On "Statistical Considerations" Sections

Ralph O'Brien, Jean Lightner Norum, John Castelloe

A well-developed "Statistical Considerations" section persuades colleagues and reviewers that solid skill and effort have gone into framing the research questions, planning the study, and forming an appropriate team. It should be written to stand mostly on its own and thus may duplicate some material found elsewhere in the proposal. The writing should be crafted mostly for the experienced researcher who has a sound basic understanding of statistical modeling, hypothesis testing, and confidence intervals, but it may include some material suitable only for the professional biostatistician. Short proposals will not have a separate section, but should still address the issues discussed herein.

Components

Primary research questions. Strictly speaking, not all studies are driven by testable hypotheses, but all studies have primary research questions and key secondary questions. Delineate them clearly, perhaps following 1-3 sentences of background information.

Design and measures. Summarize the study design and the key measures. It may be helpful to use appropriate terms such as randomized, double blind, crossover, controlled, case-control, prospective, retrospective, longitudinal, cohort, Latin squares, incomplete blocks, etc. Summarize the outcome measures and describe how you expect them to be related to the components of the study design and other predictor variables (covariates).

Statistical analysis plan. Specify the statistical techniques and strategies that will enable the study to address the primary and key secondary research questions. Cite statistical references for non-routine methods. [Example: The two groups will be compared on KMOB830430 and its metabolites using estimates and 95% confidence limits for the Nicki-Zoey odds ratio (Nicki and Zoey, 1904), which is directly related to the common Wilcoxon-Mann-Whitney test.] Restate/translate your primary research questions into estimates of effects, and

their confidence intervals, and/or into statistical hypotheses or other methods. Similar descriptions regarding secondary questions are valuable, too.

These sections often state what statistical software package and version will be used, but this usually provides little or no information about what actually will be done. However, citing a particular capability in R or SAS can be quite helpful. [Example: Using the exlatekia() function in the R library GoHeels, ...]

Randomization (if appropriate). Specify how the randomization will be done, especially if it involves blocking or stratification to control for possible confounding factors.

Sample-size analyses. State the proposed sample size and discuss its feasibility. Estimate the key inferential powers, or other measures of statistical sensitivity/precision, such as the expected widths of key confidence intervals. Strive to make your sample-size analyses congruent with the statistical methods proposed previously, and discuss any incongruencies. State how you arrived at the conjectures for all the unknowns that underlie the sample-size analysis, citing specific articles and/or summarizing analyses of preliminary data or analyses presented in unpublished works. If a sample-size analysis was not performed, state this categorically and explain why. For example, the proposal may only be a small pilot study.

If you are presenting crucial error rate analyses, state the prior probability, γ, against each null hypothesis, along with your rationale. This methodology and the "crucial" term are not common, so cite this book, one of the references given in Chapter 2, or something more appropriate to your field. Use terminology consistent with your reference.

Data management. Summarize the schema for collecting, checking, entering, and managing the data. What database software will be used? How will the database be tapped to build smaller analysis datasets? Note how you will meet modern standards for data security.

Technical support. Who will perform the necessary database and statistical work? If such people are less experienced, who will supervise the work?

Example

What follows is a "Statistical Considerations" section for the fable in Chapter 1 involving QCA as a treatment for severe malaria.

Primary research question. One of the world's most pressing health problems, malaria kills over one million people yearly, mostly children. In fact, malaria is a principal cause of more than 20% of the deaths of young children in Africa each year. Lactic acidosis—toxic levels of lactic acid in the blood—is an independent risk factor and appears to be a contributing cause of death. Dichloroacetate (DCA) is effective in reducing high blood lactate levels although its effectiveness in reducing malaria mortality has not been confirmed. Quadchloroacetate (QCA) has been shown to be clinically equivalent to DCA in reducing high blood lactate levels; further, it is less expensive to produce

than DCA and has a longer shelf life in tropical climates. The aim of the proposed research is to investigate the effectiveness of QCA in reducing mortality in children with severe malaria.

Design and measures. The sample will be 2700 children under age 13 years who present with severe malaria complicated by lactic acidosis (operationally defined elsewhere in this proposal). Untreatable cases—those judged virtually certain to die—will be excluded. There will be two study sites. A randomized, double-blind design will compare usual care only (UCO) treatment to usual care plus a single 50 mg/kg infusion of QCA. One patient will receive usual care only for every two patients who receive QCA, an allocation ratio designed to facilitate recruitment. The primary outcome measure will be death before Day 10 after beginning the assigned treatment. Various safety outcomes will be assessed, including neurological sequelae, but the incidence rates will likely be too low to support valid inferences of treatment differences, especially since that difference would come from only a single dose of QCA.

Statistical analysis plan. Data will be pooled across the two study sites, because there is no reason to believe there could be true differences between them. The primary analysis will be to compare UCO versus QCA groups on 10-day mortality rates using the likelihood ratio chi-square test for two independent proportions. Clinical efficacy will be estimated by computing 95% confidence intervals for the relative risk of death and the risk difference. Although there is no evidence or suspicion that QCA might increase mortality, customary two-sided tests and confidence intervals will be used. No interim analyses are planned, because the study will be conducted in a single rainy season (February, March, April).

Randomization. The study locale dictates that the most basic yet effective randomization scheme be used. As discussed elsewhere in this proposal, vials will be prepared and sequentially numbered for each site, so that, randomly, 2/3 contain QCA plus saline solution and 1/3 contain only saline. QCA is colorless, so blinding is maintained. The next subject treated will simply receive the substance in the vial with the next number. For a study of this size and with such a narrow patient population, no blocking or stratification schemes are needed. The randomization code list will be set and held by the study's biostatistician, with copies filed and secured at the CHI Information Technology Center and the CHI Department of Infectious and Tropical Diseases.

Sample-size analyses. Past research suggests that the mortality rate for UCO is 12-15%. Past human and animal studies on DCA (Agbenyega et al., 2003; Holloway et al., 2005) suggest that, if effective, QCA might reduce mortality 25-33% for a relative risk of 0.67-0.75. Table**??** gives a relevant set of power calculations obtained using PROC POWER in SAS 9.2.

Using the proposed total sample size of N=2700 with $\alpha = 0.05$ provides powers of 0.68–0.96 over the conjectured domain of UCO mortality rates and QCA relatives risks. Treating 2700 children during a single rainy season will require study sites in both Jamkatnia and Gabrieland. Using N=2100 could be

done in just Jamkatnia, but the range of powers falls to 0.57–0.90, which is too low.

Table A1.1: Powers for trial to treat severe malaria with QCA.

		Alpha					
		.010		.050		.100	
		Total N		Total N		Total N	
		2100	2700	2100	2700	2100	2700
Usual Care Mortality	QCA Relative Risk						
0.12	0.75	.329	.437	.569	.677	.687	.780
	0.67	.622	.757	.823	.905	.893	.948
0.15	0.75	.438	.566	.677	.783	.781	.864
	0.67	.757	.872	.905	.960	.948	.981

Data management. As discussed more fully elsewhere in this proposal, SAS 9.2 tools, in particular SAS/FSP, will be used to manage all patient information, including building the outcomes database for analyses using SAS/STAT. All data will be backed-up automatically each hour to external hard drives and daily to twin password-protected 16GB flash drives that will kept and secured off-site. Finally, the study sites have sufficient Internet access to support weekly back-up transmissions of all databases back to servers at CHI. All databases will either be kept in a de-identified state or stored with 128-bit encryption.

Technical support. Database hardware and applications programming will be the responsibility of the CHI Information Technology Center. Under the direction of Howard Batson, PhD, this group has over 20 years of relevant experience, including successfully running a case-cohort epidemiology study on HIV/AIDS transmission underway in Kenya. Statistical analyses will be headed by CHI biostatistician Neadya Gooden, PhD, with assistance from doctoral-level graduate students in biostatistics from Vernon Preston University.