

FDA Executive Summary Supplement

Statistical Issues

The sponsor provided more data from the AKH Registry and presented the results from a Bayesian analysis of the data. FDA reviewed this information below are issues identified in our review.

I. Hypothermia Treatment in AKH Registry

Our review noted that in this new Statistical Report, the sponsor clearly states that there was a series of patients in the AKH Registry for whom hypothermia was provided via the Alsius CoolGard 3000/Icy Catheter System with or without the addition of intravenous cold fluids. Clinical reviewers should be aware of the addition of intravenous cold fluids in conjunction with the use of the investigational device. Use of intravenous cold fluids may confound the treatment effect of the investigational device.

II. Survival Endpoint in the Three Published Randomized Controlled Trials

Our review noted that the sponsor changed the survival endpoint in the three published randomized controlled trials (i.e., HACA Study, Bernard Study, Idrissi Study) to the survival status at discharge/30 days. Compared with the data presented in the sponsor's previous statistical report (written in February 2004) which used different definitions for survival status, there is no change in the numbers of survivors in both the hypothermia and the normothermia groups in each of the three studies. This may be a conservative approach since there may be patients that died between 30 days and 6 months after treatment in the HACA Study.

III. Statistical Analysis of AKH Registry Data

Since the AKH Registry is a prospective, nonrandomized, observational study, the sponsor used frequency matching to select controls from patients treated conventionally (i.e., treated with normothermia). FDA has remaining questions regarding how the frequency matching was carried out to match hypothermia treated patients with conventionally treated patients. Also, appropriate methods to test if the control patients are comparable with the treated patients with respect to important demographic and baseline characteristics were not provided.

IV Bayesian Analysis

The Bayesian analysis discussed herein from Alsius was conducted by the sponsor without input from FDA. The use of prior information from different studies should be agreed upon in advance between the sponsor and FDA when the studies are very similar to the current study in terms of study endpoints, patient populations, covariates, etc. In addition, in order to guard against undetected differences, Bayesian hierarchical models are recommended and simulations are required in advance to control Type I error.

Regarding the Bayesian analysis provided by Alsius, our review found that the sponsor used a sequential approach where data from the HACA trial was used as the prior distribution for the Bernard trial, and the posterior distribution of the Bernard trial was used as the prior distribution for the Idrissi trial, and then the posterior distribution of the Idrissi trial was used as the prior distribution for the AKH Registry Study. FDA believes that it is questionable to use such sequential prior distributions in the Bayesian analysis because different cooling devices, different patient cohorts (i.e., different demographic characteristics and baseline status), and different endpoints were used in these three randomized controlled trials than the AKH observational study. Moreover, since Alsius CoolGard 3000/Icy Catheter System was not used in any of the three trials, it may not be appropriate to use the results of these trials as the prior information for the AKH Registry Study in which the Alsius CoolGard device was used.

Our review noted that the sponsor used a skeptical prior distribution assuming that the said effect is actually zero and the probability of exceeding the said effect is 5%. FDA was unable to verify this result without a detailed explanation, using mathematical expressions, for the skeptical prior distribution used in the Bayesian analysis (i.e., the mathematical form of the skeptical prior). The sponsor has not justified the 5% probability of exceeding the said effect.

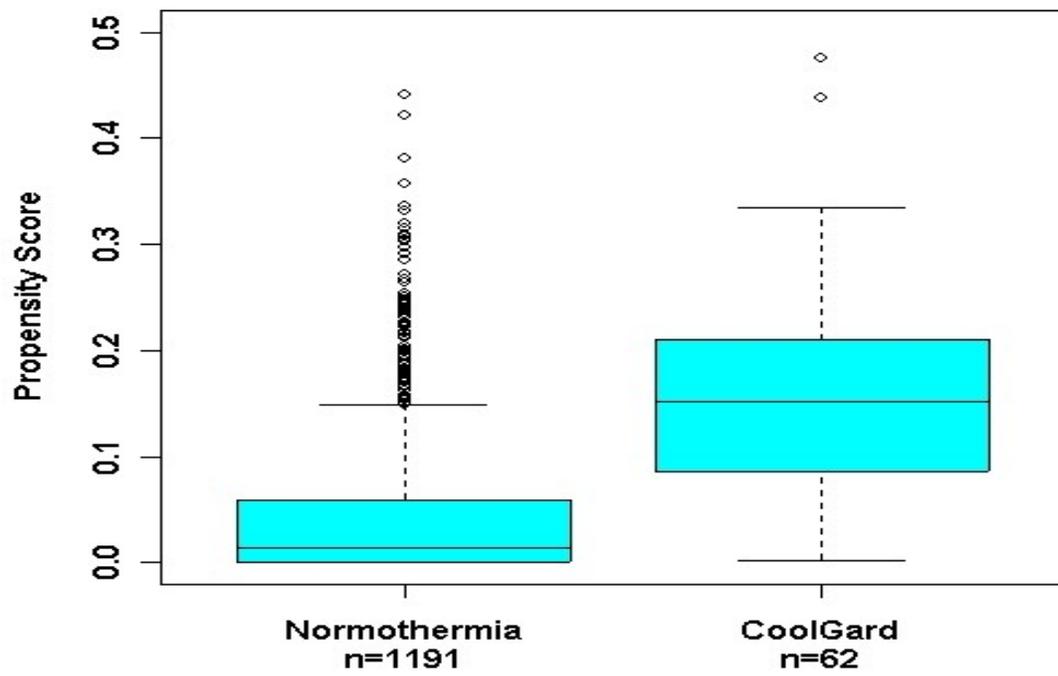
Our review notes that the distributions of the data appear different in Figures 1 and 2, where they should be very similar. Insufficient information is provided to explain why the data distributions are different in these two plots making them difficult to interpret.

Our review found that the sponsor used a logistic regression model to estimate the odds ratio between the hypothermia group and the normothermia group in the AKH study after adjusting for some important baseline covariates. The specific logistic regression model used was not given nor were the covariates included in this model. We were unable to verify the sponsor's result without this information.

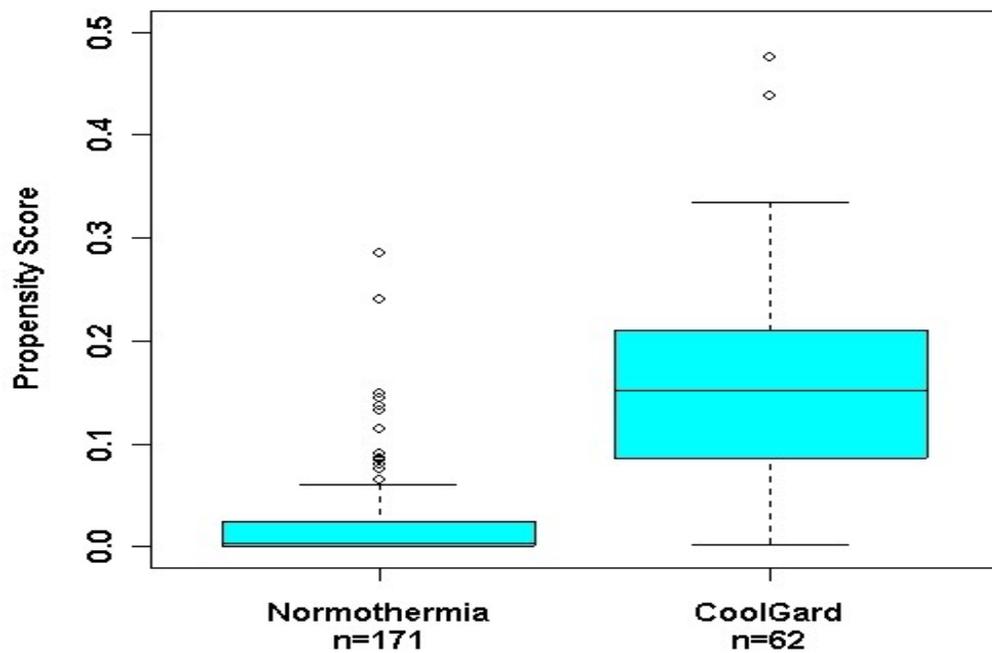
V Propensity Score Analysis

Our statistical review of the propensity score analysis reported in Alsius's February 2004 Statistical Report, using the AKH data collected during August 1991 and November 2003, shows that the estimated propensity scores obtained by FDA's statistician are similar to those presented in Alsius's Statistical Report (written on February 3, 2004) when the same propensity score model (as was used by the sponsor) was employed. However, it is not clear how the sponsor matched the CoolGard patients with the normothermia patients based on the propensity scores. The following three plots may be helpful for evaluating the propensity score analysis performed by the sponsor.

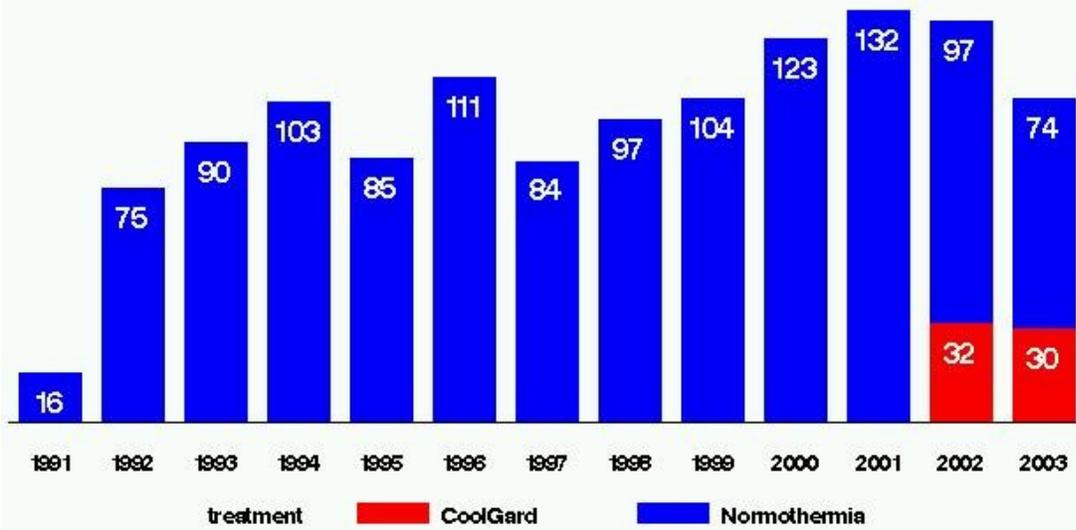
Propensity Score Distribution



Propensity Score Distribution Patients Enrolled in 2002 and 2003



AKH Registry Study Enrollment (1991–2003)



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