1. **What was the medical problem that was being addressed by this study?**

The study evaluated the efficacy of a standardized acupuncture regimen (SAR) and amitriptyline hydrochloride as a pain relief treatment for HIV-related peripheral neuropathy. A double blind, randomized, placebo-controlled methodology was used to address this problem.

2. **Were the investigators trying to study two different treatments at the same time? What are advantages of doing this? Disadvantages?**

Yes, they were trying to investigate the effects of both a nonstandard and standard medical therapy. The advantage of doing this is that they were able to study the effects of using a combination of the two treatments. In many cases, using a combination of treatments (such as anti-retroviral medications) can be very effective in slowing HIV progression and relieving the symptoms and complications associated with AIDS. A possible disadvantage might be that the study becomes very complex and hard to control for bias when studying two treatments at once.

3. **Was there good reason to think that either of the two treatments might be effective?**

Yes, there was reason to believe that these two treatments might be effective. For instance, several trials in the past have claimed the efficacy of the use of acupuncture to relieve chronic pain. Meta-analyses of these studies show a response rate of approximately 70% for acupuncture. Similarly, amitriptyline is often used to treat neuropathic pain and has even been shown as an effective treatment for “diabetic, hereditary, toxic, and idiopathic neuropathies.” However, the efficacy of these treatments is based on clinical trials in other disease conditions.

4. **The acupuncture aspect of this trial was 'placebo-controlled'. Was it double blind? Single blind? What are some of the issues about this?**

The acupuncture aspect was so-called “placebo-controlled” since the standardized acupuncture regimen was compared with “control points.” However, the control points may have produced certain effects, suggesting that it may not have been a very accurate method of control. The study was supposed to be double-blind in that the acupuncturists
were the only people unblinded to the SAR vs. control points assignments, and the pain diaries and assessments of pain relief were collected by study staff who were blinded to the treatment assignments. However, it was very possible for patients to guess their treatment better than randomly, in which case the study may not have been completely double-blind. In fact, there was a strong association between the patients’ guess and the global pain relief rating.

5. Some people are already convinced that acupuncture works. Others are convinced that it does not. What do you think? If you were already convinced one way or the other, would it be ethical for you to conduct this clinical trial?

   My prior belief about acupuncture is that it may be beneficial to some people and not others. Perhaps it helps to relieve stress, which produces positive effects in individuals suffering from certain afflictions. If I were absolutely convinced that acupuncture works for everyone, it is possible that I could bias the study in some way. Good, ethical researchers are open to all possibilities and don’t use their research to confirm their opinions or beliefs.

6. How do you interpret the confidence intervals given in the 'Results' section of the Abstract (p. 1590)? Is the evidence for an effect stronger for acupuncture or for amitriptyline?

   The confidence intervals show the range of values in which the difference between the two means may lie. At 6 weeks, the amitriptyline group (as compared to the placebo group) had a greater reduction in pain than the SAR group (as compared to the control points group). At 14 weeks, the SAR group had a greater reduction in pain as compared to the amitriptyline group.

7. The investigators randomized 250 patients. What was their basis for doing this?

   So that they would have the statistical power (90%) to detect a mean difference between treatments of 0.20 on the pain intensity scale using a type I error of .05.

8. At the end of the Statistical Analysis section, the text says "in February 1997, the monitoring board recommended closing the study because it concluded that the results were definitive for both acupuncture and amitriptyline." What does that mean, "definitive"?

   That there was enough data to safely interpret results and draw conclusions as to whether the treatments were effective.

9. How did the investigators choose the points at which the acupuncture needles were to be inserted?

   “The SAR was based on a Chinese theory that peripheral neuropathy caused by diabetes and HIV-related peripheral neuropathy have similar mechanisms.” The theory
listed specific points that were supposed to relieve pain in different areas of the body. The investigators chose their points on the basis of this theory. Eight acupuncturists also agreed on these points.

10. Why isn't amitriptyline sold over the counter?

It is a commonly abused drug in certain communities.

11. State the main conclusions of this trial in your own words.

The two treatments, SAR and amitriptyline hydrochloride, were found to be uneffective in relieving pain associated with HIV-related peripheral neuropathy. Neither treatment was more effective than the placebo. Both groups showed minor improvement in pain from average intensity to moderate or mild, but this change was not significantly different from the control points group and the placebo group. All effects were small and nonsignificant.

12. What do you think the consequences of this trial were for patients and for medical practice?

As a result of this study, medical practices may have limited their use of acupuncture and amitriptyline hydrochloride as pain relief treatments for HIV-related peripheral neuropathy. There may have been negative consequences in the past for patients who were given these uneffective treatments instead of ones that may have improved their condition. However, if the results of this study are accurate, there will be fewer negative future consequences for patients since these treatments may not be used as often or at all.

13. See the Letters to the Editor and the authors' responses. What issues are raised by the letter writers? Do you agree with what they say?

Issues:
- The investigators might have chosen the wrong points for the standardized acupuncture regimen.
- The type of acupuncture that they used was not scientific.
- The dose of amitriptyline was limited (at 75 mg/d).
- The acupuncture treatment was not standardized.

It seems to me that it would be very difficult to completely standardize the acupuncture treatment. It might be possible to do it with electrical stimulation (?). However, because there are so many different kinds of acupuncture, it would be nearly impossible to develop a treatment that would satisfy every acupuncturist on the face of the planet. In this regard, I agree more with the authors of the paper. However, I’m still not completely clear on why they didn’t use a higher dose of amitriptyline since other studies had done so in the past. I’m not sure if I know enough to have an opinion on this.
I do believe that the investigators might not have had an effective control group for SAR, and that they might have needed a group that didn’t receive acupuncture in order to address this possible limitation.

14. **How might the investigators have decided on a trial design which would have addressed the letter writers' concerns?**

   Again, I don’t believe that the investigators could have developed a trial design that would have addressed all the letter writers’ concerns. In order to completely standardize the acupuncture treatment, they would have needed to have a single acupuncturist treat all the patients, or have used electrical stimulation instead of doing it manually. However, there might be acupuncturists who insist that manual treatment works better. It seems that acupuncture is somewhat subjective.

15. **Do you think the letter writers would have said the same things about the acupuncture points if the results had turned out in favor of acupuncture?**

   Perhaps they would if it wasn’t their form of acupuncture that was validated.

16. **The 239 patients in the acupuncture part of the study all knew they were getting some kind of acupuncture. That is, among them there was really no 'pure control' group of people who didn't get any kind of acupuncture. In actual medical practice, patients get either acupuncture treatment which is believed to be effective, or none at all - they do not get an acupuncture treatment which is NOT believed to be effective. Do you think the investigators should have included a 'pure control' group?**

   I think that it would be very beneficial for the investigators to have included a ‘pure control’ group. The control point group that they did use might have affected the results in some way.

17. **Some people have done studies of acupuncture to relieve pain in dogs and horses. Is it possible to carry out the evaluations so as to rule out the possibility that the investigator's bias can affect the results?**

   Investigators in this study might not have been completely blind to the treatment assignments and may have been able to guess which treatment was used on which patients. It is possible to use statistical methods to explore the magnitude of the bias and correct for it within the study design or the results of the study. Investigators might need to be formally evaluated on their opinions and beliefs about the study.

18. **If you were suffering from peripheral neuropathy, would you want to try acupuncture? In light of this study, should your insurance company or HMO have to pay for it? Same questions for amitriptyline.**
In light of this study, I would only use acupuncture or amitriptyline if it were my last option. Instead, I would look for alternative treatments that might actually be effective. My insurance company or HMO should not have to pay for either treatment since they have been shown to be uneffective in relieving pain associated with HIV-related peripheral neuropathy.

19. Do you think there are other alternatives to the two treatments tested in this trial?

Yes, I think that there are alternatives to these treatments. Some benefits have been demonstrated through the use of lamotrigine and recombinant human nerve growth factor (http://www.thebody.com/conf/retro2001/henry4.html). Gabapentin (Neurontin), carbamazepine (Tegretol) and phenytoin (Dilantin) also may be effective in treating symptoms (http://www.atdn.org/simple/neurop.html).

20. Do you have any other comments on this clinical trial?

No.