We would like to thank Laptook et al. (1) for their response to our ‘Major concerns about late hypothermia study’ (2). However, their response suggests that the difference between their opinion and ours arises because we are using frequentist statistics and they are using Bayesian. This is not the case. There is indeed general concern at present about the potential misuse of p-values in frequentist statistical practice. We agree that generally in situations where a limited number of observations are available, the usual frequentist requirement for the significance probability to be lower than 0.05 is too strict. Results with a significance probability of 0.10 or even 0.15 may also give valuable information, and correspondingly a confidence interval (frequentist) or credibility interval (Bayesian) of 0.95 is sometimes too strict.

The heart of the matter is whether the observation that 19 of 78 neonates in group 1 (with cooling initiated in the time window from 6 to 24 hours after birth) showed adverse outcomes can be said to indicate that the associated probability p1 is smaller than the corresponding probability p0 in the control group, where 22 of 79 showed adverse outcomes. The original JAMA paper (3) discussed this in terms of the relative risk \( \text{rr} = \frac{p_1}{p_0} \), and the question is whether there are any grounds to claim, with any meaningful confidence or credibility (to use the relevant frequentist and Bayesian terms), that \( \text{rr} \) is smaller than 1.

Our primary analysis was indeed frequentist, demonstrating that with sample sizes 79 and 78 there can be no meaningful statistical difference between the probability estimates \( 19/78 = 0.244 \) and \( 22/79 = 0.278 \). The close proximity of these two estimates can be assessed in several ways, including a p-value far above the customary levels for significance (\( p = 0.75 \)), and a confidence curve with the value \( \text{rr} = 1 \) in the middle with a 95 per cent confidence interval (0.51, 1.48) (see Fig. 1 in our previous communication (2)).

We have nothing against Bayesian analyses in general, and we agree that Laptook et al.’s ‘neutral’ unimodal prior with \( \text{rr} = 1 \) is sensible if no prior knowledge on late cooling is available. The detailed shape and especially the tails of this prior probability distribution are of course rather uncertain. As our figure clearly shows, Laptook et al.’s results give little support for the claim that \( p_1 \) is smaller than \( p_0 \) (i.e. that the relative risk parameter \( \text{rr} = p_1/p_0 \) above is smaller than 1). We have also performed a sensitivity analysis on the results of the trial. We moved two infants from the control group to the cooled group, so that the outcome was death or disability for 21 of 78 infants in the cooled group and 20 of 79 in the control group. These results would indicate a slightly better outcome for the control group, which is certainly possible if there is no real difference between the two groups.

The figure displays Laptook et al.’s Bayesian prior probability distribution (in red) and two posterior probability distributions (in black) for the \( \text{rr} \) parameter. The solid black curve is the posterior using the observed data, while the dashed black curve is the posterior using the hypothetical outcomes from the sensitivity analysis. The 95 per cent credibility intervals for \( \text{rr} \) are (0.61, 1.40) and (0.68, 1.58), respectively, for the two posterior distributions. \( \text{rr} = 1.00 \) is
close to the middle (median) in all three cases. Even intervals with 70% credibility or less would cover $rr = 1.00$ in all three distributions, indicating that there is no real difference between the two groups.

In the JAMA paper Laptok et al. (3) write ‘The probability that death or disability in cooled infants was at least 1, 2, or 3% less than non-cooled infants was 71, 64, and 56%, respectively’, and further: cooling ‘compared with non-cooling resulted in a 76% probability of any reduction in death or disability’. Unfortunately, we have not been able to reproduce these numbers using Laptok et al.’s ‘neutral’ prior. According to our Bayesian calculations, the probability that death or disability in cooled infants was at least 1, 2, or 3% less than in non-cooled infants was 64, 62 and 60%, respectively, and cooling resulted in a 65% probability of any reduction in death or disability. Using the posterior distribution from the sensitivity analysis, the probabilities were 41, 59, 37 and 43%, respectively. Two observations can be made from these numbers. There is always a positive probability that death and disability in cooled infants is less than in non-cooled infants, even when the trial results indicate the opposite, but these probabilities vary greatly with small changes in the real outcome. We also see that the two posterior distributions are not very different from the prior distribution. In fact, they are heavily influenced by the prior and only to a limited degree by the results from the trial. The probabilities in the tails of the posterior distribution are also strongly influenced by the shape and width of the prior distribution, of which we have limited knowledge. The very uncertain tail probabilities in the posterior distribution should therefore definitely not be used as arguments for late cooling.

If the times when the cooling started had been given for all infants, other relevant statistical analyses could have been performed [e.g. logistic regression with time as a covariate or a Bayesian analysis with the results from late cooling of rat pups and foetal sheep as basis for a prior (2)]. Although only tested in rats, one study showed that very severe injury increased more if cooling started 12 hour after the experimental insult (4). The current patient cohorts undergoing therapeutic hypothermia, including that in Laptok et al.’s (3) ‘Late hypothermia trial’ are all milder than the original trial cohorts that showed that therapeutic hypothermia was effective. As an example; in the 2005 NICHD whole body cooling trial, the non-cooled group had 37% mortality and 40% disability in survivors (5). In the late hypothermia trial, the mortality in the non-cooled group was 11, and 19% of the survivors had disabilities (3). We do not agree that there is evidence for suggesting starting hypothermia treatment late. Also, one does not know how high the risk for harm would be (6) if one expose rather mild HIE infants to 3 days of cooling and intensive care.

CONFLICT OF INTEREST
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