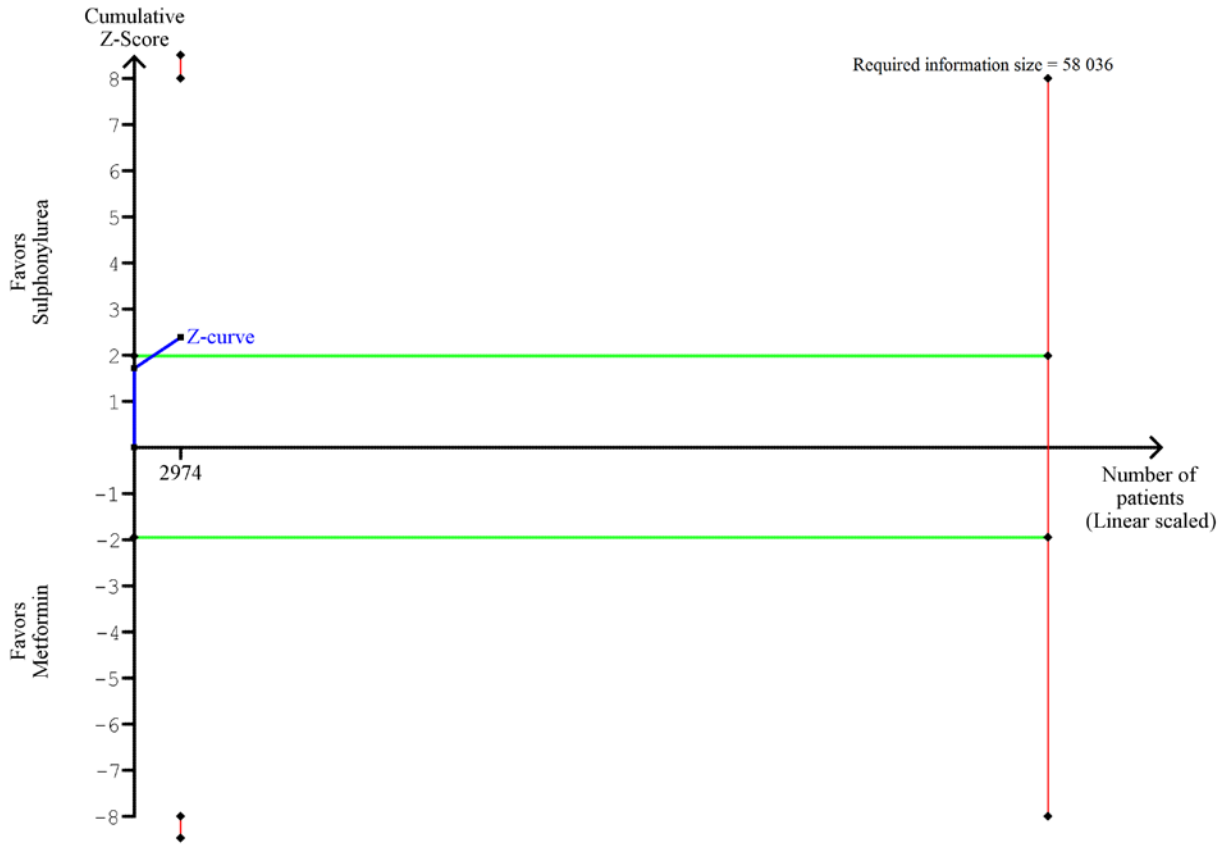
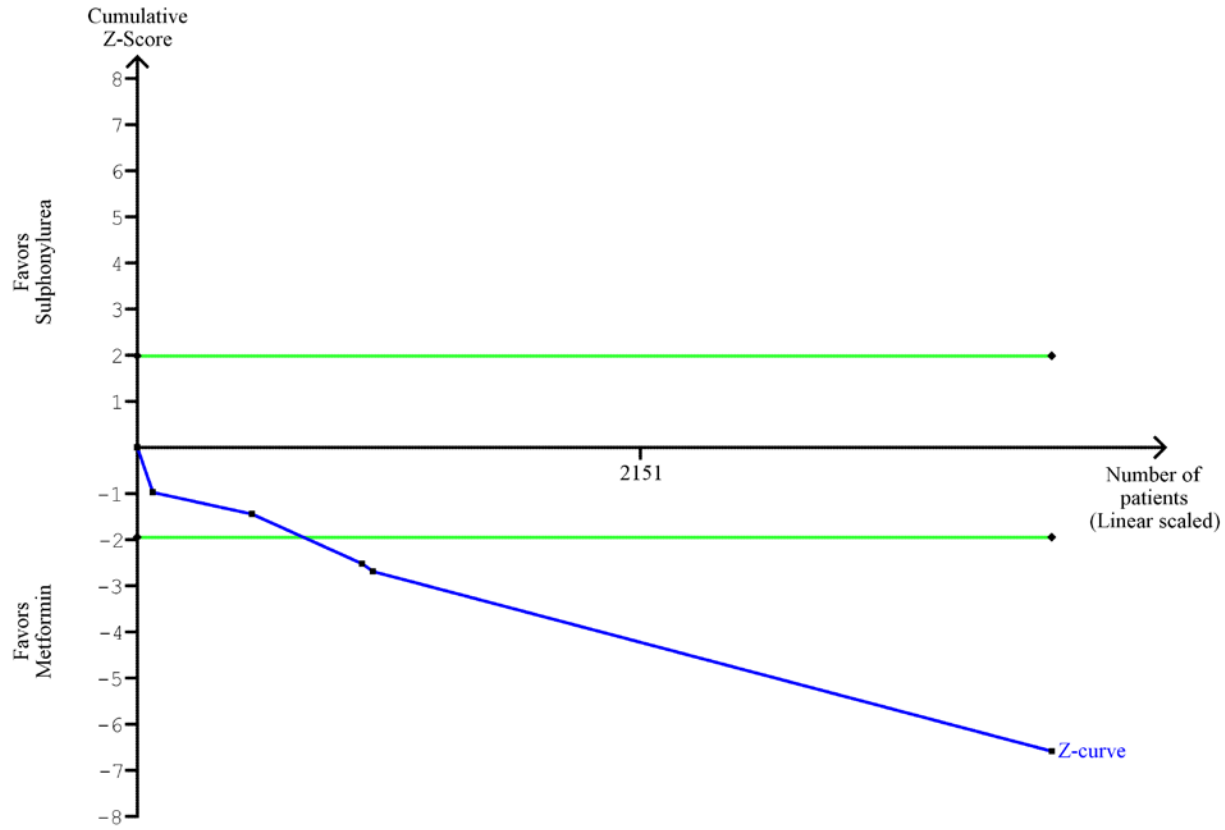
Appendix 5 (as supplied by the authors): Trial sequential analyses

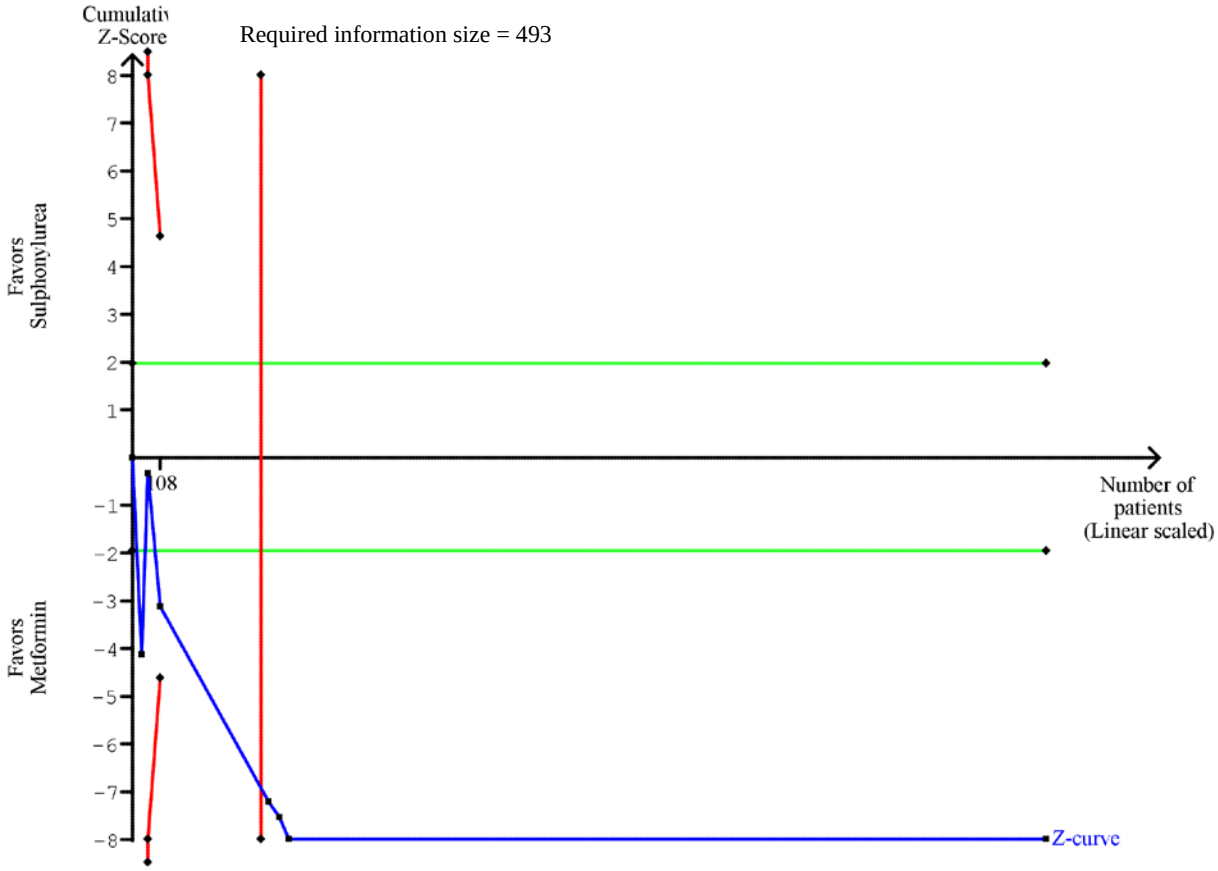


Appendix 5A. Trial sequential analysis of the effect of second- and third-generation sulphonylurea versus metformin in type 2 diabetes on nonfatal macrovascular outcomes with a two-sided α = 5%, a power of 80% anticipating, a control event proportion of 4.9%, a 10% relative risk reduction, and a diversity (D^2) of 0%. The solid blue *Z* curve indicates the cumulated *Z* score from the inverse variance model *Z* statistic, whenever a new trial is added. The solid blue cumulative *Z* curve does not crosses the red trial sequential alpha spending monitoring boundaries for a 10% relative risk reduction. Horizontal green lines illustrate traditional level of statistical significance ($p = 0.05$)

Appendix to: Hemmingsen B, Schroll JB, Lund SS, et al. Sulfonylurea versus metformin monotherapy in patients with type 2 diabetes: a Cochrane systematic review and meta-analysis of randomized clinical trials and trial sequential analysis. *CMAJ Open* 2014. DOI:10.1503/cmajo.20130073.



Appendix 5B. Trial sequential analysis of the effect of second- and third-generation sulphonylurea versus metformin in type 2 diabetes on nonfatal macrovascular outcomes with a two-sided α = 5%, a power of 80% anticipating, a control event proportion of 9.4%, a 10% relative risk reduction, and a diversity (D^2) of 79%. The solid blue *Z* curve indicates the cumulated *Z* score from the inverse variance model *Z* statistic, whenever a new trial is added. The solid blue cumulative *Z* curve does not crosses the red trial sequential alpha spending monitoring boundaries for a 10% relative risk reduction. Horizontal green lines illustrate traditional level of statistical significance ($p = 0.05$)



Appendix 5C. Trial sequential analysis of the effect of second- and third-generation sulphonylurea versus metformin in type 2 diabetes on weight (kg) with a two-sided α = 5% and a power of 80% anticipating a mean difference of 3.77 kg and a diversity (D^2) of 65% as estimated using a random-effects model. The solid blue *Z* curve indicates the cumulated *Z* score from the inverse variance model *Z* statistic, whenever a new trial is added. The solid blue cumulative *Z* curve crosses the red trial sequential alpha spending monitoring boundaries. Horizontal green lines show the traditional level of statistical significance ($p = 0.05$)