Drug and Therapeutics Committee
Training Course

Session 3.
Assessing Medicine Efficacy

Trainer’s Guide
This document was made possible through support provided by the U.S. Agency for International Development, under the terms of cooperative agreement number HRN-A-00-00-00016-00. The opinions expressed herein are those of the author(s) and do not necessarily reflect the views of the U.S. Agency for International Development.

About RPM Plus

RPM Plus works in more than 20 developing and transitional countries to provide technical assistance to strengthen pharmaceutical and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning, and in promoting the appropriate use of health commodities in the public and private sectors.

Recommended Citation

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ABBREVIATIONS AND ACRONYMS

ADR        adverse drug reaction
CI         confidence interval
DTC        Drug and Therapeutics Committee
Mg         milligram
n or N     number
RCT        randomized controlled trial
VA         visual aids
SESSION 3. ASSESSING MEDICINE EFFICACY

Purpose and Content

Session 3 is designed to provide participants with a basic guide on how to determine medicine efficacy, primarily through review of the pharmaceutical literature with an emphasis on evaluating randomized controlled trials (RCTs), systematic reviews, and meta-analyses. Systematic and thorough evaluations of the pharmaceutical literature will provide the Drug and Therapeutics Committee (DTC) with the unbiased information necessary to select appropriate medicines for the formulary.

In most countries, evaluating the pharmaceutical literature is commonly done by physicians and pharmacists. Unfortunately, this review is often done incorrectly. With the tools presented in this session and practice at home, participants will be better equipped to evaluate the literature systematically and scientifically.

Objectives

After attending this session, participants will be able to—

- Understand the importance of determining efficacy and evaluating the clinical literature
- Discuss the major types of medicine study design
- Describe the key components of a journal article
- Understand how to evaluate and interpret results of a randomized controlled trial
- Discuss the use of systematic reviews and meta-analyses in evaluating medicines

Outline

- Introduction
- Assessing medicine studies in the clinical literature
- Systematic review and meta-analysis
- Activities
- Summary

Further Readings


**Preparation and Materials**

- Read the Trainer’s Guide and the Participants’ Guide, and review the visual aids (VAs).

- Prepare for the activity of critically reading an article by—
  - Thoroughly reading all the articles and critiques of the articles (that you have obtained locally)
  - Deciding whether you want to cover one, two, or three articles

- Instruct participants to read—
  - Participants’ Guide the evening before the session presentation
  - The article(s) assigned to them

- Distribute the chosen article(s) to each participant at least one day in advance. If you are using more than one article, instruct the participants that they need only prepare to critique one article in depth but they will want to read the other article(s) so they will understand the plenary discussion during which one group will present a critique on one article. Make sure that you instruct all the members of each table group to read the same article in depth because they will be working in groups the next day.

- Ensure that you have at least two calculators per table (of five to eight people).

**Visual Aid Listing**

1. Title slide
2. Introductory graphic
3. Objectives
4. Outline
5. Introduction
6. Getting Started Evaluating an Article: Formulating the Question
7. Evidence: What Kind and How to Find It
8. Example from PubMed
9. Assessing the Quality of the Evidence: What Makes a Good Clinical Trial?
10. Evaluation of a Clinical Medicine Study
11. Checklist for Evaluating Medicine Studies (1)
12. Checklist for Evaluating Medicine Studies (2)
13. Example of an RCT (1)
14. Example of an RCT (2)
15. Example of an RCT (3)
16. Checklist for Evaluating Medicine Studies (3)
17. Checklist for Evaluating Medicine Studies (4)
18. Checklist for Evaluating Medicine Studies (5)
19. Checklist for Evaluating Medicine Studies (6)
20. Checklist for Evaluating Medicine Studies (7)
21. Example: Summary of the Key Sources of Bias in a Randomized Trial
22. Quality of RCTs: What to Look for (1)
23. Quality of RCTs: What to Look for (2)
24. Quality of RCTs: What to Look for (3)
25. Quality of RCTs: What to Look for (4)
27. Understanding the Numbers (1)
28. Understanding the Numbers (2)
29. Understanding the Numbers (3)
30. Understanding the Numbers (4)
31. Understanding the Numbers (5)
32. Understanding the Numbers (6)
33. Systematic Reviews (1)
34. Systematic Reviews (2)
35. Systematic Reviews (3)
36. Meta-analysis
37. Meta-analysis—Forest Plot
38. Potential Clinical Study Problems: Objectives
39. Potential Clinical Study Problems: Methods (1)
40. Potential Clinical Study Problems: Methods (2)
41. Potential Clinical Study Problems: Methods (3)
42. Potential Clinical Study Problems: Results and Conclusions
43. Systematic Review Problems
44. Activities
45. Summary

**Organization of the Session**

**Total time: 4–6 hours**

Reading clinical literature critically to evaluate medicine efficacy is difficult and requires time, skill, and experience. Session 3 is designed to introduce the participants to the skills needed, and difficulties encountered, in evaluating the literature to determine medicine efficacy and effectiveness. The session is long and difficult, and it will require a minimum of four hours to
complete if the participants are given an article to read critically and in detail at least one day in advance of the session. If they need time during the session to read the article, add an extra hour at least (preferably two hours) to the session if you plan to use the activity on reading and criticizing an article. Run this session from first thing in the morning, reaching the end of the group discussion by lunch time. Group presentations critiquing the articles with plenary discussion can be run after lunch.

How the activity is carried out will depend on the English language skills of the participants. A group of fluent English speakers of sufficient educational level (i.e., a degree in medicine or pharmacy) will be able to read more articles in greater depth. For such a group, you may choose to give three different articles to everyone to read but with instructions that each group need only prepare one of the articles (assigned by the facilitator) for presentation in the plenary discussion the next day. For groups with language difficulties or with participants of a lower educational level, distribute only one article in advance, and limit the plenary discussion to only the major points of this one article.

First Component: 15 minutes
VAs 1–5: Introduction

Explain that this session will be only an introduction to the topic of evaluating medicine efficacy, a difficult task requiring sophisticated skills. Ask if anyone has experience of evaluating the clinical literature for medicine efficacy.

Second Component: 60 minutes
VAs 6–26: Evaluating an Article and Methodology Used in Medicine Studies

The second component, which covers basic methodological issues, can be technical and heavy going. To keep the participants’ interest and to ensure that they understand, ask questions from time to time such as—

- What kind of evidence should we obtain?
- What do we want to know from a medicine trial?
- What kinds of study design are there?
- How do we select patients for a medicine trial?
- What is an adequate sample of patients?
- What are outcome variables? Give some examples.
- What is confounding?
- What is a control group?
- Why do we need randomization?

Bring out in the discussion how important answering the research question is for methodology. A good understanding now of the basic methodological components of a study will enable the participants to better understand the later discussion about the various methodological problems frequently encountered in the literature.
Third Component: 30 minutes  
VAs 27–32: Understanding the Numbers (Interpreting the Data)

The third component covers the common measures for assessing medicine efficacy. Refer to the Participants’ Guide, and demonstrate the calculations on an overhead projector or blackboard.

Fourth Component: 15 minutes  
VAs 33–37: Systematic Reviews and Meta-analysis

Stress the importance of systematic reviews and the advantages to DTC members in using them.

Fifth Component: 20 minutes  
VAs 38–43: Common Problems with Clinical Studies and Systematic Reviews

The fifth component is best started by asking the participants to brainstorm common problems with clinical studies, and then use the VAs to summarize the main problems. Try to avoid simply reading the slides to the participants. You need not cover every point because all the points are in the Participants’ Guide. Point out that a reader needs to study an article carefully before accepting what is said in the article’s conclusions.

Sixth Component: 120 minutes  
VA 44: Activities

Activity 1. Comparing Antimicrobial Medicines for Pneumonia (15 minutes)

This activity is optional depending on the skill levels of the participants. Higher level participants will find this much too easy. Responses to look for in the discussion are in italics below the questions.

For activity 1, assume that your DTC is considering the formulary addition of a new antimicrobial medicine to treat lower respiratory tract infections in children. The medicine study abstract you have just read concludes that this medicine’s efficacy is equal to a combination of antibiotics in treating pneumonia in hospitalized children. This study looked at 35 children in the treatment group and 43 in the control group. The setting was a large university hospital. This study was an open-label study, and children receiving a new antimicrobial were compared with other children in the hospital who were receiving different antibiotic combination regimens to treat pneumonia. Patients were chosen to receive this antibiotic by the physician depending on the severity of the pneumonia. The medicine requested for the formulary was typically given to children with less severe pneumonia (based on the judgment of the physician), and the combination medicine therapy was reserved for children who appeared to be sicker and at higher risk. Results showed that the study medicine was equally effective as a combination of antibiotics and was less costly. No difference in the incidence of adverse drug reactions (ADRs) was found. The manufacturer of the medicine sponsored the study.
You are especially interested in such a medicine since it is less costly and the study shows that it is effective. Safety information is limited at the early stages of its marketing.

- How would you describe the study design? Is it valid?

  Non-random, non-blinded, biased, comparative medicine trial. Not valid

- What are the controls in the study?

  The study lacks proper control because the children treated with the new medicine had milder pneumonia than the so-called control group of those treated with the old regime of two medicines.

- How are the patients randomized?

  They are not randomized. The individual physicians decided which regime to prescribe based on the severity of pneumonia.

- What kinds of bias can be introduced into this study?

  Selection bias—Only the milder cases were given the new medicine; the more severe cases received the old regime of two medicines.

  Measurement bias—All patients and physicians knew which regime had been prescribed so the judgment of prescribers concerning outcome and occurrence of ADRs could have been influenced by their opinions about the two medicine regimes. More hard evidence of outcome and safety is needed.

  Confounding bias—The two groups being compared were different in terms of severity of pneumonia as well as being exposed to different medicine regimes, both of which (severity and medicine regime) are related to the outcome (recovery from pneumonia).

- Are the results of this study usable in your country?

  No.

Activity 2. Interpreting the Data: The Helsinki Heart Study
(15 minutes)

This activity should always be done to ensure that all participants understand how to calculate measures of efficacy.

- Subjects: 4,081 asymptomatic men aged 40–55 with dyslipidemia (total cholesterol minus high-density lipoprotein > 5.2 mmole/liter)
• **Treatment:** gemfibrozil 600 milligram (mg) twice daily (2,051 men) or matched placebo (2,030 men) in a five-year randomized double-blind study

• **Results:** number of events (fatal, nonfatal myocardial infarction, or cardiac death)
  - Gemfibrozil—56 events
  - Placebo—84 events

Please calculate the following—

- Event rate for placebo = \( \frac{84}{2,030} = 4.13\% \)
- Event rate for gemfibrozil = \( \frac{56}{2,051} = 2.73\% \)
- Relative risk reduction = \( 1 - \left( \frac{2.73}{4.13} \right) = 34\% \)
  —large reduction in risk of myocardial infarction, cardiac death
- Absolute risk reduction = \( 4.13 - 2.73 = 1.4\% \)
  —small number of people benefit from the reduced risk
- Number needed to treat for 5 years to prevent 1 event = \( \frac{1}{1.41} = 71 \)
  —need to treat 71 patients to see the beneficial effect in one patient

**Activity 3. Critically Evaluating an Article**

(45 minutes)

This activity should be used if time permits.

There are three articles for review and discussion by the participants (which you already have). You can use any or all of them in this activity. You may want to use all three articles for higher level participants and just one article for lower level participants. If using more than one article, have at least two groups review the same article so that adequate discussion can result from the presentations.

Assuming that all have read their assigned articles the night before, the groups should spend 60 minutes discussing and preparing a presentation of a critique of their assigned articles. The next 30 minutes is spent on five-minute presentations by three groups you pick at random. Each presentation should be on a different article if all three articles are used. After each presentation, the group that also reviewed the article should be invited to report on which points they agree and disagree and then the floor should be opened to general questions and discussion. The groups should be briefed in how to give their presentations, including the following points—

- A succinct summary of what the study is about
- The strong points
- The weak points
- Whether the conclusions of the study are justified
Activity 4. Critically Interpreting the Data: A Medicine Trial to Compare Artesunate with Mefloquine to Treat Malaria (45 minutes)

This activity can be done in addition if time allows and the skill levels of the participants are sufficient. The answers are in italics in the two grids. (Source: Looareesuwan S, Viravan C, Vanijanonta S et al. 1992. Randomised Trial of Artesunate and Mefloquine Alone and in Sequence for Acute Uncomplicated Falciparum Malaria. *Lancet* 339:821–24.)
Answers to Exercises

Dosage Regimen and Baseline Characteristics in Trials

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Looareesuwane et al. (1992)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Artesunate N=42</td>
</tr>
<tr>
<td>Dosage regimen</td>
<td>100 mg then 50 mg q 12 h for 5 days (total 600 mg)</td>
</tr>
<tr>
<td>Proportion male [n (%)]</td>
<td>38 (90.5%)</td>
</tr>
<tr>
<td>Age [mean (standard deviation)]</td>
<td>27 (9.2)</td>
</tr>
<tr>
<td>Parasite count [mean(range)]</td>
<td>14,195</td>
</tr>
<tr>
<td></td>
<td>(172, 180, 950)</td>
</tr>
</tbody>
</table>

Efficacy Results from Looareesuwane et al. (1992)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Artesunate N=42</th>
<th>Mefloquine N=43</th>
<th>Difference in Means (95% confidence interval [CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever clearance time [mean (std dev)]</td>
<td>35.1 (23.4)</td>
<td>69.7 (37.5)</td>
<td>-34.6 (-48.1, -21.1)</td>
</tr>
<tr>
<td>Parasite clearance time [mean (std dev)]</td>
<td>35.9 (10.1)</td>
<td>63.5 (25.5)</td>
<td>-27.6 (-36.0, -19.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Artesunate N=42</th>
<th>Mefloquine N=43</th>
<th>Relative risk (95% CI)</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients cured at 28 days [n (%)]</td>
<td>35</td>
<td>30</td>
<td>1.19 (0.94, 1.56)</td>
<td>13.6% (-4.7, 31.3)</td>
</tr>
<tr>
<td>Patients completing 28 days follow-up [n (%)]</td>
<td>40</td>
<td>37</td>
<td>1.11 (0.96, 1.32)</td>
<td>9.2% (-3.9, 23.4)</td>
</tr>
</tbody>
</table>

Seventh Component: 15 minutes
VA 45: Summary

Summarize the key points of the session and allow time for questions.