trial report meets the criteria for inclusion in CENTRAL. You need only read each article to the point where it is possible to make a decision about the eligibility and classification of the study report.

The sections below are a guide to the sequence of decisions you need to make when you decide 1) whether or not a published report of a study is eligible for CENTRAL, and 2) whether an eligible report should be classified as an RCT or CCT.

2.1 Are the participants in the study living human beings?

Participants in trials eligible for inclusion in CENTRAL must be living human beings. Therefore, studies that are performed solely with non-human animals, *in vitro*, or as simulation exercises are not eligible for inclusion in CENTRAL. Common examples of studies that are not eligible in this regard are studies carried out in cadavers or on detached body parts, such as extracted teeth, that are not replaced in living humans. If the participants in the study are living human beings, or body parts that are incorporated into living human beings (eg, corneas) the study report may be eligible for inclusion in CENTRAL.

2.2 Does the study concern an intervention related to health care?

All trial reports eligible for inclusion in CENTRAL must involve an intervention related to health care. Some examples are treatments used to treat physical or mental diseases, prevention regimens, screening programs, and diagnostic tests. However, even where a study has been performed in healthy people and may not concern health care directly, it should be included in CENTRAL if it contains information that is relevant to the evaluation of a health care intervention. Thus, the subject of the study may be an evaluation of medication side effects carried out in healthy volunteers, or an intervention designed to affect athletic performance.

Some other examples of interventions that are eligible for inclusion in CENTRAL are interventions designed to determine outcomes related to medical education, medical costs, or the carrying out of health research.

If the study is carried out in living human beings and is a healthcare intervention, the study report may be eligible for inclusion in CENTRAL.

2.3 Is the study experimental?

Reports of experimental studies, but not observational studies, are eligible for inclusion in CENTRAL. Observational studies are studies in which the investigator observes and does not alter the participant's experience in any way. For example, an observational study may follow all patients in a given medical practice who get a new surgery and compare them to those who were not. Examples of observational designs are follow-up studies, case series, case-control studies, and cohort studies (see Appendix B: Glossary). Observational studies are the most common type of clinical and epidemiological research.

Experimental studies are studies in which the investigator manipulates some factor within the study in order to observe the effect of the manipulation.[10] Whereas investigators in an observational study might review the records of patients who received a new medication in order to assess how the patients fared on the medication, investigators in an experimental study would assign patients to take a new medication as part of a preplanned trial, and then assess how the patients fared on the medication. Even if the investigators themselves gave the new medication to the patients, and later decided to study the results of the medication regimen, the study would be considered observational unless the investigators assigned patients to take the new medication as part of a preplanned trial.

If the study is carried out in living human beings, is a healthcare intervention, and is experimental, the study report may be eligible for inclusion in CENTRAL.

2.4 Does the study include a comparison intervention?

Only reports of controlled trials, that is, studies that incorporate a comparison intervention group within the study as a basis for evaluating the effects of the intervention of interest, are eligible for inclusion in CENTRAL. Reports of uncontrolled trials, that is, studies that contain only a single intervention, are not eligible for inclusion in CENTRAL.

An example of an uncontrolled trial is when investigators give a new treatment, such as counseling for behavior change, to a group of participants, then assess whether participants changed their behavior and had the desired outcome. In a controlled trial, investigators assign

one group of participants to counseling and assign a second group of participants to another intervention (say standard care), then compare the outcomes for the two groups. If the conduct of the study includes only one intervention group, the study is not a controlled trial and thus is not eligible for inclusion in CENTRAL.

Sometimes a report will say in the title that the study is "noncomparative" or "uncontrolled". In these cases, the abstract or methods sections should still be read in order to confirm that only one intervention was included in the study.

Generally, a controlled trial requires concurrent enrollment, intervention, and followup of all participants. For example, if investigators enroll one group of patients into their study and give them a new medication, and later enroll a second group of patients into their study and give that group a different medication, the two groups are not concurrent and the study thus is not eligible for inclusion in CENTRAL. Frequently, investigators will compare the experience of study participants to that of a historical cohort (ie, a similar group of individuals from the past). Because the historical comparison group is not concurrently enrolled, treated, and followed with the study participants, the study is not considered to be a controlled trial.

An example of a controlled trial in which participants receive interventions at different times is a "crossover trial." In a crossover trial, patients are allocated to receive two or more interventions (which could be a period with no intervention) in a specified order. Crossover trials are eligible for inclusion in CENTRAL.

If the study is carried out in living human beings, is a healthcare intervention, is experimental, and controlled (i.e contains at least one comparison intervention given concurrently with the test intervention, or using a crossover design), the study report may be eligible for inclusion in CENTRAL.

2.5 How were the different intervention groups created?

Trial reports eligible for inclusion in CENTRAL must have definitely or possibly used some form of randomization or quasi-randomization to form the different intervention groups.

2.5.1 Were participants definitely assigned to interventions using randomization?

Randomization is the assignment of a study participant to an intervention using a random process or method.[11] The purpose of randomization is to achieve an unbiased distribution of participants across intervention groups. Specific methods of *randomization* include the use of a table of random numbers or its electronic equivalent, a pseudo-random generator. Methods for concealing the next assignment from the person enrolling study participants include sequentially ordered vials, a telephone call to a central office, or a pre-ordered list of treatment assignments.

The method of *randomization* is distinguished from the way in which the next assignment is concealed from the person enrolling study participants. For instance, a computer may generate a random sequence of treatments which are in turn assigned to the study participants, using pre-ordered sealed envelopes. The method of randomization in this case is by computer, and the way in which the next assignment is concealed from the person enrolling study participants is pre-ordered sealed envelopes. Random assignment to interventions is indicated in a trial report by the use of phrases such as "randomly assigned", "randomly allocated", "randomized", or some other variant of the term "random" in the discussion of participant assignments to intervention. If the report does not use some variant of the term "random" it cannot be assumed that randomization was used.

Note that the term "randomly *selected*" indicates that some method of random sampling was used to select participants for a study from a larger pool of eligible individuals. This does *not* imply random *allocation* of those participants to treatment and comparison groups within the study. Occasionally, an author will use "randomly *selected*" in the sense of "*randomly selected to serve in a treatment or control group*". In this case, the author is using the term to mean "randomly *allocated*". However, as a general rule the term "randomly *selected*" is not enough to establish that random allocation was used; there should be other indications in the text that random allocation has been used.

If the study is carried out in living human beings, is a healthcare intervention, is experimental, is controlled (ie contains at least one comparison intervention given concurrently with the test intervention, or using a cross-over design), and the participants are randomized, the study report is eligible for inclusion in CENTRAL.

2.5.2 Were participants definitely assigned to interventions using quasi-randomization?

Quasi-randomization is the assignment of a study participant to an intervention using some process that is not strictly random, but is intended to have the same effect as randomization, i.e., an unbiased distribution of participants across intervention groups. Usually this is done by assigning participants alternately to one of two treatments, or by using some independently established piece of information, such as a study participant's hospital registration number, social security number, or birthdate. For example, participants with an even number could be assigned to receive the test treatment while participants with an odd number would be assigned to the comparison treatment. Quasi-random allocation to treatment is usually indicated either by some variant of the term "quasi-random" or by a specification of the actual quasi-random allocation method in the discussion of participant assignments to intervention.

If participants are quasi-randomly allocated to different interventions, the study is experimental and contains at least one comparison intervention, the study concerns health care,

and the study is carried out in living human beings, the study report is eligible for inclusion in CENTRAL and it should be classified as a CCT. If study participants were not specified as either randomly or quasi-randomly allocated to different interventions, the study report may still possibly be eligible for inclusion in CENTRAL.

2.5.3 Were participants possibly assigned to interventions using either randomization or quasi-randomization?

Sometimes a study report will not explain how participants were assigned to interventions, but the possibility of random or quasi-random assignment cannot be ruled out. If participants were possibly assigned to interventions using some random or quasi-random method of allocation, the study report is eligible for inclusion in CENTRAL, and should be classified as a CCT.

It is important not to stop reading a report until you are sure that randomization or quasi-randomization was definitely used. In cases of possible randomization or possible quasi-randomization, you must read the entire report to be sure there is no definite evidence of randomization or quasi-randomization. Sometimes the study design becomes clear very late in the report, even the Discussion section.

Sometimes there are terms that give clues that a trial may be randomized, but in and of themselves these terms do not confirm randomization or quasi-randomization. Thus, if the report only contains these terms, and none stating how assignment was made, it cannot be classified as RCT.

An example of clue terms are “blind” or “masked.” Both “blind” and “masked” are used to refer to studies in which the study participants and/or the investigator(s) who measure the outcome events are deliberately kept unaware of the group to which the participants have been assigned. The purpose of “blinding” the study participants or investigator(s) is to minimize the bias that might result from knowing which intervention a participant is receiving. It often implies that assignment of the participants to the groups was done in a random or quasi-random manner. Some authors, particularly in vision research, prefer to use the term “masked” rather than “blind”. If both the investigator(s) and the participants are kept unaware, the study is referred to as “double-blind” or “double masked”; if only one or the other, “single-blind” or “single masked”. If those performing the statistical analysis are also unaware of the groups to which the participants belong, the study is described as “triple-blind” or “triple masked”.

Another example of a clue term is “crossover”, which refers to a study design in which two or more interventions are administered in a specified order. If the first treatment in the sequence is specified to have been assigned randomly then the crossover study is classified as an RCT, as described in the previous section. Most of the time, however, it is not possible to tell

whether or not the order was random. These studies should be classified as CCTs.

A third example of a clue term is "Latin Square". A "Latin Square" design is a type of crossover study and thus a report of a "Latin Square" design study should be considered a CCT unless randomization is specifically mentioned, in which case the study should be considered an RCT, as described in the previous section.

Sometimes none of the above terms are present in the study report, but random or quasi-random allocation to interventions cannot be ruled out. In this case, the study report is eligible for inclusion in CENTRAL and should be classified as a CCT.

2.5.4 Were participants definitely assigned to interventions using some method other than randomization or quasi-randomization?

If participants were definitely assigned to interventions using some method other than randomization or quasi-randomization, the trial report is not eligible for inclusion in CENTRAL.

A common example of an allocation method that is not randomization or quasi-randomization is when participants are allocated to a particular intervention because it is clinically appropriate for them. Another example sometimes seen is when participants are allowed to select the intervention they prefer.

2.6 How to classify reviews, meta-analyses, and other reports that provide information about controlled trials

Most reports of trials will be straightforward and can be classified by following the decisions outlined above. However, there are cases in which it is clear that a trial being discussed is either a CCT or RCT, but nonetheless it is not clear how to classify the report. Two examples of this situation are reviews (including systematic reviews and meta-analyses) and reports that do not present results from a trial.

In general, reports which present information from studies which are RCTs or CCTs are classified as RCTs or CCTs. Articles that refer to or cite an RCT or CCT do not justify classifying that report as an RCT or CCT, however.

Some reports focus on single RCTs or CCTs but do not present trial results. If these reports provide information that is relevant to the conduct and outcome of an RCT or CCT, they are eligible for inclusion in CENTRAL. Eligible reports include those focused on the design and methods, protocol, baseline data, and recruitment or follow-up for a trial. For example, an article describing the design of a randomized controlled trial would be classified as RCT, and an article presenting an analysis of quality-of-life data from the placebo group of a quasi-randomized

controlled trial would be classified as CCT. An article discussing problems with follow-up in a quasi-randomized controlled trial would be classified as CCT, a report presenting the results of a natural history follow-up to a randomized trial would be classified as RCT, and a re-analysis of data from a randomized controlled trial would be an RCT.

Reviews (including narrative reviews, systematic reviews, and meta-analyses) often use information from several controlled trials as part of the evidence for their conclusions. Unless the review provides new information about at least one controlled trial, however, the report of the review is not generally classified as RCT or CCT. For example, a review that pools data from several published randomized controlled trials is not considered an RCT. However, a report which includes both a meta-analysis and also previously unpublished (as far as can be detected) information about the results of a controlled trial would qualify as an RCT or CCT.

Correspondence and editorials that contain complete reports of trials can be classified as RCTs or CCTs using the guidelines in Section 2.1-2.5. For example, a letter which describes and presents the results of a randomized pilot study conducted by the authors (and which does not cite publication elsewhere) would be classified as an RCT. However, correspondence and editorials often discuss clinical trials and it can be difficult to decide how to classify these publications. One should not refer to the original report in evaluating the design of a study described in a letter, rather, the assessment of study design should be made from the correspondence itself. If the author of the correspondence has described the study in sufficient detail to classify it as an RCT or CCT, and it appears that the correspondence is not merely reiterating data already presented elsewhere, then the correspondence is eligible for inclusion in CENTRAL. For example, a letter from the investigators of a multicenter randomized trial in which they present their rationale for using specific outcome criteria might be classified as an RCT.

2.7 Additional resources in this manual for identifying and classifying RCTs and CCTs

On the next pages are figures showing the typical steps in the conduct of an RCT or CCT (Figure 1) and the sequence of decisions to be made in identifying and classifying a trial for CENTRAL (Figure 2). In addition, Appendix A of this Manual provides a short outline of key concepts in the identification and classification of RCTs and CCTs for CENTRAL. Appendix A contains additional detail about some situations which may be encountered only rarely, and should be reviewed and kept for reference.

Figure 1
Steps in conducting a randomized or quasi-randomized clinical trial

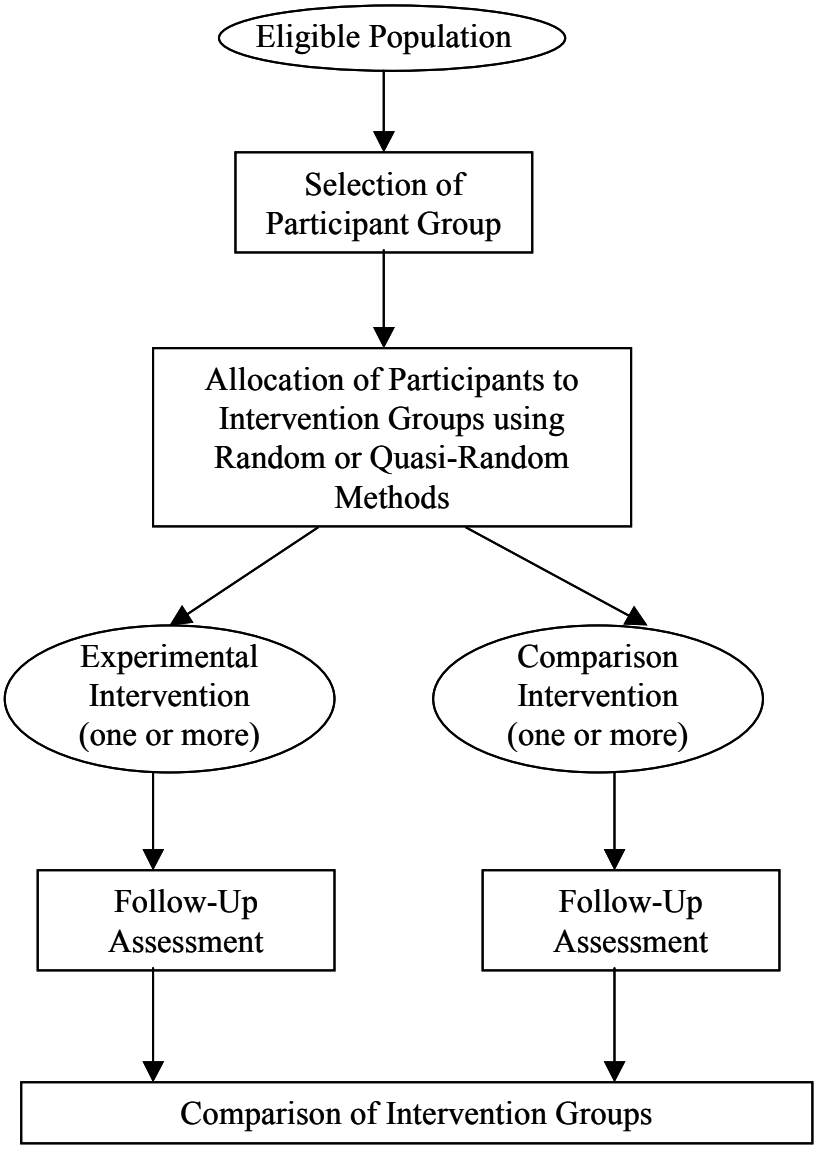
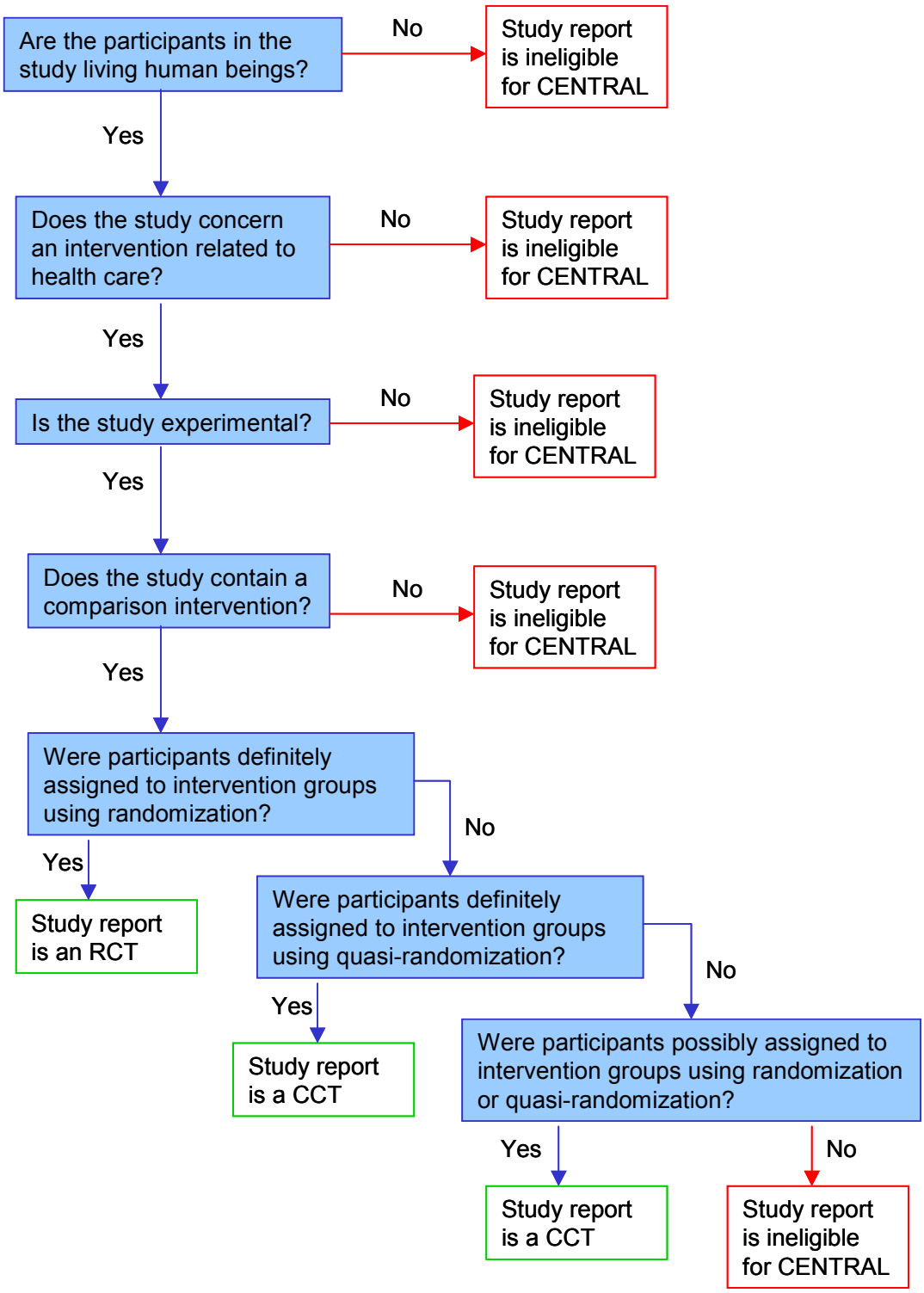


Figure 2
Decision tree for identification and classification of RCTs and CCTs



REFERENCES

1. Chalmers I, Dickersin K, Chalmers TC. Getting to grips with Archie Cochrane's agenda. BMJ 1992; 305:7868.

2. Dickersin K, Scherer R, Lefebvre C. Identification of relevant studies for systematic reviews. BMJ 1994; 309:1286-91.

3. Adams CE, Power A, Frederick K, Lefebvre C. An investigation of the adequacy of MEDLINE searches for randomized controlled trials (RCTs) of the effects of mental health care. Psychol Med 1994; 24:741-8.

4. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized controlled trials and recommendations of clinical experts. JAMA 1992; 268:240-247.

5. See Cochrane brochure at http://www.cochrane.org/cochrane/cc-broch/htm#CC

6. Editorial. Cochrane's Legacy. Lancet 1992; 340:1131-2.

7. Schuyler PL, Dickersin K, Scherer R, Wright ND. Identification of randomized clinical trials using MEDLINE. (Unpublished material).

8. Lefebvre C, Kelleher TA, Tihanov G. Identification of randomized controlled trials using MEDLINE: the situation in 1993. Presented at "An Evidence-Based Health Care System: The Case for Clinical Trial Registries". National Institutes of Health, Office of Medical Applications of Research, Bethesda, MD, Dec. 6, 1993.

9. The eligibility criteria were decided at the Cochrane Workshop on "Building a Register of RCTs", at Green College, Oxford, United Kingdom, Sunday, November 8, 1992.

10. Definition is adapted from Meinert, Curtis L., *Clinical Trials Design, Conduct, and Analysis*, New York: Oxford University Press, 1986.

11. Definition is adapted from Meinert, Curtis L., *Clinical Trials Design, Conduct, and Analysis*, New York: Oxford University Press, 1986.

3. SELF-ASSESSMENT EXERCISE WITH MEDLINE CITATION EXAMPLES

This exercise will provide you with experience in identifying and classifying the types of RCTs and CCTs (i.e., quasi-randomized trials, possible RCTs and possible quasi-randomized trials) of health care you will normally meet during a search. It will also provide you with experience in classifying studies based only on titles and abstracts, and therefore will be valuable if you are performing a search (such as of books of conference proceedings) of reports which contain only titles and abstracts. Please feel free to use the preceding sections, Appendix A, the Glossary and whatever notes you have made during your training as aids to help you identify and codify the trials.

3.1 Instructions

The following pages contain 45 examples of the types of abstracts you may encounter as you search journals for reports of RCTs and CCTs. The necessary reference information is provided so each abstract can be retrieved and viewed from PubMed (http://www.pubmed.gov). Reports should be coded on the answer sheets either as **RCT** (Randomized Controlled Trial), **CCT** (Controlled Clinical Trial), or **N/A** (None of the Above).

Study these abstracts carefully, asking the following questions in each case:

Q.1 *Based on the information contained in this abstract, is this a report of a comparison of alternative forms of care ?*
YES: GO TO Q.2
NO: GO TO THE NEXT REPORT

Q.2 *How were the comparison groups formed* ?
RANDOMIZED CODE AS **RCT**
QUASI-RANDOMIZED CODE AS **CCT**
POSSIBLY RANDOMIZED OR QUASI-RANDOMIZED CODE AS **CCT**
NONE OF THE ABOVE CODE AS **N/A**

When you have decided whether you should code them "**RCT**", "**CCT**", or "**N/A**", make the appropriate entry on the Coding Sheet provided on the next page.

The correct codes for each article and some comments regarding them are to be found starting on page III-8. Please do not look at the answers until after you have completed the exercise.

3.2 Coding Sheet:

EXAMPLE	AUTHORS	CODE
1	Arnold LE, Kleykamp D, Votolato NA, Taylor WA, Kontras SB, and Tobin K. Gamma-linolenic acid for attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine. Biol Psychiatry 1989; 25:222-8.	
2	Barbaro G, Di Lorenzo G, Soldini M, Parrotto S, Bellomo G, Belloni G, Grisorio B, and Barbarini G. Hepatic glutathione deficiency in chronic hepatitis C: quantitative evaluation in patients who are HIV positive and HIV negative and correlations with plasmatic and lymphocytic concentrations and with the activity of the liver disease. Am J Gastroenterol 1996; 91:2569-73.	
3	Barbey JT, Sale ME, Woosley RL, Shi J, Melikian AP, and Hinderling PH. Pharmacokinetic, pharmacodynamic, and safety evaluation of an accelerated dose titration regimen of sotalol in healthy middle-aged subjects. Clin Pharmacol Ther 1999; 66:91-9.	
4	Blumenthal PD, Gaffikin L, Affandi B, Bongiovanni A, McGrath J, and Glew G. Training for Norplant implant removal: assessment of learning curves and competency. Obstet Gynecol 1997; 89:174-8.	
5	Bozorgzadeh A, Pizzi WF, Barie PS, Khaneja SC, LaMaute HR, Mandava N, Richards N, and Noorollah H. The duration of antibiotic administration in penetrating abdominal trauma. Am J Surg 1999; 177:125-31.	
6	Britt MT, LaBree LD, Lloyd MA, Minckler DS, Heuer DK, Baerveldt G, and Varma R. Randomized clinical trial of the 350-mm2 versus the 500-mm2 Baerveldt implant: longer term results: is bigger better? Ophthalmology 1999; 106:2312-8.	
7	Cabezas E. Medical versus surgical abortion. Int J Gynaecol Obstet 1998; 63(Suppl. 1):S141-6.	
8	Des Jarlais DC, Paone D, Milliken J, Turner CF, Miller H, Gribble J, Shi Q, Hagan H, and Friedman SR. Audio-computer interviewing to measure risk behaviour for HIV among injecting drug users: a quasi-randomised trial. Lancet 1999; 353:1657-61.	

9	Duncan E, Wolkin A, Angrist B, Sanfilipo M, Wieland S, Cooper T B, and Rotrosen J. Plasma homovanillic acid in neuroleptic responsive and nonresponsive schizophrenics. Biol Psychiatry 1993; 34:523-8.	
10	Flor H, Denke C, Schaefer M, and Grusser S. Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. Lancet 2001; 357:1763-4.	
11	Folmar S, Oates-Williams F, Sharp P, Reboussin D, Smith J, Cheshire K, Macer J, Potvin Klein K, and Herrington D. Recruitment of participants for the Estrogen Replacement and Atherosclerosis (ERA) trial. A comparison of costs, yields, and participant characteristics from community- and hospital-based recruitment strategies. Control Clin Trials 2001; 2:13-25.	
12	Glazier R, Goel V, Holzapfel S, Summers A, Pugh P, and Yeung M. Written patient information about triple-marker screening: a randomized, controlled trial. Obstet Gynecol 1997; 90:769-74.	
13	Goradia VK, Mullen DJ, Boucher HR, Parks BG, and O'Donnell JB. Cyclic loading of rotator cuff repairs: a comparison of bioabsorbable tacks with metal suture anchors and transosseous sutures. Arthroscopy 2001; 17:360-4.	
14	Harewood GC, Yacavone RF, Locke GR. 3rd, and Wiersema MJ. Prospective comparison of endoscopy patient satisfaction surveys: e- mail versus standard mail versus telephone. Am J Gastroenterol 2001; 96:3312-7.	
15	Haylock BJ, Coppin CM, Jackson J, Basco VE, and Wilson KS. Locoregional first recurrence after mastectomy: prospective cohort studies with and without immediate chemotherapy. Int J Radiat Oncol Biol Phys 2000; 46:355-62.	
16	Hilbert J, Messig M, Kuye O, and Friedman H. Evaluation of interaction between fluconazole and an oral contraceptive in healthy women. Obstet Gynecol 2001; 98:218-23.	
17	Holowaty P, Feldman L, Harvey B, and Shortt L. Cigarette smoking in multicultural, urban high school students. J Adolesc Health 2000; 27:281-288.	

18	Hudson PB, Boake R, Trachtenberg J, Romas NA, Rosenblatt S, Narayan P, Geller J, Lieber MM, Elhilali M, Norman R, Patterson L, Perreault JP, Malek GH, Bruskewitz RC, Roy JB, Ko A, Jacobsen CA, and Stoner E. Efficacy of finasteride is maintained in patients with benign prostatic hyperplasia treated for 5 years. The North American Finasteride Study Group. Urology 1999; 53:690-5.	
19	Jadad AR, Carroll D, Glynn CJ, and McQuay HJ. Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study. J Pain Symptom Manage 1995; 10:13-20.	
20	Keefer L, and Blanchard EB. The effects of relaxation response meditation on the symptoms of irritable bowel syndrome: results of a controlled treatment study. Behav Res Ther 2001; 39:801-11.	
21	King AC, Saylor KE, Foster S, Killen JD, Telch MJ, Farquhar JW, and Flora JA. Promoting dietary change in adolescents: a school-based approach for modifying and maintaining healthful behavior. Am J Prev Med 1988; 4:68-74.	
22	Lujan HJ, Mathews HL, Gamelli RL, and Jones SB. Human immune cells mediate catecholamine secretion from adrenal chromaffin cells. Crit Care Med 1998; 26:1218-24.	
23	Lundell L, Miettinen P, Myrvold HE, Pedersen SA, Liedman B, Hatlebakk JG, Julkonen R, Levander K, Carlsson J, Lamm M, and Wiklund I. Continued (5-year) followup of a randomized clinical study comparing antireflux surgery and omeprazole in gastroesophageal reflux disease. J Am Coll Surg 2001; 192:172-9.	
24	Mawer C, Ignatenko N, Wares D, Strelis A, Golubchikova V, Yanova G, Lyagoshina T, Sharaburova O, and Banatval N. Comparison of the effectiveness of WHO short-course chemotherapy and standard Russian antituberculous regimens in Tomsk, western Siberia. Lancet 2001; 358:445-9.	
25	McCarrick MJ, and Kemp JG. The effect of strength training and reduced training on rotator cuff musculature. Clin Biomech (Bristol, Avon) 2000; 15(Suppl. 1):S42-5.	

26	Moore AA, Sium A, Partridge JM, Hays RD, and Adams J. A randomized trial of office-based screening for common problems in older persons. Am J Med 1997; 102:371-8.	
27	Oner B. Preferences and expectations of innovator-ritualist types in relation to sex of university students in a Turkish sample. Psychol Rep 2000; 87:23-33.	
28	Phan TM, Foster CS, Boruchoff SA, Zagachin LM, and Colvin RB. Topical fibronectin in the treatment of persistent corneal epithelial defects and trophic ulcers. Am J Ophthalmol 1987; 104:494-501.	
29	Pitt C, Sanchez-Ramos L, and Kaunitz AM. Adjunctive intravaginal metronidazole for the prevention of postcesarean endometritis: a randomized controlled trial. Obstet Gynecol 2001; 98:745-50.	
30	Rainer G, Menapace R, Findl O, Petternel V, Kiss B, and Georgopoulos M. Effect of topical brimonidine on intraocular pressure after small incision cataract surgery. J Cataract Refract Surg 2001; 27:1227-31.	
31	Ruiz-Irastorza G, Khamashta MA, Castellino G, and Hughes GR. Systemic lupus erythematosus. Lancet 2001; 357:1027-32.	
32	Sayer JW, Gutteridge C, Syndercombe-Court D, Wilkinson P, and Timmis AD. Circadian activity of the endogenous fibrinolytic system in stable coronary artery disease: effects of beta-adrenoreceptor blockers and angiotensin-converting enzyme inhibitors. J Am Coll Cardiol 1998; 32:1962-8.	
33	Sheather-Reid RB, and Cohen M. Efficacy of analgesics in chronic pain: a series of N-of-1 studies. J Pain Symptom Manage 1998; 15:244-52.	
34	Shen WK, Jahangir A, Beinborn D, Lohse CM, Hodge DO, Rea RF, and Hammill SC. Utility of a single-stage isoproterenol tilt table test in adults: a randomized comparison with passive head-up tilt. J Am Coll Cardiol 1999; 33:985-90.	
35	Sparkes AH, Caney SM, Sturgess CP, and Gruffydd-Jones TJ. The clinical efficacy of topical and systemic therapy for the treatment of feline ocular chlamydiosis. J Feline Med Surg 1999; 1:31-5.	

36	Sweat M, Gregorich S, Sangiwa G, Furlonge C, Balmer D, Kamenga C, Grinstead O, and Coates T. Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania. Lancet 2000; 356:113-21.	
37	Thompson DR, and Meddis R. A prospective evaluation of in-hospital counselling for first time myocardial infarction men. J Psychosom Res 1990; 34:237-48.	
38	Urschel JD, Vasan H, and Blewett CJ. A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2002; 183:274-9.	
39	Van Tinteren H, Hoekstra OS, Smit EF, Verboom P, and Boers M. Toward less futile surgery in non-small cell lung cancer? A randomized clinical trial to evaluate the cost-effectiveness of positron emission tomography. Control Clin Trials 2001; 22:89-98.	
40	Vega JD, Ochsner JL, Jeevanandam V, McGiffin DC, McCurry KR, Mentzer RM. Jr, Stringham JC, Pierson RN. 3rd, Frazier OH, Menkis AH, Staples ED, Modry DL, Emery R, Piccione W. Jr, Carrier M, Hendry PJ, Aziz S, Furukawa S, and Pham SM. A multicenter, rando- mized, controlled trial of Celsior for flush and hypothermic storage of cardiac allografts. Ann Thorac Surg 2001; 71:1442-7.	
41	Yamanouchi T, Ogata N, Tagaya T, Kawasaki T, Sekino N, Funato H, Akaoka L, and Miyashita H. Clinical usefulness of serum 1,5-anhydroglucitol in monitoring glycaemic control. Lancet 1996; 347:1514-8.	
42	Yao FY, Terrault NA, Freise C, Maslow L, and Bass NM. Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched, untreated cohort. Hepatology 2001; 34:411-6.	
43	Zanchetti A, and Omboni S. Comparison of candesartan versus enalapril in essential hypertension. Italian Candesartan Study Group. Am J Hypertens 2001; 14:129-34.	

44	Zander M, Madsbad S, Madsen JL, and Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. Lancet 2002; 359:824-30.	
45	Zheng L, Pereira PN, Somphone P, Nikaido T, and Tagami J. Effect of hydrostatic pressure on regional bond strengths of compomers to dentine. J Dent 2000; 28:501-8.	

3.3 Correct classifications and rationales for abstract examples.

1. AU: Arnold LE, Kleykamp D, Votolato NA, Taylor WA, Kontras SB, and Tobin K.
TI: Gamma-linolenic acid for attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine
SO: Biol Psychiatry
YR: 1989 Jan. VL: 25 NO: 2 PG: 222-8

Article classification: RCT

This is an example of a study in which all participants received the same interventions in a Latin square design, and the participants were randomized to lines in the square. This study is eligible for inclusion in the Cochrane Library as an RCT.

2. AU: Barbaro G, Di Lorenzo G, Soldini M, Parrotto S, Bellomo G, Belloni G, Grisorio B, and Barbarini G.
TI: Hepatic glutathione deficiency in chronic hepatitis C: quantitative evaluation in patients who are HIV positive and HIV negative and correlations with plasmatic and lymphocytic concentrations and with the activity of the liver disease
SO: Am J Gastroenterol
YR: 1996 Dec. VL: 91 NO: 12 PG: 2569-73

Article classification: N/A

This is an example of a study in which the participants are divided into two groups defined by some pre-existing characteristic of the participants. Here the two groups consist of patients with Hepatitis C who are either HIV-infected or HIV-negative. The purpose of this study is to compare the characteristics of the two groups, and there is no comparison between different interventions. This study is not eligible for inclusion in the Cochrane Library.

3. AU: Barbey JT, Sale ME, Woosley RL, Shi J, Melikian AP, and Hinderling PH.
TI: Pharmacokinetic, pharmacodynamic, and safety evaluation of an accelerated dose titration regimen of sotalol in healthy middle-aged subjects
SO: Clin Pharmacol Ther
YR: 1999 July VL: 66 NO: 1 PG: 91-9

Article classification: CCT

This is a controlled trial comparing dose titration schedules. It is an example of a controlled comparison of dose amounts, dose timing, or titration regimens, and it is eligible for inclusion in

the Cochrane Library.

4. AU: Blumenthal PD, Gaffikin L, Affandi B, Bongiovanni A, McGrath J, and Glew G.
TI: Training for Norplant implant removal: assessment of learning curves and competency
SO: Obstet Gynecol
YR: 1997 Feb. VL: 89 NO: 2 PG: 174-8

Article classification: RCT

This is a randomized trial of physician education. It is eligible for inclusion in the Cochrane Library.

5. AU: Bozorgzadeh A, Pizzi WF, Barie PS, Khaneja SC, LaMaute HR, Mandava N, Richards N, and Noorollah H.
TI: The duration of antibiotic administration in penetrating abdominal trauma
SO: Am J Surg
YR: 1999 Feb. VL: 177 NO: 2 PG: 125-31

Article classification: RCT

This is a randomized trial comparing two durations of intravenous cefoxitin use. It is an example of the randomized comparison of the same treatment for two different durations, and it is eligible for inclusion in the Cochrane Library.

6. AU: Britt MT, LaBree LD, Lloyd MA, Minckler DS, Heuer DK, Baerveldt G, and Varma R.
TI: Randomized clinical trial of the 350-mm2 versus the 500-mm2 Baerveldt implant: longer term results: is bigger better?
SO: Ophthalmology
YR: 1999 Dec. VL: 106 NO: 12 PG: 2312-8

Article classification: RCT

This is an example of a study in which the method of randomization is explicitly stated. It is eligible for inclusion in the Cochrane Library as an RCT.

7. AU: Cabezas E.
TI: Medical versus surgical abortion
SO: Int J Gynaecol Obstet
YR: 1998 Dec. VL: 63 Suppl 1 PG: S141-6

Article classification: N/A

This is an example of a study in which the participants (or their doctors) selected the treatments. This is not a random or quasi-random method of allocation, and therefore this study is not eligible for inclusion in the Cochrane Library.

8. AU: Des Jarlais DC, Paone D, Milliken J, Turner CF, Miller H, Gribble J, Shi Q, Hagan H, and Friedman SR.
TI: Audio-computer interviewing to measure risk behaviour for HIV among injecting drug users: a quasi-randomised trial
SO: Lancet
YR: 1999 May VL: 353 NO: 9165 PG: 1657-61

Article classification: CCT

This is an example of a study in which quasi-randomization was explicitly stated to have been used. This study is eligible for inclusion in the Cochrane Library as a CCT.

9. AU: Duncan E, Wolkin A, Angrist B, Sanfilipo M, Wieland S, Cooper TB, and Rotrosen J.
TI: Plasma homovanillic acid in neuroleptic responsive and nonresponsive schizophrenics
SO: Biol Psychiatry
YR: 1993 Oct. VL: 34 NO: 8 PG: 523-8

Article classification: N/A

This is an example of a study in which the participants are divided into two groups defined by some characteristic of the participants. Here the two groups are responders and non-responders to psychiatric medication. The purpose of this study is to compare the characteristics of the two groups, and there is no comparison between different interventions. This study is not eligible for inclusion in the Cochrane Library.

10. AU: Flor H, Denke C, Schaefer M, and Grusser S.
TI: Effect of sensory discrimination training on cortical reorganisation and phantom limb pain
SO: Lancet
YR: 2001 June VL: 357 NO: 9270 PG: 1763-4

Article classification: CCT

This is an example of a trial in which the method of group assignment is not specified. It is

possible that participants were randomly or quasi-randomly assigned to groups, and therefore this trial is eligible for inclusion in the Cochrane Library as a CCT.

11. AU: Folmar S, Oates-Williams F, Sharp P, Reboussin D, Smith J, Cheshire K, Macer J, Potvin Klein K, and Herrington D.
TI: Recruitment of participants for the Estrogen Replacement and Atherosclerosis (ERA) trial. a comparison of costs, yields, and participant characteristics from community- and hospital-based recruitment strategies
SO: Control Clin Trials
YR: 2001 Feb. VL: 22 NO: 1 PG: 13-25

Article classification: RCT

This is an article about recruitment for a randomized controlled trial. It is an example of an article about the design, protocol development, recruitment strategies, or conduct of a randomized controlled trial, and it is eligible for inclusion in the Cochrane Library.

12. AU: Glazier R, Goel V, Holzapfel S, Summers A, Pugh P, and Yeung M.
TI: Written patient information about triple-marker screening: a randomized, controlled trial
SO: Obstet Gynecol
YR: 1997 Nov. VL: 90 NO: 5 PG: 769-74

Article classification: RCT

This is an example of a randomized controlled trial concerning the education of non-health professionals about health or disease. It is eligible for inclusion in the Cochrane Library.

13. AU: Goradia VK, Mullen DJ, Boucher HR, Parks BG, and O'Donnell JB.
TI: Cyclic loading of rotator cuff repairs: A comparison of bioabsorbable tacks with metal suture anchors and transosseous sutures
SO: Arthroscopy
YR: 2001 Apr. VL: 17 NO: 4 PG: 360-4

Article classification: N/A

This is an example of a randomized study which is carried out in cadavers and therefore is not eligible for inclusion in the Cochrane Library.

14. AU: Harewood GC, Yacavone RF, Locke GR. 3rd, and Wiersema MJ.
TI: Prospective comparison of endoscopy patient satisfaction surveys: e- mail versus standard mail versus telephone

SO: Am J Gastroenterol
YR: 2001 Dec. VL: 96 NO: 12 PG: 3312-7

Article classification: RCT

This is a randomized clinical trial designed to determine outcomes related to health research, such as follow-up rates or response rates to a survey. It is eligible for inclusion in the Cochrane Library.

15. AU: Haylock BJ, Coppin CM, Jackson J, Basco VE, and Wilson KS.
TI: Locoregional first recurrence after mastectomy: prospective cohort studies with and without immediate chemotherapy
SO: Int J Radiat Oncol Biol Phys
YR: 2000 Jan. VL: 46 NO: 2 PG: 355-62

Article classification: N/A

This is an example of a study in which the results in an intervention group are compared to results in a subsequent control group. The initial chemotherapy group and the subsequent control group were not allocated to treatment at the same time, and therefore this study is not eligible for inclusion in the Cochrane Library.

16. AU: Hilbert J, Messig M, Kuye O, and Friedman H.
TI: Evaluation of interaction between fluconazole and an oral contraceptive in healthy women
SO: Obstet Gynecol
YR: 2001 Aug. VL: 98 NO: 2 PG: 218-23

Article classification: RCT

This is an example of a crossover study in which all participants receive the same treatments, but in a randomized order. The study is eligible for inclusion in the Cochrane Library.

17. AU: Holowaty P, Feldman L, Harvey B, and Shortt L.
TI: Cigarette smoking in multicultural, urban high school students
SO: J Adolesc Health
YR: 2000 Oct. VL: 27 NO: 4 PG: 281-288

Article classification: N/A

This is an example of a study in which the phrase "randomly selected" is used. The participants were randomly selected to participate in the study, but they were not randomly selected to participate in different intervention groups. Studies in which participants are randomly selected to participate but are not randomly or quasi-randomly allocated to different interventions are not eligible for inclusion in the Cochrane Library.

18. AU: Hudson PB, Boake R, Trachtenberg J, Romas NA, Rosenblatt S, Narayan P, Geller J, Lieber MM, Elhilali M, Norman R, Patterson L, Perreault JP, Malek GH, Bruskewitz RC, Roy JB, Ko A, Jacobsen CA, and Stoner E.
TI: Efficacy of finasteride is maintained in patients with benign prostatic hyperplasia treated for 5 years. The North American Finasteride Study Group
SO: Urology
YR: 1999 Apr. VL: 53 NO: 4 PG: 690-5

Article classification: RCT

This is a report of an open-label extension of a randomized controlled trial. It is an example of a follow-up to a randomized controlled trial, and it is eligible for inclusion in the Cochrane Library.

19. AU: Jadad AR, Carroll D, Glynn CJ, and McQuay HJ.
TI: Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomized, double-blind crossover study
SO: J Pain Symptom Manage
YR: 1995 Jan. VL: 10 NO: 1 PG: 13-20

Article classification: RCT

This is a systematic review that has been done in conjunction with a randomized controlled trial. The article is eligible for inclusion in the Cochrane Library.

20. AU: Keefer L, and Blanchard EB.
TI: The effects of relaxation response meditation on the symptoms of irritable bowel syndrome: results of a controlled treatment study
SO: Behav Res Ther
YR: 2001 July VL: 39 NO: 7 PG: 801-11

Article classification: RCT

This is a study that used matching to construct pairs of similar participants. \The participants were then randomized, each member of the matched pair to receive a different treatment. This study is eligible for inclusion in the Cochrane Library.

21. AU: King AC, Saylor KE, Foster S, Killen JD, Telch MJ, Farquhar JW, and Flora JA.
TI: Promoting dietary change in adolescents: a school-based approach for modifying and maintaining healthful behavior
SO: Am J Prev Med
YR: 1988 Mar.- Apr. VL: 4 NO: 2 PG: 68-74

Article classification: RCT

This is an example of a trial in which randomization was not carried out individual by individual, but group by group. In this case, the groups were school classes, but other examples might be churches, medical practices, or entire communities. These studies are eligible for inclusion in the Cochrane Library.

22. AU: Lujan HJ, Mathews HL, Gamelli RL, and Jones SB.
TI: Human immune cells mediate catecholamine secretion from adrenal chromaffin cells
SO: Crit Care Med
YR: 1998 July VL: 26 NO: 7 PG: 1218-24

Article classification: N/A

This is an example of a randomized study which is carried out exclusively *in vitro* and therefore is not eligible for inclusion in the Cochrane Library. A controlled study which is done *in vitro* and also in living human beings, however, could be eligible for inclusion in the Cochrane Library.

23. AU: Lundell L, Miettinen P, Myrvold HE, Pedersen SA, Liedman B, Hatlebakk JG, Julkonen R, Levander K, Carlsson J, Lamm M, and Wiklund I.
TI: Continued (5-year) followup of a randomized clinical study comparing antireflux surgery and omeprazole in gastroesophageal reflux disease
SO: J Am Coll Surg
YR: 2001 Feb. VL: 192 NO: 2 PG: 172-9; discussion 179-81
Article classification: RCT

This is a report of followup to a randomized controlled trial. It is eligible for inclusion in the Cochrane Library.

24. AU: Mawer C, Ignatenko N, Wares D, Strelis A, Golubchikova V, Yanova G, Lyagoshina T, Sharaburova O, and Banatvala N.
TI: Comparison of the effectiveness of WHO short-course chemotherapy and standard Russian antituberculous regimens in Tomsk, western Siberia
SO: Lancet
YR: 2001 Aug. VL: 358 NO: 9280 PG: 445-9

Article classification: CCT

This is an example of a trial in which the method of allocation to groups is not specified. The method used could have been randomization or quasi-randomization and therefore this study is eligible for inclusion in the Cochrane Library as a CCT.

25. AU: McCarrick MJ, and Kemp JG.
TI: The effect of strength training and reduced training on rotator cuff musculature
SO: Clin Biomech (Bristol, Avon)
YR: 2000 VL: 15 Suppl 1 PG: S42-5

Article classification: RCT

This is a randomized trial testing the effects of an intervention upon physical strength. It is an example of an intervention concerning exercise or athletic performance, and it is eligible for inclusion in the Cochrane Library.

26. AU: Moore AA, Siu A, Partridge JM, Hays RD, and Adams J.
TI: A randomized trial of office-based screening for common problems in older persons
SO: Am J Med
YR: 1997 Apr. VL: 102 NO: 4 PG: 371-8

Article classification: RCT

This is an example of a randomized clinical trial of a screening program. Although some review groups may not include it in their register, this study is eligible for inclusion in the Cochrane Library.

27. AU: Oner B.
TI: Preferences and expectations of innovator-ritualist types in relation to sex of university students in a Turkish sample
SO: Psychol Rep

YR: 2000 Aug. VL: 87 NO: 1 PG: 23-33

Article classification: N/A

This is a randomized study which is not explicitly health related. It is not eligible for inclusion in the Cochrane Library.

28. AU: Phan TM, Foster CS, Boruchoff SA, Zagachin LM, and Colvin RB.
TI: Topical fibronectin in the treatment of persistent corneal epithelial defects and trophic ulcers
SO: Am J Ophthalmol
YR: 1987 Nov. VL: 104 NO: 5 PG: 494-501

Article classification: N/A

This is an example of a Phase I trial in which all participants received the same intervention. It is not eligible for inclusion in the Cochrane Library.

29. AU: Pitt C, Sanchez-Ramos L, and Kaunitz AM.
TI: Adjunctive intravaginal metronidazole for the prevention of postcesarean endometritis: a randomized controlled trial
SO: Obstet Gynecol
YR: 2001 Nov. VL: 98 NO: 5 Pt 1 PG: 745-50

Article classification: RCT

This is an example of a randomized clinical trial of a preventive intervention. This study is eligible for inclusion in the Cochrane Library.

30. AU: Rainer G, Menapace R, Findl O, Petternel V, Kiss B, and Georgopoulos M.
TI: Effect of topical brimonidine on intraocular pressure after small incision cataract surgery
SO: J Cataract Refract Surg
YR: 2001 Aug. VL: 27 NO: 8 PG: 1227-31

Article classification: RCT

This is an example of a trial in which different body parts of each participant were randomized to treatment. In this case, the body parts were eyes, but other examples might be teeth or arms. These studies are eligible for inclusion in the Cochrane Library.

31. AU: Ruiz-Irastorza G, Khamashta MA, Castellino G, and Hughes GR.
TI: Systemic lupus erythematosus
SO: Lancet
YR: 2001 Mar. VL: 357 NO: 9261 PG: 1027-32

Article classification: N/A

This is an example of a review article that does not present new information about an individual controlled trial. It is not eligible for inclusion in the Cochrane Library.

32. AU: Sayer JW, Gutteridge C, Syndercombe-Court D, Wilkinson P, and Timmis AD.
TI: Circadian activity of the endogenous fibrinolytic system in stable coronary artery disease: effects of beta-adrenoreceptor blockers and angiotensin-converting enzyme inhibitors
SO: J Am Coll Cardiol
YR: 1998 Dec. VL: 32 NO: 7 PG: 1962-8

Article classification: N/A

This is an example of a study in which all participants receive the same treatments in the same order. This article is not eligible for inclusion in the Cochrane Library.

33. AU: Sheather-Reid RB, and Cohen M.
TI: Efficacy of analgesics in chronic pain: a series of N-of-1 studies
SO: J Pain Symptom Manage
YR: 1998 Apr. VL: 15 NO: 4 PG: 244-52

Article classification: CCT
This is an example of a series of controlled trials, each with a single participant. In this type of trial, also called an N-of-1 design, the participant serves as his or her own control. This study is eligible for inclusion in the Cochrane Library.

34. AU: Shen WK, Jahangir A, Beinborn D, Lohse CM, Hodge DO, Rea RF, and Hammill SC.
TI: Utility of a single-stage isoproterenol tilt table test in adults: a randomized comparison with passive head-up tilt
SO: J Am Coll Cardiol
YR: 1999 Mar. VL: 33 NO: 4 PG: 985-90

Article classification: RCT

This study uses the randomly ordered application of two diagnostic tests in order to test the value of one of the tests. It is an example of a trial of a diagnostic instrument, test or technique, and it is eligible for inclusion in the Cochrane Library.

35. AU: Sparkes AH, Caney SM, Sturgess CP, and Gruffydd-Jones TJ.
TI: The clinical efficacy of topical and systemic therapy for the treatment of feline ocular chlamydiosis
SO: J Feline Med Surg
YR: 1999 Mar. VL: 1 NO: 1 PG: 31-5

Article classification: N/A

This is an example of a randomized study which is carried out exclusively in animals and is therefore not eligible for inclusion in the Cochrane Library. A study which is carried out in animals and in human beings, however, could be eligible for inclusion in the Library.

36. AU: Sweat M, Gregorich S, Sangiwa G, Furlonge C, Balmer D, Kamenga C, Grinstead O, and Coates T.
TI: Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania
SO: Lancet
YR: 2000 July VL: 356 NO: 9224 PG: 113-21

Article classification: N/A

This is an example of a randomized clinical trial which uses a hypothetical cohort. It does not involve real human beings, and therefore it is not eligible for inclusion in the Cochrance Library.

37. AU: Thompson DR, and Meddis R.
TI: A prospective evaluation of in-hospital counselling for first time myocardial infarction men
SO: J Psychosom Res
YR: 1990 VL: 34 NO: 3 PG: 237-48

Article classification: RCT

This is an example of a randomized controlled trial concerning mental health outcomes. It is eligible for inclusion in the Cochrane Library.

38. AU: Urschel JD, Vasan H, and Blewett CJ.
TI: A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer
SO: Am J Surg
YR: 2002 Mar. VL: 183 NO: 3 PG: 274-9

Article classification: N/A

This is an example of a meta-analysis that does not contain new information about an individual controlled trial. It is not eligible for inclusion in the Cochrane Library.

39. AU: Van Tinteren H, Hoekstra OS, Smit EF, Verboom P, and Boers M.
TI: Toward less futile surgery in non-small cell lung cancer? A randomized clinical trial to evaluate the cost-effectiveness of positron emission tomography
SO: Control Clin Trials
YR: 2001 Feb. VL: 22 NO: 1 PG: 89-98

Article classification: RCT

This is a randomized clinical trial testing for cost-effectiveness differences between two interventions. This study is eligible for inclusion in the Cochrane Library.

40. AU: Vega JD, Ochsner JL, Jeevanandam V, McGiffin DC, McCurry KR, Mentzer RM. Jr, Stringham JC, Pierson RN. 3rd, Frazier OH, Menkis AH, Staples ED, Modry DL, Emery RW, Piccione W. Jr, Carrier M, Hendry PJ, Aziz S, Furukawa S, and Pham SM.
TI: A multicenter, randomized, controlled trial of Celsior for flush and hypothermic storage of cardiac allografts
SO: Ann Thorac Surg
YR: 2001 May VL: 71 NO: 5 PG: 1442-7

Article classification: RCT

This is an example of a randomized study carried out in donor organs. Because the donor organs are placed into the bodies of living human beings, the study is eligible for inclusion in the Cochrane Library.

41. AU: Yamanouchi T, Ogata N, Tagaya T, Kawasaki T, Sekino N, Funato H, Akaoka L, and Miyashita H.
TI: Clinical usefulness of serum 1,5-anhydroglucitol in monitoring glycaemic control

SO: Lancet
YR: 1996 June VL: 347 NO: 9014 PG: 1514-8

Article classification: CCT

This is an example of a trial in which the method of allocation to groups is not specified. The method used could have been randomization or quasi-randomization and therefore this study is eligible for inclusion in the Cochrane Library as a CCT.

42. AU: Yao FY, Terrault NA, Freise C, Maslow L, and Bass NM.
TI: Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched, untreated cohort
SO: Hepatology
YR: 2001 Aug. VL: 34 NO: 2 PG: 411-6

Article classification: N/A

This is a study in which the participants were given the treatment being investigated, then compared to a matched historical comparison group of non-participants, who were not given the treatment. This study is not eligible for inclusion in the Cochrane Library.

43. AU: Zanchetti A, and Omboni S.
TI: Comparison of candesartan versus enalapril in essential hypertension. Italian Candesartan Study Group
SO: Am J Hypertens
YR: 2001 Feb. VL: 14 NO: 2 PG: 129-34

Article classification: RCT

This is an example of a randomized controlled trial in which two or more interventions are compared. The study is eligible for inclusion in the Cochrane Library.

44. AU: Zander M, Madsbad S, Madsen JL, and Holst JJ.
TI: Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study
SO: Lancet
YR: 2002 Mar. VL: 359 NO: 9309 PG: 824-30

Article classification: CCT

This is an example of a study in which the method of allocation to treatment groups is quasi-random. Although the investigators do not use the terms "quasi-random" or "quasi-randomization", alternation is a method which is not truly random but is intended to achieve the effect of randomization. Additional examples of quasi-randomization techniques are odd-even numbers, days of the week, or patient social security numbers. This study is eligible for inclusion in the Cochrane Library as a CCT.

45. AU: Zheng L, Pereira PN, Somphone P, Nikaido T, and Tagami J.
TI: Effect of hydrostatic pressure on regional bond strengths of compomers to dentine
SO: J Dent
YR: 2000 Sept. VL: 28 NO: 7 PG: 501-8

Article classification: N/A

This is an example of a randomized trial carried out on extracted teeth. Because extracted teeth are removed from human beings, and not implanted in living human beings, the article is not eligible for inclusion in the Cochrane Library.

4. SELF-ASSESSMENT EXERCISE WITH FULL TEXT EXAMPLES OF ARTICLES FROM THE BIOMEDICAL LITERATURE

This exercise will provide you with experience in identifying and classifying the types of RCTs and CCTs (i.e., quasi-randomized trials, possible RCTs and possible quasi-randomized trials) of health care you will normally encounter during a search. Please feel free to use the preceding sections, Appendix A, the Glossary and whatever notes you have made during your training as aids to help you identify and code the trials.

4.1 Instructions

Pages IV-2 and IV-3 contain references to 17 examples of the types of reports you may encounter as you search journals for reports of RCTs and CCTs. Please use the reference information to obtain the full text article. Please contact your local medical library if you are unable to find any of the references. Reports should be coded on the answer sheets either as **RCT** (Randomized Controlled Trial), **CCT** (Controlled Clinical Trial), or **N/A** (None of the Above).

Study these extracts carefully, asking the following questions in each case:

Q.1 *Is this a report of a comparison of alternative forms of care ?*

YES: GO TO Q.2

NO: GO TO THE NEXT REPORT

Q.2 *How were the comparison groups formed* ?

RANDOMIZED CODE AS **RCT**

QUASI-RANDOMIZED CODE AS **CCT**

POSSIBLY RANDOMIZED OR QUASI-RANDOMIZED CODE AS **CCT**

NONE OF THE ABOVE CODE AS **N/A**

When you have decided whether you should code them "**RCT**", "**CCT**", or "**N/A**", make the appropriate entry on the Coding Sheet provided on page IV-2.

The correct codes for each article and some comments regarding them are to be found beginning on page IV-4. Please do not look at the answers until after you have completed the exercise.

EXAMPLE	AUTHORS	CODE
1	Lee TM, Su SF, Chou TF, and Tsai CH. Pharmacologic preconditioning of estrogen by activation of the myocardial adenosine triphosphate-sensitive potassium channel in patients undergoing coronary angioplasty. J Am Coll Cardiol 2002; 39:871-7.	
2	Robertson MD, Henderson RA, Vist GE, and Rumsey RDE. Extended effects of evening meal carbohydrate-to-fat ratio on fasting and postprandial substrate metabolism. Am J Clin Nutr 2002; 75:505-10.	
3	Koniak-Griffin D, Anderson NLR, Brecht ML, Verzemnieks I, Lesser J, and Kim S. Public health nursing care for adolescent mothers: impact on infant health and selected maternal outcomes at 1 year postbirth. J Adolesc Health 2000; 183:396-9.	
4	Lin JL, Tan DT, Hsu KH, and Yu CC. Environmental lead exposure and progressive renal insufficiency. Arch Intern Med 2001; 161:264-271.	
5	Stiegemeier MJ. Clinical evaluation of a multi-purpose disinfecting solution used without a manual rubbing step. Clinical Ed., Case Reports & Scientific Posters. Sun. Dec. 10, 2000, American Academy of Optometry Annual Meeting. Poster #67 (CL-221).	
6	Wang J, Fonn D, Simpson TL, and Jones L. The measurement of corneal epithelial thickness using optical coherence tomography in response to hypoxia induced by soft contact lens and eye closure. Clinical Ed., Case Reports & Scientific Posters. Sun. Dec. 10, 2000, American Academy of Optometry Annual Meeting. Poster #58 (CL-115).	
7	Wakefield M, Banham D, McCaul K, Martin J, Ruffin R, Badcock N, and Roberts L. Effect of feedback regarding urinary cotinine and brief tailored advice on home smoking restrictions among low-income parents of children with asthma: a controlled trial. Prevent Med 2002; 34:58-65.	
8	Scott S, Spender Q, Doolan M, Jacobs B, and Aspland H. Multicentre controlled trial of parenting groups for childhood antisocial behaviour in clinical practice. BMJ 2001; 323:1-7.	

9	Teixeira F, Mosqueda-Taylor A, Montaño S, and Dominguez-Soto L. Treatment of recurrent oral ulcers with mometasone furoate lotion. Postgrad Med J 1999; 75:574.	
10	McLachlan RI, O'Donnell L, Stanton PG, Balourdos G, Frydenberg M, De Kretser DM, and Robertson DM. Effects of testosterone plus medroxyprogesterone acetate on semen quality, reproductive hormones, and germ cell populations in normal young men. J Clin Endocrinol Metab 2002; 87:546-556.	
11	Stodieck S, Steinhoff BJ, Kolmsee S, and Van Rijckevorsel K. Effect of levetiracetam in patients with epilepsy and interictal epileptiform discharges. Seizure 2001; 10:583-587.	
12	Moore B, and the VIP Study Group. Comparing the usability of two visual acuity tests with preschool age children. Clinical Ed., Case Reports & Scientific Posters. Mon. Dec. 11, 2000, American Academy of Optometry Annual Meeting. Poster #98 (PO-140).	
13	Hardy KJ, O'Brien SV, and Furlong NJ. Information given to patients before appointments and its effect on non-attendance rate. BMJ 2001; 323:1298-1300.	
14	Mamalakis G, Kafatos A, Manios Y, Kalogeropoulos N, and Andrikopoulos N. Adipose fat quality vs quantity: Relationships with children's serum lipid levels. Prevent Med 2001; 33:525-535.	
15	Sanchez-Muniz FJ, Merinero MC, Rodriguez-Gil S, Ordovas JM, Rodenas S, and Cuesta C. Dietary fat saturation affects apolipoprotein AII levels and HDL composition in postmenopausal women. J Nutr 2002; 132:50-54.	
16	Ficarra A, and Sorkin R. Assessment of intraocular pressure in children by digital tension. Clinical Ed., Case Reports & Scientific Posters. Mon. Dec. 11, 2000, American Academy of Optometry Annual Meeting. Poster #111 (PO-129).	
17	Jeandervin M, Walline JJ, Mitchell GL, Mutti DO, and Zadnik K. Use of the experience sampling method for near work assessment in children. Clinical Ed., Case Reports & Scientific Posters. Mon. Dec. 11, 2000, American Academy of Optometry Annual Meeting. Poster #111 (PO-129).	

4.2 Correct classifications and rationales for full-text examples

This exercise has been designed to illustrate four different categories of reports of trials you may encounter during your search. These are:

- Randomized clinical trials (to be coded as "**RCT**");
- Quasi-randomized clinical trials (to be coded as "**CCT**");
- Possible RCTs or CCTs (to be coded as "**CCT**"); and
- Clinical trials and studies that are *not* RCTs or CCTs (to be coded as **"N/A"**).

1. (Explicit) Randomized Clinical Trials (RCTs)

Sometimes the authors state explicitly, usually by using some variant of the term "random", that they have conducted a randomized clinical trial. Regardless of whether the key terms appear in the Title, Abstract, Methods section, or general text, all reports where authors describe their work as an RCT should be marked. These reports will be classified as publication type (PT) RANDOMIZED CONTROLLED TRIAL by the National Library of Medicine, (NLM) and will be included in CENTRAL.

1.1 Key words found in Abstract and/or Methods

Sometimes key words are found in the Title and there is therefore no need to read the Abstract or the remainder of the article. This is a rare occurrence, however, and the more common situation is to find key words in the Abstract and/or Methods sections. The following articles indicate that they describe RCTs in key words in the Abstract and/or Methods section.

Example 1

> Lee TM, Su SF, Chou TF, and Tsai CH. Pharmacologic preconditioning of estrogen by activation of the myocardial adenosine triphosphate-sensitive potassium channel in patients undergoing coronary angioplasty. J Am Coll Cardiol 2002; 39:871-7.

The Abstract contains the key words ***randomly allocated***. The Methods section further states that "*patients were **randomly allocated** to one of the five groups...*"

CODE: **RCT**

Example 2

Robertson MD, Henderson RA, Vist GE, and Rumsey RDE. Extended effects of evening meal carbohydrate-to-fat ratio on fasting and postprandial substrate metabolism. Am J Clin Nutr 2002; 75:505-10.

In the Abstract it is stated that the study contains two different treatments; "*On 2 occasions, the subjects received a high-fat evening meal (62% of energy from fat) and on the other 2 occasions the subjects received a low-fat evening meal (16% of energy from fat).*" This describes a crossover trial. However, key words regarding the method of allocation to the order of treatments is not found until the Subjects and Methods section, in which the subjects are described as "*studied on 4 occasions allocated in **random** order*."

CODE: **RCT**

Example 3

Koniak-Griffin D, Anderson NLR, Brecht ML, Verzemnieks I, Lesser J, and Kim S. Public health nursing care for adolescent mothers: impact on infant health and selected maternal outcomes at 1 year postbirth. J Adolesc Health 2000; 183:396-9.

The title and abstract of this report do not indicate whether or not this is a randomized trial. The key words, ***randomized** into the EIP or TPHN groups,* appear in the first paragraph of the Methods section, and the details of the randomization procedure are in the Procedures subsection.

CODE: **RCT**

1.2 Key words found elsewhere in the text

Sometimes, details concerning the study design are well hidden within the text of an article, usually (but not always) in the Methods section. In particular, information concerning the method used for allocation to comparison groups may be buried deep within the details describing the patient population, their clinical condition, the study environment, and so forth. Unless or until it is certain that the study described in an article is neither comparative nor prospective, it is extremely important to read every word the authors provide.

Example 4

Lin JL, Tan DT, Hsu KH, and Yu CC. Environmental lead exposure and progressive renal insufficiency. Arch Intern Med 2001; 161:264-271.

The Abstract describes both a prospective longitudinal study and "*a **controlled** clinical trial."* In the Patients, Materials, and Methods section under Chelation Clinical Trial (on the third page of the report) it is stated that, "*Thirty-six patients ... were **randomly assigned** to either the control or the study group* (1:2)." This report is tricky because it describes both an observational study in which patients were divided into two groups for observation according to their body lead burden, and a subsidiary clinical trial utilizing random allocation. The report is considered to be an RCT because of the clinical trial. If the study had only been a prospective observational study, the report would not have been eligible for CENTRAL.

CODE: **RCT**

1.3 RCTs which are not reported as full articles

Brief descriptions of RCTs and even full reports of RCTs can sometimes be found embedded in traditional review articles, which may not appear at first glance to be a type of article worth investigating. Reports of RCTs can sometimes also be found in published Abstracts or in the Letters section of a journal issue. Sometimes journals will publish supplemental issues of conference proceedings where RCTs were reported, and research has shown that many of these are not published later as full articles.

Example 5

Stiegemeier MJ. Clinical evaluation of a multi-purpose disinfecting solution used without a manual rubbing step. Clinical Ed., Case Reports & Scientific Posters. Sun. Dec. 10, 2000. Poster #67 (CL-221).

This is a published abstract from a conference poster. No indication of the study design is given in the Title. The Methods section of the Abstract states that this was "*a 30-day, **randomized**, patient-observed **masked** study*" and patients were "***randomly assigned***" to one of the two regimens.

CODE: **RCT**

Example 6

Wang J, Fonn D, Simpson TL, and Jones L. The measurement of corneal epithelial thickness using optical coherence tomography in response to hypoxia induced by soft contact lens and eye closure. Clinical Ed., Case Reports & Scientific Posters. Sun. Dec. 10, 2000 Poster #58 (CL-115).

This is a published abstract from a conference poster. The Methods section of the Abstract states that "*one eye (**randomly selected**) of twenty healthy non contact lens wearers ...*

was patched ... and the contralateral eye acted as control." In this case, the phrase **randomly selected** is used to mean randomly allocated to treatment. This is an example of using healthy participants to test a health-care related intervention. It is also an example of body parts within participants, rather than individual participants, being randomized to different interventions.

CODE: **RCT**

2. Quasi-Randomized Clinical Trials

Quasi-randomized clinical trials are similar to RCTs in many respects, except that the method used to allocate study participants to the comparison groups is not statistically random and is not stated to be so. Instead, allocation is done in some manner which is intended (whether successful or not) to be effectively random. Usually this is done by assigning patients alternately to one of two treatments, or by using some previously assigned number, such as hospital registration or social security number (e.g. patients with an odd registration number are assigned to receive Treatment A and patients with an even registration number are assigned to receive Treatment B). The potential for selection bias is greater with quasi-randomized trials than with randomized controlled trials, because the person responsible for making the treatment assignment is aware of what the next treatment assignment will be and can decide to enroll or not to enroll a participant on the basis of that knowledge.

These reports will be indexed as publication type (PT) "CONTROLLED CLINICAL TRIAL" by the NLM and will be included in CENTRAL as CCTs.

2.1 CCTs using alternation

Example 7

Wakefield M, Banham D, McCaul K, Martin J, Ruffin R, Badcock N, and Roberts L. Effect of feedback regarding urinary cotinine and brief tailored advice on home smoking restrictions among low-income parents of children with asthma: A controlled trial. Prevent Med 2002; 34:58-65.

The title of this paper contains the key words "***controlled trial***". Under Participants and Methods, the third paragraph mentions that the families were "*allocated to the control or intervention group*" but it is not until the Intervention Elements section on the third page of the article that the method of allocation is specified. The first sentence in the Intervention Elements section states: "*Families were **allocated by alternate week** to either an intervention group or a control group*."

CODE: **CCT**

2.2 CCTs using a previously defined number

Example 8

Scott S, Spender Q, Doolan M, Jacobs B, and Aspland H. Multicentre controlled trial of parenting groups for childhood antisocial behaviour in clinical practice. BMJ 2001; 323:1-7.

The title of this paper contains the key words "***controlled trial***". In the Abstract, the authors state that they performed the trial "*with* ***allocation by date of referral.***" In the Methods Section, under Assignment, it is stated that, "*Allocation was determined by* ***date of receipt of referral letter***".

CODE: **CCT**

3. Possible RCTs or CCTs

There are numerous reports that describe prospective, comparative studies that provide insufficient (or even contradictory) information concerning the study design, making it impossible to determine the method(s) used for allocation to treatment groups. These studies are given the benefit of the doubt and should be included in CENTRAL. Those preparing systematic reviews will thus be offered the opportunity of seeking clarification from the author(s) about the method of allocation used. The NLM will index them as publication type (PT) "CONTROLLED CLINICAL TRIAL".

3.1 Insufficient information

Insufficient information is given in the following articles to determine with certainty whether these are reports of RCTs, but it is possible that they are and therefore they should be "flagged" for inclusion.

Example 9

Teixeira F, Mosqueda-Taylor A, Montaño S, and Dominguez-Soto L. Treatment of recurrent oral ulcers with mometasone furoate lotion. Postgrad Med J 1999; 75:574.

This is a letter describing a clinical trial. In the second paragraph the authors state, "*we studied 35 patients*" who were given one treatment, and "*[a]nother group of 35 patients"* were "treated as controls." No information is given on how the treatment and control groups were determined. The use of randomization or quasi-randomization to allocate participants to

intervention groups cannot be ruled out, and therefore the report should be included in CENTRAL.

CODE: **CCT**

Example 10

McLachlan RI, O'Donnell L, Stanton PG, Balourdos G, Frydenberg M, De Kretser DM, and Robertson DM. Effects of testosterone plus medroxyprogesterone acetate on semen quality, reproductive hormones, and germ cell populations in normal young men. J Clin Endocrinol Metab 2002; 87:546-556.

In this study, men about to undergo vasectomy either proceeded directly to surgery or were given one of two different treatments for one of three different durations. There were therefore a total of seven intervention groups in the study. However, the article never explains how allocation to the intervention groups was decided. The use of randomization or quasi-randomization to allocate participants to intervention groups cannot be ruled out, and therefore this report should be included in CENTRAL. It should be noted here that this study is not, strictly speaking, a clinical trial; rather, it is a controlled pharmaceutical experiment in healthy people.

CODE: **CCT**

Example 11

Stodieck S, Steinhoff BJ, Kolmsee S, and Van Rijckevorsel K Effect of levetiracetam in patients with epilepsy and interictal epileptiform discharges. Seizure 2001; 10:583-587.

The abstract of this article describes the study as a, "***double-blind, placebo-controlled, crossover*** *study*." In the Methods section the study design is described as follows: "*eligible patients received a single-day supply of levetiracetam ... or* ***placebo*** *in a* ***double-blind crossover*** *design."* It is possible that the allocation to the first treatment (study treatment or placebo) could have been randomized or quasi-randomized, and therefore this study should be included in CENTRAL.

CODE: **CCT**

Example 12

Moore B, and the VIP Study Group. Comparing the usability of two visual acuity tests with preschool age children. Clinical Ed., Case Reports & Scientific Posters. Mon. Dec. 11, 2000. Poster #98 (PO-140).

This is a published abstract from a conference poster. In this study, children were given two visual acuity tests. In the Methods section of the abstract, it is stated that "*[t]he testing order was balanced between the two tests*." This is a type of crossover study. Without any specification of the order of the tests, it is not possible to tell whether the study was randomized, quasi-randomized, or neither. Because it is possible that the allocation to a particular ordering of tests could have been randomized or quasi-randomized, this study should be included in CENTRAL.

CODE: **CCT**

4. Clinical trials and studies that are not RCTs or CCTs

Not every study termed a "trial" or "clinical trial" is an RCT or CCT. Some articles report prospective studies that are experimental but not comparative. These could include "phase I" (safety and dosage) and some "phase II" (small efficacy) clinical trials that are neither randomized nor controlled. Other reports describe comparative studies where the method of assigning participants to the comparison groups was not intended to be random or effectively random. For example, in case-control studies, the "control" subjects are deliberately selected for their similarity to the "case" subjects in certain respects, such as sex or age. In addition, the exposure or "intervention" in case-control studies is not under the control of the investigators as it is in clinical trials.

Some comparative studies that are not RCTs make use of "historical" controls, i.e. patients who received an intervention over a time period prior to that in which the test group received an alternative intervention. Another type of comparison group used in studies that are not RCTs might be a group of individuals receiving an intervention at another location or under the care of another provider, but who were not assigned this care as part of a prospectively planned study using a specific method of allocation (such as randomization).

Finally, some studies may appear to be RCTs at first, since it may be stated that subjects were "chosen randomly". However, random selection does not necessarily imply random allocation to comparison groups. In some cases the comparison is made on groups of participants allocated according to clinical condition using two or more different tests. In other words, the people are used as measuring instruments to test the equipment's ability to distinguish between them. This kind of study is not an RCT, as it does not compare interventions. On the other hand, groups of one or more participants randomly assigned to receive one type of diagnostic test, and then another, followed by comparison of those results, would be an RCT.

4.1 Examples of studies which are not RCTs or CCTs

The following articles may appear at first glance to be reports of possible RCTs or CCTs, but they are not.

Example 13

Hardy KJ, O'Brien SV, and Furlong NJ. Information given to patients before appointments and its effect on non-attendance rate. BMJ 2001; 323:1298-1300.

This study compares the results of information given to a recent group of outpatients compared to a historical group of outpatients. In the abstract, the study is described as a "***non-randomised, controlled*** *study,"* so it is clear that the study is not an RCT. However, it is a controlled study, so the reader should ask whether it might be quasi-randomized. The abstract provides conclusive evidence that the study is not possibly quasi-randomized when it describes comparing the new patients to "*1336* ***historical controls*** *from the same clinic in the three years before.*" Since these groups were not treated concurrently, nor was a formal method used to randomly or quasi-randomly allocate participants to the two interventions, this article cannot be a report of an RCT or a CCT.

CODE: **N/A**

Example 14

Mamalakis G, Kafatos A, Manios Y, Kalogeropoulos N, and Andrikopoulos N. Adipose fat quality vs quantity: Relationships with children's serum lipid levels. Prevent Med 2001; 33:525-535.

It is stated in the Abstract that "*Pupils came from 40 schools* ***randomly selected*** *among 541 primary schools."* However, the description of the study makes it clear that there was no intervention administered during the study. Rather, the article describes an observational study in which children were observed over time but not allocated to interventions. Since this is an observational study, this article is not eligible for CENTRAL.

CODE: **N/A**

Example 15

Sanchez-Muniz FJ, Merinero MC, Rodriguez-Gil S, Ordovas JM, Rodenas S, and Cuesta C. Dietary fat saturation affects apolipoprotein AII levels and HDL composition in postmenopausal women. J Nutr 2002; 132:50-54.

This article reports a small crossover study, similar in design to that presented in Examples 11-13, but with an important difference. Under the heading "Experimental design" in the Subjects and Methods section, the authors state that, "*Study participants were assigned to two consecutive 28-d experimental periods. In the first period, all participants consumed a diet enriched in oleic acid, using high oleic acid sunflower oil as the only culinary fat. This was followed by a second diet period rich in palmitic acid from palmolein.*" In this study, all participants received the same sequence of treatments, so there is no possibility that the first treatment of the sequence was randomized or quasi-randomized. This study is therefore not eligible for CENTRAL.

CODE: **N/A**

Example 16

Ficarra A, and Sorkin R. Assessment of intraocular pressure in children by digital tension. Clinical Ed., Case Reports & Scientific Posters. Mon. Dec. 11, 2000. Poster #111 (PO-129).

This abstract is from a poster reporting a small crossover study, similar in design to that presented in Examples 11-13, but with an important difference. The study was conducted to determine how digital tension compares to Goldmann tonometry for measuring intraocular pressure in children. The authors state that, "*The examining doctor determined the digital tension (DT) of the child three times... A **masked** examiner then measured the pressure of the child with Goldmann tonometry (GT).*" Despite the fact that the keyword "masked" is used, it appears from the description of the study procedures that all participants received the same sequence of treatments. This study is therefore not eligible for CENTRAL.

CODE: **N/A**

Example 17

Jeandervin M, Walline JJ, Mitchell GL, Mutti DO, and Zadnik K. Use of the experience sampling method for near work assessment in children. Clinical Ed., Case Reports & Scientific Posters. Mon. Dec. 11, 2000. Poster #111 (PO-129).

This abstract reports a small study of the feasibility of a method for assessing daily visual tasks in children. Under Methods, the authors state the "*Thirty-one children were **randomly** paged after school ... and on weekends ... for seven consecutive days*." The intervention was random paging, and all participants received the same intervention.Despite the use of the keyword "randomly", the article is not eligible for inclusion in CENTRAL.

CODE: **N/A**

5. TEST JOURNAL SEARCH

The purpose of this exercise is to give you experience of a full-text search and to test your ability as a journal handsearcher.

5.1 Equipment:

To complete this exercise, you will need to search a volume of a journal. If the group you are working with does not have a gold standard to use for the test journal search, please contact the US Cochrane Center (cochrane@brown.edu) or (401)863-9950 and a volume of a journal will be assigned.

5.2 Instructions:

1. Take the journal volume you were assigned, and make a copy of the volume table of contents. If there is not a table of contents for the entire volume, copy the table of contents for each issue within the volume.

2. Working systematically, search through the entire journal issue from cover to cover, paying attention to editorials and letters as well as full articles, and identify each report of a randomized controlled trial (code as RCT), quasi-randomized controlled trial (code as CCT), possible RCT (code as CCT), and possible quasi-randomized controlled trial (code as CCT).

3. Code each potentially eligible report in the manner demonstrated in the self-assessment exercises; i.e. **RCT** (Randomized Controlled Trial) or **CCT** (quasi-randomized and possibly randomized or quasi-randomized controlled trial).

4. On the table of contents you have copied, mark **RCT** or **CCT** to the left of each potentially eligible trial report which you have identified.

5. When you have completed your full-text search, and marked each eligible trial report on the copied table of contents, copy the first page of each trial report that you have identified as an RCT or CCT. For each report, if you have used information only from the first page to classify the report, you do not need to copy any other pages. However, if you have used information from other pages of the report to classify the report, copy the pages from the report up to and including the page where it first became clear to you how to classify the report.

6. For each report, underline the phrases or sentences in the report that you used to classify the report as a CCT or RCT. This will aid you in remembering why you

classified the report as you did, and will also aid your instructor in understanding your rationale for classifying reports as you did.

7. Put your name at the top of the copied table of contents and staple the table of contents to the journal report pages. Return your copied table of contents and copied journal report pages to your Instructor.

8. We would appreciate it if you would also take this opportunity to complete the brief evaluation form in Appendix C and return this to: US Cochrane Center, Brown University, 169 Angell Street, Box G-S2, Providence, RI 02912.

Prior to undertaking this search you are advised to read the following notes as they may help you:

5.3 Notes

1. It is essential that you have read and understood Sections 1 and 2 and Appendix A of this manual. Now is the time to ask your Instructor about any points you are still unsure of.

2. **There is no time limit to this exercise.** Please feel free to take as long as you like. What is being tested is not how *fast* but how *thoroughly* you search through the text and how *precise* your understanding is of the sort of trials you are looking for.

3. Make use of all the notes you have made, along with the information contained in your training manual. The answers to the examples used in the self-assessment exercises may be relevant when it comes to coding the trials you have found.

4. You will be searching a bona fide issue of a biomedical journal. There are no trick entries or specially prepared traps for you to look for. By adhering to the criteria laid out in this training program, you should be fully equipped to identify all the reports of RCTs and CCTs to be found in this issue.

5. Because they contained so many examples of RCTs and CCTs, out of necessity, the self-assessment exercises in Sections 3 and 4 were very unrepresentative samples of journal articles. Despite its strength as an evaluative tool, the randomized controlled trial is still not as frequently reported as other forms of evaluation. Don't be surprised if your yield of RCTs and CCTs remains in single figures.

6. **Remember - as a handsearcher, you will rarely need to read an entire article all the way through**. You need only read an article to the point where you are able to make a firm decision to classify it as either an RCT, CCT, or N/A.

CRITERIA FOR RANDOMIZED CONTROLLED TRIALS (RCTS) AND CONTROLLED CLINICAL TRIALS (CCTS)

- **AN RCT OR CCT MUST COMPARE INTERVENTIONS IN LIVING HUMAN BEINGS**

  - The study must not be carried out exclusively *in vitro*. (If a study includes an *in vitro* component but is also carried out *in vivo*, it may be an RCT or CCT.)

  - The study may not be carried out exclusively in animals. (If a study is carried out in animals and in humans, it may be an RCT or CCT.)

  - The study must be carried out on actual human beings, not on a hypothetical cohort or as a simulation exercise.

  - The study must be carried out on living human beings, not on cadavers.

  - The study may be carried out on body parts or organs of living humans, such as legs, teeth or eyes. For example, patients with a vision problem affecting both eyes may each have one eye randomly allocated to receive a new treatment and the other eye allocated to receive the standard treatment.

  - The study may not be carried out on human parts that are outside of living humans, e.g., extracted teeth.

  - The study may be carried out on human parts that are replaced in living humans, e.g., donor organs or blood.

  - The study may compare interventions in groups of humans, such as communities, schools, or medical practices. For example, several churches may participate in a smoking cessation campaign. The members of some churches may randomly be allocated to a smoking cessation intervention that includes an exercise component, and members of other churches may be allocated to the standard smoking cessation intervention.

  - The study may compare interventions in a single person, if the person receives two or more treatments in a randomly (or quasi-randomly) determined order. This type of study design is usually called an N-of-1 design.

- **AN RCT OR CCT MUST BE RELATED TO HEALTH STATUS, HEALTH CARE, OR HEALTH RESEARCH**

  - The intervention may be a drug, surgical, or behavioral treatment or prevention of disease or injury.
  - The intervention may be a screening program.
  - The intervention may be a diagnostic instrument, test or technique.
  - The intervention may be a comparison of dose amounts, dose timing, or titration regimens.
  - The intervention may be a comparison of the same intervention at two or more different durations.
  - The intervention may be the medical education of physicians or other health professionals, or the education of patients or other non-health professionals about health or disease.
  - The health-related outcomes include psychological or psychiatric health, as well as any behavioral outcomes that are explicitly related to health.
  - The health-related outcomes include athletic performance.
  - The health-related outcomes include differences in expense or cost-effectiveness.
  - The health-related outcomes may be related to health research, such as follow-up rates or response rates to a survey.
  - The study may be randomized but be ineligible for inclusion in the Cochrane Library if the subject matter is not health related (i.e., does not fit into one of the above categories).

- **AN RCT OR CCT MUST BE EXPERIMENTAL**

  - An intervention must be given to the participants. The intervention must be planned before the study begins, and the investigators must control which participants are exposed to the intervention.
  - The results of the intervention must be measured after exposure to the intervention.

- **AN RCT OR CCT MUST CONTAIN TWO OR MORE INTERVENTIONS**

  - The study may compare any two or more interventions to each other, including treatment to no treatment, one or more active treatments to placebo, or a conventional treatment to some new treatment.

  - The study may not give all participants the same two or more interventions in the same order. For example, if all participants are given placebo first and then active medication, the study is not an RCT or CCT.

  - The study may give all participants the same two or more interventions if the order of interventions is definitely or possibly randomized or quasi-randomized. This is sometimes called a crossover study design, in which all participants receive each of two or more interventions in a definite order. An example of a crossover study design is the Latin Square.

- **AN RCT MUST HAVE PARTICIPANTS DEFINITELY ASSIGNED TO INTERVENTIONS BY RANDOMIZATION**

  - The article may explicitly state that participants were assigned to interventions by means of a random number table or other mathematical randomization technique, in which case the article is an RCT.

  - If the article states that participants were randomized, but does not state the method of randomization, it is assumed that randomization took place and the article is an RCT, unless there is strong evidence to the contrary.

  - If the article does not explicitly state that a randomization technique was used, or that participants were randomized, the article is not an RCT.

- **A CCT MUST HAVE PARTICIPANTS ASSIGNED TO INTERVENTIONS BY EITHER: 1) QUASI-RANDOMIZATION, OR 2) POSSIBLE RANDOMIZATION OR QUASI-RANDOMIZATION**

- **A CCT MAY HAVE PARTICIPANTS DEFINITELY ASSIGNED TO INTERVENTIONS BY QUASI-RANDOMIZATION**

  - The article may explicitly state that participants were quasi-randomly assigned to interventions, in which case the study is a CCT.

  - If the article explicitly states that participants were allocated to intervention groups using a method that we know approximates but does not meet the criteria of mathematical

randomization, the allocation method is quasi-randomization and the study is considered a CCT. Examples of quasi-randomization techniques include alternation, odd-even numbers, days of the week, social security number, and medical record number.

- **A CCT MAY HAVE PARTICIPANTS POSSIBLY ASSIGNED TO INTERVENTIONS BY RANDOMIZATION OR QUASI-RANDOMIZATION**

  - If the article states that participants were allocated to different interventions, but does not specify how the participants were assigned to particular interventions, and the participants may have been randomly or quasi-randomly assigned, the study is a CCT.

- **IF THE METHOD OF ASSIGNMENT TO TREATMENT WAS DEFINITELY NOT RANDOM AND NOT QUASI-RANDOM, THE STUDY IS NOT AN RCT OR CCT AND IS NOT ELIGIBLE FOR CENTRAL**

- **SOME EXAMPLES OF NON-RCT, NON-CCT ASSIGNMENT**

  - If the article states that participants were randomly selected to participate in a study but it does not appear that the participants were definitely or possibly randomly or quasi-randomly allocated to different interventions, the article is not an RCT or CCT.

  - If the article states that participants were allocated to intervention groups using a method which we know to be neither randomization nor quasi-randomization, the article is not an RCT or CCT. Examples of allocation methods that are neither random nor quasi-random include clinical reasons for assignment to particular treatments, or participants' selection of their own treatment.

  - Another example of non-random, non-quasi-random assignment is the assignment of all participants seen in the beginning of the trial to one intervention, and all the participants at the end of the trial to a different intervention. This is not a random or quasi-random method of assigning patients to interventions. For example, if the investigators decide that all patients seen from January to June will receive standard treatment and all patients seen from July to December will receive a new treatment, the study is not an RCT or CCT.

  - A final example of non-random, non-quasi-random assignment is the comparison of trial participants to persons who did not participate in the trial. The study may not compare results of an intervention planned and allocated by the investigators to results of another intervention that was not planned and allocated by the investigators. An intervention not planned and allocated by the investigators may be found in a historical control comparison group, a concurrent control comparison group, or a subsequent control

comparison group. In such cases, the comparison group was definitely not formed by a random or quasi-random method. For example, if the investigators select some patients to receive a new treatment and then compare the results of that new treatment to the results generally seen from conventional treatment, the study is not an RCT or CCT.

- Lastly, if the purpose of the article is not to compare different treatments but solely to compare different types of participants, such as sick individuals compared to healthy individuals, the article is not an RCT or CCT. For example, a study comparing lung capacity during exercise in a group of asthma patients and a group of matched healthy controls is not an RCT or CCT.

- **SOME ADDITIONAL NOTES:**

- **REVIEWS AND META-ANALYSES**

  - Reviews are reports that summarize the knowledge to date about some medical condition or an intervention. Reviews may refer to a series of both published and unpublished trials but do not usually report new information about any one controlled trial. Reviews are therefore usually not considered to be RCTs or CCTs.

  - Systematic reviews, including meta-analyses, are reviews that use statistical methods to summarize the results of multiple studies. Systematic reviews also rely on a series of both published and unpublished trials but do not usually report new information about any one controlled trial. Such reviews are therefore not considered to be RCTs or CCTs.

  - Sometimes a meta-analysis or review presents new information about a controlled trial, or will be done in conjunction with a new RCT or CCT. In such cases the meta-analysis or review is considered an RCT or CCT

- **PHASE I, PHASE II, PHASE III AND PHASE IV TRIALS**

  - Phase I trials are often dose ranging trials which are done to determine the maximum dose of a new medication that can be safely given to a patient. They are often not controlled trials. However, when Phase I trials use randomization or quasi-randomization to compare intervention regimens, they are considered RCTs or CCTs.

  - Phase II trials are done to test the efficacy of a new medication or intervention. When Phase I trials use randomization or quasi-randomization to compare intervention regimens, they are considered RCTs or CCTs.

- Phase III trials are done to determine the effectiveness and possible adverse reactions for a new intervention. Most Phase III trials are randomized, and this will usually be stated explicitly in the title or abstract. Phase III trials which do not explicitly mention randomization are considered CCTs, unless the article states that the study is not a comparative or controlled study, in which case the trial is not an RCT or CCT.

- Phase IV trials are done to monitor the toxicity and utility of an intervention after the efficacy of the intervention has been proven. When Phase IV trials use randomization or quasi-randomization to compare interventions they are considered RCTs or CCTs.

- **ADDITIONAL ISSUES SURROUNDING RANDOMIZED TRIALS**

  - When an article provides new information about the planning, design, protocol development, recruitment strategies, or conduct of an RCT or CCT, the article is considered an RCT or CCT. By itself, the statement that a clinical trial is being planned or has begun is not sufficient to make an article an RCT.

  - When an article presents baseline data on randomized participants from an RCT or CCT, the article is an RCT or CCT even when no results of the intervention comparison are presented

  - When an article presents preliminary results of an RCT, the article is an RCT

  - When an article presents new data, a new analysis, or new information about the participants, outcome criteria, or some other aspect of a previously published RCT, the article is an RCT

  - When an article presents the results of a follow-up to an RCT, such as an open-label extension or a naturalistic follow-up, the article is considered an RCT

GLOSSARY

Many of the entries in this Glossary have been used verbatim or were derived from:

> Cooper, Harris M. and Hedges, Larry V., Editors, *The Handbook of Research Synthesis,* New York: Russell Sage Foundation, 1994.
>
> Last, John M., *A Dictionary of Epidemiology, 2nd Edition,* New York: Oxford University Press, 1988.
>
> Meinert, Curtis L., *Clinical Trials Design, Conduct, and Analysis,* New York: Oxford University Press, 1986.

Bold italic print has been used to denote terms that are defined elsewhere in the Glossary.

allocation The process of making a *treatment allocation.* (Meinert, p.282)

assignment unit See experimental unit.

bias Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth. (Last, p.13)

bibliographic database A machine-readable file of information about documents. Most often consists of bibliographic citations, although some databases provide abstracts or summaries of a document's contents, the sponsoring institutions, list of terms reflecting the document's contents, and so on. Typically can be searched using a variety of fields (e.g. author's name, keywords in title, year of publication, sponsoring agency). (Cooper and Hedges, p.532)

bibliographic search An exploration of the published literature for reports of interest. Typically conducted by scanning periodicals, paper indexes, and reference lists of selected articles (a "hand" search) or by means of computer-based software that accesses existing listings of references or bibliographic databases ("electronic" search), such as *MEDLINE.* (Cooper and Hedges, p.532)

blind(ed) study (Syn: **masked study**) A study in which the observer(s) and/or subjects are kept ignorant of the group to which the subjects are assigned, as in an experiment, or of the population from which the subjects come, as in a non-experimental study. When both the observer and subjects are kept ignorant, we refer to a ***double-blind*** study. If the statistical analysis is also done in ignorance of the group to which subjects belong, the study is sometimes described as ***triple-blind***. The intent of keeping subjects and/or investigators blinded, i.e. unaware of knowledge that might introduce a ***bias,*** is to eliminated the effects of such biases. To avoid confusion about the meaning of the word "blind " some authors prefer to describe such studies as "masked". (Last, p.17)

case-control study (Syn: case comparison study, case compeer study, case history study, case referent study, ***retrospective study)*** A study that starts with the identification of persons with the disease (or other outcome variable) of interest, and a suitable *control* (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently an attribute is present or, if quantitative, the levels of the attribute, in each of the groups. Such a study can be called "retrospective" because it starts after the onset of disease and looks back to postulated causal factors. Cases and controls in a case control study may be accumulated "prospectively; "that is, as each new case is diagnosed it is entered in the study. Nevertheless, such a study may still be called "retrospective" because it looks back from the outcome to its causes. The terms "cases"

and "controls" are sometimes used to describe subjects in a ***randomized controlled trial*** but, the term "case control study" should not be used to describe such a study. (Last, p. 20)

cohort study See **prospective study**.

clinical trial (Syn: therapeutic trial) A research activity that involves the administration of a test regimen to humans to evaluate its efficacy and safety. The term is subject to wide variation in usage, from the first use in humans without any ***control treatment*** to a rigorously designed and executed experiment involving test and control treatments and ***randomization***. See also **community trial**. (Last, p. 25)

community trial Experiment in which the unit of allocation to receive a preventive or therapeutic regimen is an entire community or political subdivision. Examples include the trials of fluoridation of drinking water, and of heart disease prevention in North Karelia (Finland) and California. See also **clinical trial**. (Last, p.27)

comparative clinical trial Any ***clinical trial*** involving two or more ***treatment groups***. (Meinert, p.285) See also **controlled clinical trial; randomized clinical trial; randomized controlled trial.**

comparative study A ***study*** involving two or more defined groups of patients in which groups are compared, one with another, in order to make a judgement regarding the influence of some factor, condition, trait, or procedure that is present or applied to one group but not to the other(s). Synonymous with ***controlled clinical trial*** if the study entails comparison of different treatments involving patients enrolled and treated over the same period of time. (Meinert, p.285)

comparison group The group of patients designated or selected for comparison with all other groups in a ***study***. The ***control-treated group*** of patients in a ***controlled clinical trial***. (Meinert, p.285)

concurrent control See **controls, concurrent.**

control

1. (v.) To regulate, restrain, correct, restore to normal.

2. (n. or adj.) Applied to many communicable and some noncommunicable conditions, “control" means ongoing operations or programs aimed at reducing the incidence and/or prevalence, or eliminating such conditions.

3. (n.) As used in the expressions ***case-control study*** and ***randomized control(led) trial,*** "control" means person(s) in a comparison group that differs, respectively, in disease experience or allocation to a regimen, from the subjects in the study.

4. (v.) In statistics, "control" means to adjust for or take into account extraneous influences or observations.

5. (adj.) In the expression "control variable", we refer to an independent variable other than the hypothetical causal variable that has a potential effect on the dependent variable and is subject to control by analysis.

The use of the noun "control" to describe the comparison groups in a case-control study and a randomized control(led) trial can confuse the uninitiated, e.g. ethical review committees; the essential ethical distinction is that there may be no intervention in the lives or health status of the controls in a case-control study, whereas controls in a randomized controlled trial may be asked to undergo a procedure or regimen that may affect their health; their informed consent is therefore essential. Consent may not be required (save to gain access to medical records) to study controls in a case-control study. As M. W. Susser[1] has pointed out, the use of the word "control" as a verb, adjective, and noun may confuse even careful readers. The verb is best used in the sense of controlling sources of extraneous variation in the dependent variable, whether by design or analysis. The verb is also used in the sense of controlling disease or its causes. The adjective is best used to describe control variables in contradistinction to uncontrolled and confounding variables. The adjective can also be used to describe a control group assembled for comparison with a group of cases or with an experimental group. The noun is best used to designate the members of a control group. (Last, p.30)

[1] *Causal Thinking in the Health Sciences*. New York: Oxford,1973.

control group See **control-treated group**.

control treatment The drug, device, test, or procedure administered in a ***clinical trial*** that serves as the standard against which ***test treatments*** are evaluated. The control treatment may consist of a ***placebo*** medication, sham procedure, a standard treatment regimen, or no treatment of any kind, depending on the study design. (Meinert, p. 285)

controls, concurrent Controls based on data that is collected over the same period of time as that used to generate all other data in the study. (Meinert, p.285) See controls, historical for opposing term.

controls, historical Persons or patients used for comparison who had the condition or treatment under study at a different time, generally at an earlier period than the study group or cases.

Historical controls are often unsatisfactory because other factors affecting the condition under study may have changed to an unknown extent in the time elapsed. (Last p.30) See **controls, concurrent** for opposing term.

controls, matched Controls who are selected so that they are similar to the study group, or cases, in specific characteristics. Some commonly used matching variables are age, sex, race, and socioeconomic status. (Last p.31)

control-treated group (Syn: **control group, comparison group**)

1. The group of patients assigned to the ***control treatment***.

2. The group of patients in a trial who received the ***control treatment***, whether or not originally assigned to that treatment. (Meinert, p.285)

controlled clinical trial A ***clinical trial*** involving one or more ***test treatments,*** at least one ***control treatment,*** and concurrent enrollment, ***treatment,*** and follow-up of all patients in the trial. (Meinert, p.286)

crossover treatment design A treatment design that calls for the administration of two or more of the ***study treatments*** in a specified order to ***experimental units*** in the ***trial***. (Meinert, p.296)

double-blind (Syn: **double-blinded, double-masked, double-mask**)

1. A procedure in a ***clinical trial*** for issuing and administering ***treatment assignments*** by code number in order to keep study patients and all members of the clinical staff, especially those responsible for patient treatment and data collection, from knowing the assigned treatments. The procedure is designed to ensure that ascertainment of outcome is not biased by knowledge of the group to which an individual was assigned. "Double" refers to both parties, i.e. the observer(s) in contact with the subjects, and the subjects in the study and control groups. (Meinert, p.288; Last, p.39)

2. Any condition in which two different groups of people are purposely denied access to a piece of information in order to keep that information from influencing some measurement, observation, or process. (Meinert, p.288)

double-blinded clinical trial (Syn: **double-masked clinical trial, double-blind(ed) study, blind(ed) trial, masked trial, blind(ed) study, masked study**) A **clinical trial** with **double-blind** administration of the study **treatments**. (Meinert, p. 288)

experimental study A study in which conditions are under the direct control of the investigator. In epidemiology, a study in which the population is selected for a planned trial of a regimen whose effects are measured by comparing the outcome of the regimen in the experimental group with the outcome of another regimen in a control group. To avoid **bias** members of the experimental and ***control groups*** should be comparable except in the regimen that is offered them. Allocation of individuals to experimental or ***control groups*** is ideally by ***randomization***. In a ***randomized controlled trial,*** individuals are randomly allocated; in some experiments, e.g. fluoridation of drinking water, whole communities have been (non- randomly) allocated to experimental and ***control groups***. (Last p.45)

experimental unit or group (Syn: **treatment assignment unit**) The unit used in the treatment assignment or allocation process, usually a patient, but the unit may be made up of multiple individuals (such as in a ***trial*** involving treatment of a family unit or an entire hospital ward) or may be a part of an individual (such as an eye or a tooth).

haphazard A process occurring without any apparent order or pattern. Distinct from ***random*** in that there is no mathematical basis for characterizing a haphazard process.

historical control See **controls, historical**.

intervention (Syn: **treatment**) A drug, device, procedure, or regimen being tested in a ***clinical trial.***

intervention trial Technically, any ***clinical trial,*** since administration of any ***treatment*** in a trial setting is a form of intervention. However, the term is usually reserved for trials in which the ***test treatment*** entails life-style changes. (Meinert, p.292)

latin square An n X n square arrangement of n copies of the latin letters A, B, C, ..., such that each letter appears in each row and column exactly once.

An example of a 4 X 4 latin square:

ABCD
BCDA
CDAB
DABC

A latin square study design is a type of ***crossover*** study design.

mask(ed) (Syn: **blind(ed)**) A condition imposed on an individual (or group of individuals) for the purpose of keeping that individual or group of individuals from knowing or learning of some fact or observation, such as ***treatment assignment***. (Meinert, p.293) Preferred by some authors to ***blind(ed)*** due to the potential for confusion with other meanings of the word "blind".

matched control See **controls, matched**.

matching placebo A pill (capsule or tablet) that is designed to resemble in shape, texture, size, taste, etc., a therapeutically active drug and that is used as the ***control treatment***. (Meinert, p.293)

MEDLINE An acronym for MEDLARS on Line. (MEDLARS is an acronym for Medical Literature Analysis and Retrieval System and comprises 18 databases.) The most frequently used electronic database within MEDLARS, it contains more than 11 million citations from over 4,600 selected medical and scientific journals from 1966 to the present, with some selected articles back to 1963. Compiled by the National Library of Medicine. The paper version of MEDLINE is *Index Medicus*. (Cooper and Hedges, p.537)

MeSH Medical Subject Headings The controlled vocabulary index created by the National Library of Medicine to index published articles listed in *Index Medicus* and MEDLINE. It contains approximately 20,000 terms. (Cooper and Hedges, p.537)

meta-analysis A combination of the prefix “meta”, used in the sense of “later or more highly organized or specialized form of” with the word analysis. Refers to the qualitative and quantitative analysis of one or more previous clinical studies for the purpose of integrating the findings, usually involving the pooling of data across studies.

observational study (Syn: non-experimental study, survey) Epidemiologic study in situations where nature is allowed to take its course; changes or differences in one characteristic are studied in relation to changes or differences in other(s), without the ***intervention*** of the investigator. (Last p. 91)

open clinical trial (Syn: open trial)

1. A ***clinical trial*** in which a study physician or study patient decides on the ***treatment*** to be administered. A non-random clinical trial.

2. A non-masked ***clinical trial***.

3. A ***clinical trial*** with an open sequential design.

(Meinert, p. 296)

open label trial

1. A non-masked drug trial.

2. Any non-masked trial.

(Meinert, p.296)

partially masked clinical trial

1. A ***clinical trial*** in which some, but not all, of the study ***treatments*** are administered in a ***single-*** or ***double-masked*** fashion.

2. A ***clinical trial*** in which some, but not all, of the staff in a clinic are ***masked*** to the ***treatment*** assignment. (Meinert, p.297)

phase I trial The first stage in testing a new drug in human beings. Performed as part of an approved *Investigational New Drug Application* under Food and Drug Administration guidelines. The studies are usually done to generate preliminary information on the chemical action and safety of the drug using normal healthy volunteers. Usually done without a ***comparison group***. (Meinert, p. 297)

phase II trial The second stage in testing a new drug in human beings. Performed as part of an approved *Investigational New Drug Application* under Food and Drug Administration guidelines. Generally carried out on patients with the disease or condition of interest. The main purpose is to provide preliminary information on treatment efficacy and to supplement information on safety obtained from ***phase* I *trials***. Usually, but not always, designed to include a ***control treatment*** and ***random allocation*** of patients to ***treatment***. (Meinert, p.297)

phase III trial The third and usually final stage in testing a new drug in human beings. Performed as part of an approved *Investigational New Drug Application* under Food and Drug Administration guidelines. Concerned primarily with assessment of dosage effects and efficacy and safety. Usually designed to include a ***control treatment*** and ***random allocation*** to ***treatment***. Once this phase is completed, the drug manufacturer may request permission to market the drug by submission of a *New Drug Application* to the Food and Drug Administration, assuming that the results of the ***phase* I, II** and **III *trials*** are consistent with such a request. (Meinert, p.298)

phase IV trial Generally, a ***randomized controlled trial*** that is designed to evaluate the long-term safety and efficacy of a drug for a given indication and that is done with Food and Drug Administration approval. Usually carried out after licensure of the drug for that indication. (Meinert, p.298)

placebo (Syn: ***sham procedure)*** An inert medication or procedure given as a substitute for an active medication or procedure, where the patient is not informed whether he is receiving the active or inert medication or procedure.

placebo-controlled clinical trial A ***clinical trial*** in which patients assigned to the ***control treatment*** receive a ***placebo***. (Meinert, p.298)

placebo treatment

1. A ***treatment*** involving the use of a ***placebo***.

2. A ***treatment*** that is harmless.

(Meinert, p.298)

prospective study (Syn: **prospective follow-up study**) A study in which people with a specific attribute or characteristic are identified and then observed for some period of time thereafter for the occurrence of the outcome or condition of interest, usually disease or death. The study may or may not involve a ***comparison group***. ***Clinical trials*** represent a special subset of prospective follow-up studies. (Meinert, p.299)

Publication Type Controlled Clinical Trial National Library of Medicine publication type for reports of ***controlled clinical trials*****:**

> A clinical trial involving one or more test treatments, at least one control treatment, specified outcome measures for evaluating the studied intervention, and [an intended to be bias-free] method of assigning patients to the test treatment. The treatment may be drugs, devices, or procedures studied for diagnostic, therapeutic, or prophylactic effectiveness. Control measures include placebos, active medicine, no-treatment, dosage forms and regimens, historical comparisons, etc. When randomization using mathematical techniques, such as the use of a random numbers table, is employed to assign patients to test or control treatments, the trial is characterized as a RANDOMIZED CONTROLLED TRIAL. However, trials employing treatment allocation methods such as coin flips, odd-even numbers, patient social security numbers, days of the week, medical record numbers, or other such pseudo- or quasi-random processes are simply designated as controlled clinical trials.

Publication Type Randomized Controlled Trial National Library of Medicine publication type for reports of ***randomized controlled trials***:

> A clinical trial that involves at least one test treatment and one control treatment, concurrent enrollment and follow-up of the test- and control-treated groups, and in

which the treatments to be administered are selected by a random process, such as the use of a random numbers table. Treatment allocations using coin flips, odd-even numbers, patient social security numbers, days of the week, medical record numbers, or other such pseudo- or quasi-random processes, are not truly randomized and a trial employing any of these techniques for patient assignment is designated simply a CONTROLLED CLINICAL TRIAL.

random Governed by chance; not completely determined by other factors, as opposed to deterministic. (Last p.110)

random allocation See **randomization**.

randomization Allocation of individuals to groups, e.g. for experimental and control regimens, by chance. Within the limits of chance variation, randomization should make the ***control*** and ***experimental groups*** similar at the start of an investigation and ensure that personal judgement and prejudices of the investigator do not influence ***allocation***. Randomization or random assignment should not be confused with ***haphazard*** assignment. Random assignment follows a predetermined plan that is usually devised with the aid of a table of random numbers. The pattern of assignment may appear to be haphazard, but this arises from the haphazard nature with which digits occur in a table of random numbers, and not from the haphazard whim of the investigator in allocating patients. (Last p. 110)

randomized controlled trial (RCT) (Syn: **randomized clinical trial, randomized control trial, randomized controlled clinical trial**) An experiment in which subjects in a population are ***randomly allocated*** into groups, usually called "study" and "control" groups, to receive or not to receive an ***experimental preventive or therapeutic procedure, maneuver, or intervention***. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups, respectively. RCTs are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology. (Last, p. 110)

register, registry In epidemiology the term "register" is applied to the file of data concerning all cases of a particular disease or other health-related condition in a defined population such that the cases can be related to a population base. The *register* is the actual document, and the *registry* is the system of ongoing registration. (Last, p.112)

sham procedure A procedure designed to resemble the real one and that is performed on a patient for the purpose of ***masking*** the patient or the patient's study physician as to whether the patient has received the real procedure. (Meinert, p.302)

single-blind(ed) (Syn: **single-mask(ed)**) A condition in which certain persons (e.g. the study physicians) are informed of some fact or condition, whereas other persons (e.g. patients) are purposefully denied information regarding that fact or condition. (Meinert, p.302)

single-blind(ed) clinical trial (Syn: **single-mask(ed) clinical trial**)

1. A ***clinical trial*** in which ***treatments*** are administered in such a manner that patients in the trial are not informed of whether they have been assigned to the ***test*** or ***control treatment,*** but clinic staff are.

2. A ***clinical trial*** in which the patient knows the ***treatment*** assigned, but the treating physician, examiner, or observer does not.

(Meinert, p.302)

study

1. A general term used to refer to anyone of a variety of research activities involving the collection, analysis, or interpretation of data.

2. Sometimes used as a synonym for ***clinical trial***.

3. A project involving multiple types of investigations, only one of which is a ***clinical trial*** (e.g. as in the Coronary Artery Surgery Study, since it includes both a clinical trial and an uncontrolled ***prospective follow-up study***).

(Meinert, p.303)

study group

1. Any defined group of patients on whom data are collected.

2. The entire group of patients included in a ***study***.

3. Often synonymous with ***treatment group***.

4. The group of investigators carrying out a study. (Meinert, p.304)

study treatment General term used to refer to either a ***test*** or a ***control treatment***. (Meinert, p.304)

systematic review See ***meta-analysis***.

test group A group of patients defined by the study design - patients assigned to the ***test treatment*** in a ***clinical trial*** - who are contrasted with the ***control group*** of patients to reach a conclusion regarding some factor, condition, or treatment. (Meinert, p.305)

test-treated group

1. The group of patients assigned to the ***test treatment***.

2. The group of patients who receive the ***test treatment***.

(Meinert, p. 305)

test treatment The drug, device, or procedure to be evaluated in a particular ***trial***. (Meinert, p.305)

treatment

1. The act of treating, as in caring for a patient.

2. The specific regimen, method, ***intervention,*** or procedure being tested in a ***clinical trial***.

(Meinert, p.305)

treatment allocation

1. The process of assigning patients to ***treatment***.

2. The ***treatment assignment*** of a particular patient. (Meinert, p. 305)

treatment arm Term sometimes used in place of ***study treatment,*** or ***study group,*** especially in cancer ***trials***. (Meinert, p. 305)

treatment assignment The ***treatment*** to be administered to the ***experimental unit***. (Meinert, p.305)

treatment crossover Any change of ***treatment*** for a patient in a ***clinical trial*** involving a switch of ***study treatments***. The switch may be planned, such as in a ***crossover*** trial, or may be unplanned. (Meinert, p.306)

trial See clinical trial.

triple-blind(ed) (Syn: **triple-mask(ed)**) ***Double-blinded*** or ***double-masked*** plus blinding or masking for the individual or group of individuals responsible for treatment monitoring. (Meinert, p.307)

triple-blind(ed) clinical trial (Syn: **triple-mask(ed) clinical trial**) A ***double-blind clinical trial*** in which data analyses done for treatment monitoring are presented to the individual or group responsible for such monitoring in a way that conceals the identity of the ***treatment groups***. (Meinert, p.307)

uncontrolled clinical trial A ***clinical trial*** that does not involve a ***control treatment***. (Meinert, p.307)

HANDSEARCHER TRAINING EVALUATION

Once you have completed the Training Manual for Handsearchers, please complete this evaluation. Honest and constructive comments, however critical, enable us to make future training more effective. It is not necessary to include your name on the evaluation form. Please send the evaluation form to: US Cochrane Center, Brown University, 169 Angell Street, Box G-S2, Providence, RI 02912
or fax to: (401)863-9944.

SECTION 1: INTRODUCTION

Please circle the entry you most agree with.

The pace was: Too fast Just right Too slow

The content was: Easy to follow Difficult in parts Too difficult to follow

Please give examples of those points in Section 1 you found difficult to follow:

The presentation was: Excellent Good Average Patchy Poor

Please give details of those parts of the presentation in Section 1 which you think could be improved, and how you would improve them.

Section 1 was: Useful Not useful No opinion

SECTION 2: IDENTIFYING AND CLASSIFYING REPORTS ELIGIBLE FOR CENTRAL

Please circle the entry you most agree with.

The pace was:	Too fast	Just right	Too slow
The content was:	Easy to follow	Difficult in parts	Too difficult to follow

Please give examples of those points in Section 2 you found difficult to follow:

_____

_____

_____

The presentation was:	Excellent	Good	Average	Patchy	Poor

Please give details of those parts of the presentation in Section 2 which you think could be improved, and how you would improve them.

_____

_____

_____

Section 2 was:	Useful	Not useful	No opinion

SECTION 3: SELF-ASSESSMENT EXERCISE WITH ABSTRACT EXAMPLES

Please circle the entry you most agree with.

The pace was: Too fast Just right Too slow

The content was: Easy to follow Difficult in parts Too difficult to follow

Please give examples of those points in Section 3 you found difficult to follow:

The presentation was: Excellent Good Average Patchy Poor

Please give details of those parts of the presentation in Section 3 which you think could be improved, and how you would improve them.

Section 3 was: Useful Not useful No opinion

SECTION 4: SELF ASSESSMENT EXERCISE WITH FULL-TEXT ARTICLE EXAMPLES

Please circle the entry you most agree with.

The pace was: Too fast Just right Too slow

The content was: Easy to follow Difficult in parts Too difficult to follow

Please give examples of those points in Section 4 you found difficult to follow:

The presentation was: Excellent Good Average Patchy Poor

Please give details of those parts of the presentation in Section 4 which you think could be improved, and how you would improve them.

Section 4 was: Useful Not useful No opinion

SECTION 5: HANDSEARCHING TEST

The parts of the full-text journal search I found most useful were:

The parts of the full-text journal search I found least useful were:

Did you find Appendix A: Criteria for Randomized Controlled Trials (RCTs) and Controlled Clinical Trials (CCTs) useful? Please explain:

Did you find Appendix B: Glossary useful? Please explain:

Overall, the parts of the Training Manual for Handsearchers I found most useful were:

Overall, the parts of the Training Manual for Handsearchers I found least useful were:

Overall, the training was: _____

Excellent Good Satisfactory Barely adequate Poor

Additional Comments:

Thank you very much for completing the Training Manual for Handsearcher evaluation and helping us make this training more effective.

Thank you!