Appendix 6 (as supplied by the authors): Details of Optimal Information Size (OIS) analysis

The methods used are adapted from formal interim monitoring boundaries applied to cumulative meta-analysis. First, the OIS sample size was selected so that the smallest treatment effect that would be judged clinically worthwhile would be reliably detected. To determine the OIS we considered an 8.9% overall annual mortality event rate (8) for the control group and a 20% relative risk reduction with cardiac resynchronization therapy, with 90% power and a significance level of 0.01 two sided. Second, using OIS as the sample size, the Lan–DeMets sequential monitoring boundary was constructed. That is, considering a cumulative meta-analysis as trials are conducted over time,with OIS as the required sample size and calculating the group sequential stopping boundaries for the Lan-DeMets alpha-spending function with the rate of alpha-spending defined by the O'Brien-Fleming procedure, the approximate monitoring boundaries for the cumulative meta-analysis were determined.(16–18) Third, in interpreting the results, if this sequential monitoring boundary is crossed, then this indicates that the cumulative evidence is now reliable and conclusive.

References*
16. Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. *Control Clin Trials* 1997;18:580-93.
17. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659-63.
18. Fleming TR, Harrington DP, O'Brien PC. Designs for group sequential tests. *Control Clin Trials* 1984;5:348-61.

*Reference numbers correspond to those in the main article.