

**CME**

**An Approach to reading Clinical Research ‘The M.A.A.R.I.E Framework’**

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**Abstract:**

The M.A.A.R.I.E. framework is the basis for a step-by-step approach to reading the clinical research literature. The six elements of the M.A.A.R.I.E. framework; Method, Assignment, Assessment, Results, Interpretation, Extrapolation and the three questions associated with each element form the basis for a step-by-step approach to reading the medical evidence. The paper discusses the use of this framework in form of a checklist taking example of a real journal article employing Clinical Experimental design model. Hope this checklist will be useful to young and upcoming researchers to evaluate epidemiologic literature systematically.

**Key Words:** Approach to read paper, Clinical Research, M.A.A.R.I.E framework

Critical appraisal of the reported research is important in today’s era of Evidence Based Medicine. The M.A.A.R.I.E. framework outlined below is one of the frameworks which use a step-by-step approach to reading and appraising the clinical research literature. The six elements of the M.A.A.R.I.E. framework; Method, Assignment, Assessment, Results, Interpretation, Extrapolation and the three questions associated with each element form the basis for a step-by-step approach to reading the medical evidence. This checklist can be useful to young and upcoming researchers to evaluate epidemiologic literature systematically. However, it is important to note that M.A.A.R.I.E. is applicable only to the analytical type of epidemiological studies. An example of a generic MAARIE is shown below.

**MAARIE Questionnaire:**

**Method- The purpose and population for the investigation**

**Study hypothesis:** What is the study question being investigated?

**Study population:** What population is being investigated and what are the inclusion and exclusion criteria for the subjects of the investigation?

**Sample size and statistical power:** How many individuals are included in the study and in the control groups and what is the statistical power?

**Assignment- Selection of participants for the study and control groups**

**Process:** What method is used to identify and assign participants to study and control groups?

**Confounding variables:** Are there differences between study and control groups, other than the factor being investigated that may affect the outcome of the investigation?

**Masking or blinding:** Are the participants and/or the investigators aware of the participants’ assignment to a particular study or control group?

**Assessment- Measurement of outcomes or endpoints in the study and Control groups**

**Appropriate:** Does the measurement of outcomes address the study’s question?

**Accurate and precise:** Is the measurement of outcomes an accurate and precise measure of the phenomenon that the investigators seek to assess?

**Complete and unaffected by**

**observation:** Is the follow-up of participants nearly 100% complete and is it affected by the participants' or the investigators knowledge of the study or control group assignment?

**Results- Comparison of outcomes in the study and control groups**

**Estimation:** What is the magnitude or strength of the association or relationship?

**Inference:** What statistical technique(s) are used to perform statistical significance testing?

**Adjustment:** What statistical techniques(s) are used to take into account or control for potential confounding variables?

**Interpretation- Meaning of the results for those included in the Investigation**

**Contributory cause or efficacy:** Does the factor being investigated alter the probability that the disease will occur (contributory cause) or work to reduce the probability of undesirable outcomes (efficacy)?

**Harms and interactions:** Are adverse effects and/or interactions that affect the meaning of the results identified?

**Subgroups:** Are the outcomes observed in subgroups within the investigation different from outcomes observed in the overall investigation?

**Extrapolation- Meaning for those not included in investigation**

**To similar individuals, groups or populations:** Do the investigators extrapolate or extend the conclusions to individuals, groups, or populations that are similar to those who participated in the investigation?

**Beyond the data:** Do the investigators extrapolate by extending the conclusions beyond the dose, duration, or other characteristics of the investigation?

**To other populations:** Do the investigators extrapolate to populations or settings that are quite different from those in the investigation?

A real journal article employing Clinical Experimental design was chosen model and responded to the MAARIE questionnaire.

**Please download Article:** Corey L, Wald A, Patel R, et al. Once-Daily Valacyclovir to Reduce Risk of Transmission of Genital Herpes. N Engl J Med 2004; 350:11-20.

**Now we proceed step by step using MAARIE Questionnaire as follows: Method- The purpose and population for the investigation**

**Study hypothesis:** Once daily dose of Valacyclovir reduces the risk of transmission of genital herpes in the susceptible partner.

**Research Question:** Does once daily dose of Valacyclovir reduce the risk of transmission of genital herpes in susceptible partner?

**The study population being investigated:** Was heterosexual couples who were serologically discordant for HSV-2 infection from 96 study sites.

**The inclusion criteria:** For the HSV-2–seropositive source partner were; an age of 18 years or older, presence of recurrent genital herpes with fewer than 10 episodes per year, and nonuse of any daily antiviral therapy. The inclusion criteria for the susceptible partner were; an age of 18 years or older and HSV-2 seronegativity on Western blots analysis. The relationship between the source partner and the susceptible partner was required to be monogamous. Both partners were required to be immunocompetent and in good health and the couple to be using effective contraception.

**The exclusion criteria:** Of the 4034 screened couples, 1385 of the susceptible partners (34.3 percent) were HSV-2–positive at the time of screening and hence were ineligible, 799 of the source partners (19.8 percent) were not HSV-2–positive and hence were ineligible, and 352 couples (8.7 percent) declined to take part.

**Sample size:** 1484 immuno-competent, heterosexual, monogamous couples: one with clinically symptomatic genital HSV-2 and one susceptible to HSV-2 was the population investigated. Of the 1484 source partners, 743 were in the Valacyclovir group and 741 in the placebo group, and they took their assigned study medication.

**Statistical power:** Because this study was designed to detect a 75 percent difference between valacyclovir and placebo in the rates of clinically symptomatic disease, it was estimated that 28 confirmed cases of genital HSV-2 infection were required for 90 percent power with a two-tailed test of proportions at the 5 percent significance level. It was estimated that random assignment of 750 couples to each treatment group would achieve these assumptions.

**Assignment- Selection of participants for the study and control groups**

The HSV-2-seropositive partners were randomly assigned, in a 1:1 ratio, to 500 mg of valacyclovir once daily or to matching placebo. At each visit, safer sex practices, including the use of condoms during sexual intercourse, were discussed with each partner, and standardized counseling was provided when signs and symptoms of genital herpes were recognized. Randomization was performed at a central site in blocks of 10 to ensure balance between the groups. Randomization was stratified according to the sex and HSV-1 status of the susceptible partners.

**Confounding variables:** The differences between study and control groups, other than the factors being investigated that might affect the outcome of the investigation/ can influence the likelihood of transmission are: 1.frequency of sexual contact; 2. frequency of (Level of) condom usage; 3.sex of susceptible partner, 4.duration of relationship and 5.duration of infection in source partner.

**Masking or blinding:** There is no mention whether the participants and/or

the investigators were aware of the participants' assignment to a particular study or control group. But an end-points committee, whose members were blinded to the treatment assignment, reviewed all cases of genital herpes clinically diagnosed during the study. This committee also reviewed all cases in which the susceptible partner had an abnormal genital symptom or sign during the study, as well as all cases of genital herpes confirmed by laboratory analysis.

**Assessment- Measurement of outcomes or endpoints in the study and control groups**

**Appropriateness:** The predefined primary end point of the study was the reduction in transmission of symptomatic genital herpes in the susceptible partner. And the study question is, “does once daily dose of Valacyclovir reduce the risk of transmission of genital herpes in susceptible partner”? The study concludes that once-daily suppressive therapy with valacyclovir significantly reduces the risk of transmission of genital herpes among heterosexual, HSV-2-discordant couples.

**Accuracy and Precision:** Clinically symptomatic genital herpes was defined according to the presence of clinical signs and symptoms and was confirmed by isolation of HSV-2 in culture, detection of HSV-2 DNA by PCR, or HSV-2 seroconversion in the susceptible partner during the course of the trial. Thus the measurement of outcomes is an accurate and precise measure of the phenomenon that the investigators sought to assess.

**Complete and unaffected by observation:**

The follow-up of participants is not affected by the participants' or the investigators' knowledge of the study or control group assignment. An end-points committee, whose members were blinded to the treatment assignment, reviewed all cases of genital herpes clinically diagnosed during the study. This committee also reviewed all cases in which the

susceptible partner had an abnormal genital symptom or sign during the study, as well as all cases of genital herpes confirmed by laboratory analysis. It is mentioned that, of the 1484 participating couples, 1159 (78.1 percent) completed the study. Reasons for withdrawal among the remaining 325 couples were based on the source partner's reason and included 82 who withdrew voluntarily (28 assigned to valacyclovir and 54 to placebo), 99 who were lost to follow-up (53 and 46, respectively), 66 whose relationship was dissolved (33 and 33, respectively), 16 who had an adverse event (11 and 5, respectively), 16 for whom there were protocol violations (8 and 8, respectively), 13 who decided to attempt pregnancy (6 and 7, respectively), 9 who reported frequent recurrences while taking the study medication (1 and 8, respectively), and 24 who withdrew for other reasons (18 and 6, respectively). The total number of withdrawals and the reasons for withdrawal were similar for the couples whose source partner was assigned to take valacyclovir (21 percent) and those whose source partner was assigned to take placebo (23 percent). However, voluntary withdrawal was more frequent among source partners who were randomly assigned to placebo than among those who were randomly assigned to valacyclovir (54 v/s 28,  $P=0.003$ ), probably because of the frequent recurrences among the placebo-treated source partners.

### **Results- Comparison of outcomes in the study and control groups**

**Estimation:** Clinically symptomatic HSV-2 infection developed in 4 of 743 susceptible partners who were given valacyclovir, as compared with 16 of 741 who were given placebo (hazard ratio, 0.25; 95 percent confidence interval, 0.08 to 0.75;  $P=0.008$ ).

Susceptible partners who were given placebo are at 4 times more risk of acquiring clinically symptomatic HSV-2 infection as compared to susceptible

partners who were given valacyclovir. Overall, acquisition of HSV-2 was observed in 14 of the susceptible partners who received valacyclovir (1.9 percent), as compared with 27 (3.6 percent) who received placebo (hazard ratio, 0.52; 95 percent confidence interval, 0.27 to 0.99;  $P=0.04$ ). Susceptible partners who were given placebo are 2 times more at risk of overall, acquisition of HSV-2 as compared to susceptible partners who were given valacyclovir.

**Inference:** Hazard ratio (Cox-proportional-hazards model with covariates defined according to stratum of treatment), Confidence interval, Two tailed test of proportion ( $P<0.001$ ). Stratified version of fisher's exact test, Log-rank-test, Interaction tests.

**Adjustment:** Potential confounding variables are mentioned earlier. Exploratory covariate analyses were performed for both clinical and overall HSV-2 acquisition. Condom use was defined as a time-dependent covariate. In these multivariate analyses, factors found to influence the risk of HSV-2 transmission significantly were female sex of the susceptible partner, greater number of sexual contacts, and shorter duration of genital herpes in the source partner as previously mentioned. There was no evidence that valacyclovir had a reduced therapeutic effect when efficacy was examined among subgroups defined by these covariates.

### **Interpretation- Meaning of the results for those included in the investigation**

**Contributory cause or efficacy:** The study demonstrates that oral valacyclovir taken by immunocompetent persons with recurrent genital HSV-2 infection significantly reduces the rates of HSV reactivation, sub-clinical shedding, and transmission of genital herpes to a susceptible partner. A 500-mg dose of valacyclovir taken once daily reduced the risks of acquisition of symptomatic genital herpes and acquisition of HSV-2 infection

overall by susceptible, HSV-2–seronegative heterosexual partners. The results of the trial demonstrate the effectiveness of treating the source partner with an antiviral agent to reduce the risk of transmission of a sexually transmitted viral disease. The results were in addition to any effects that may have been attributable to counseling or safer-sex practices used by the study population.

**Harms and interactions:** The frequency of adverse effects was similar in the placebo and valacyclovir groups and was similar to those reported in studies of valacyclovir in immunocompetent persons with genital herpes. No serious adverse events were considered by the investigators to be related to use of the study medication. HSV-2 isolates were available for sensitivity testing from 11 of the 20 cases of symptomatic new infection. All 11 isolates were sensitive to acyclovir, with plaque-neutralization titers of less than 0.2 µg per milliliter.

**Subgroups:** In these multivariate analyses, factors found to influence the risk of HSV-2 transmission significantly were female sex of the susceptible partner, greater number of sexual contacts, and shorter duration of genital herpes in the source partner.

There was no evidence that valacyclovir had a reduced therapeutic effect when efficacy was examined among subgroups defined by these covariates.

**Extrapolation- Meaning for those not included in the investigation**

**To similar individuals, groups or populations:** The authors have extended the conclusions of the study to individuals having similar characteristics.

**Beyond the data:** The investigators do not extrapolate by extending the conclusions beyond the dose, duration. But investigators have mentioned that because the observed reduction in the rate of transmission of genital herpes with valacyclovir is clinically relevant but not complete, it is important that disclosure of genital herpes to the susceptible partner and the practice

of safer sex continue, since both may reduce the risk of transmission of genital herpes. However, the study does not define the levels of condom use in combination with valacyclovir therapy that would provide optimal or suboptimal protection.

**To other populations:** The investigators have tried to extrapolate both the biologic and cost-effectiveness aspects of the data in this study to other settings as following;

They have mentioned that, ” It is likely that the transmission effects we found are applicable to nonmonogamous heterosexual couples. Valacyclovir is effective in suppressing genital herpes in men who have sex with men. However, as shown in the trial, sexual transmission is influenced by sexual behavior and biologic factors. Most instances of HSV-2 transmission occur with source partners who do not have a history of genital herpes, and few studies describing daily antiviral medication in such persons are available. Additional studies to evaluate whether suppressive therapy will prevent transmission among couples with a source partner with subclinical HSV-2 infection, couples in whom the susceptible partner is immune-compromised, and homosexual couples should be undertaken. Studies in which the susceptible partner is pregnant are of special importance because of the high risk of acquisition of HSV-1 or HSV-2 infection in this setting. The few cases of asymptomatic HSV-1 acquisition in this study were not sufficient to allow us to determine whether valacyclovir would reduce the risk of HSV-1 transmission.”

**Recommendation:**

1. M.A.A.R.I.E framework can be used as Systematic Guideline/Checklist to evaluate articles.
2. The M.A.A.R.I.E. step by step approach to reading medical literature by postgraduate students can be taken up through Journal Clubs.