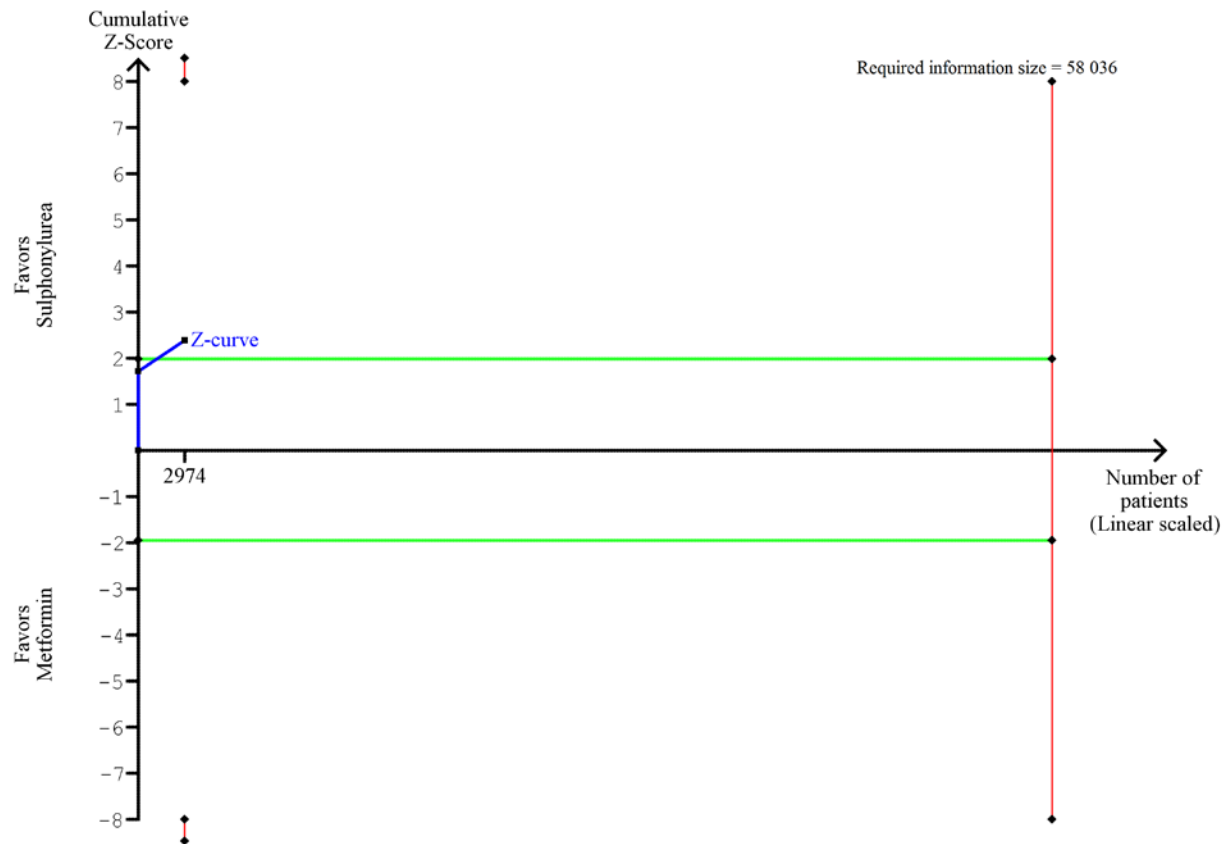
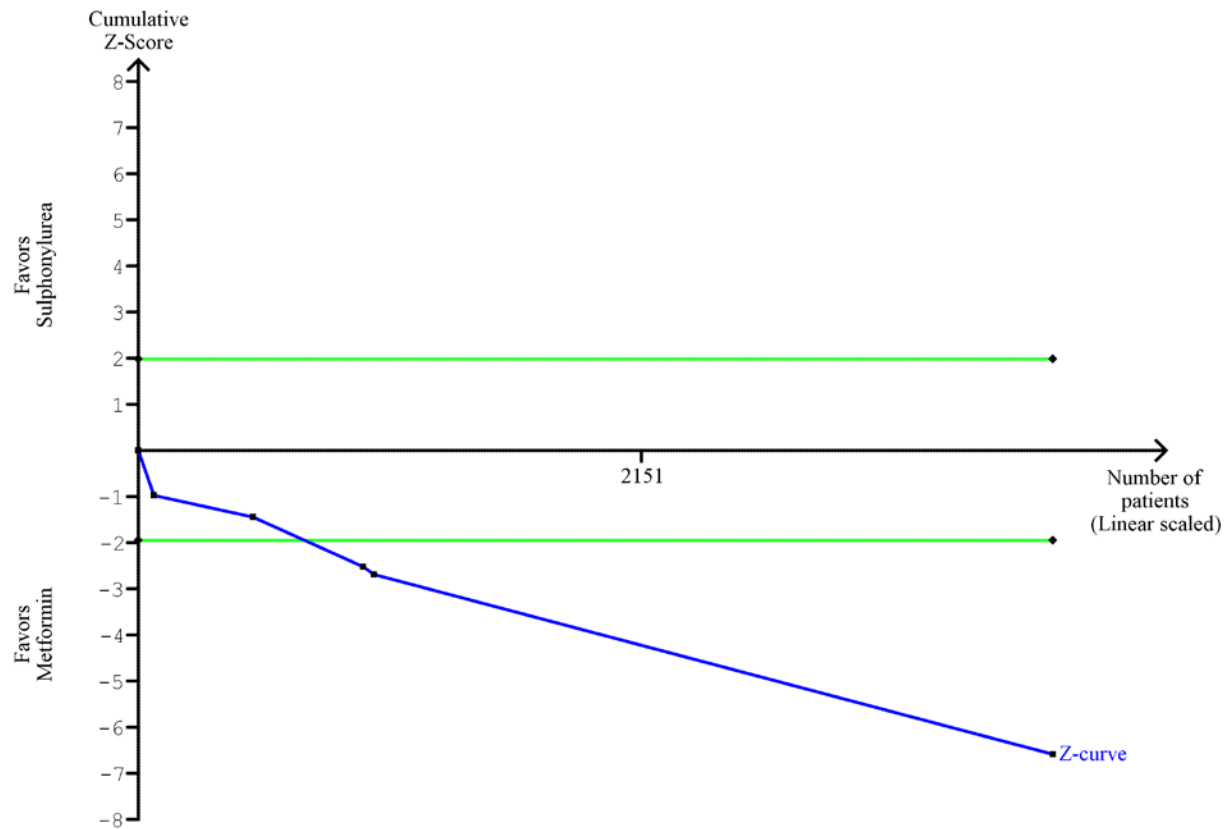


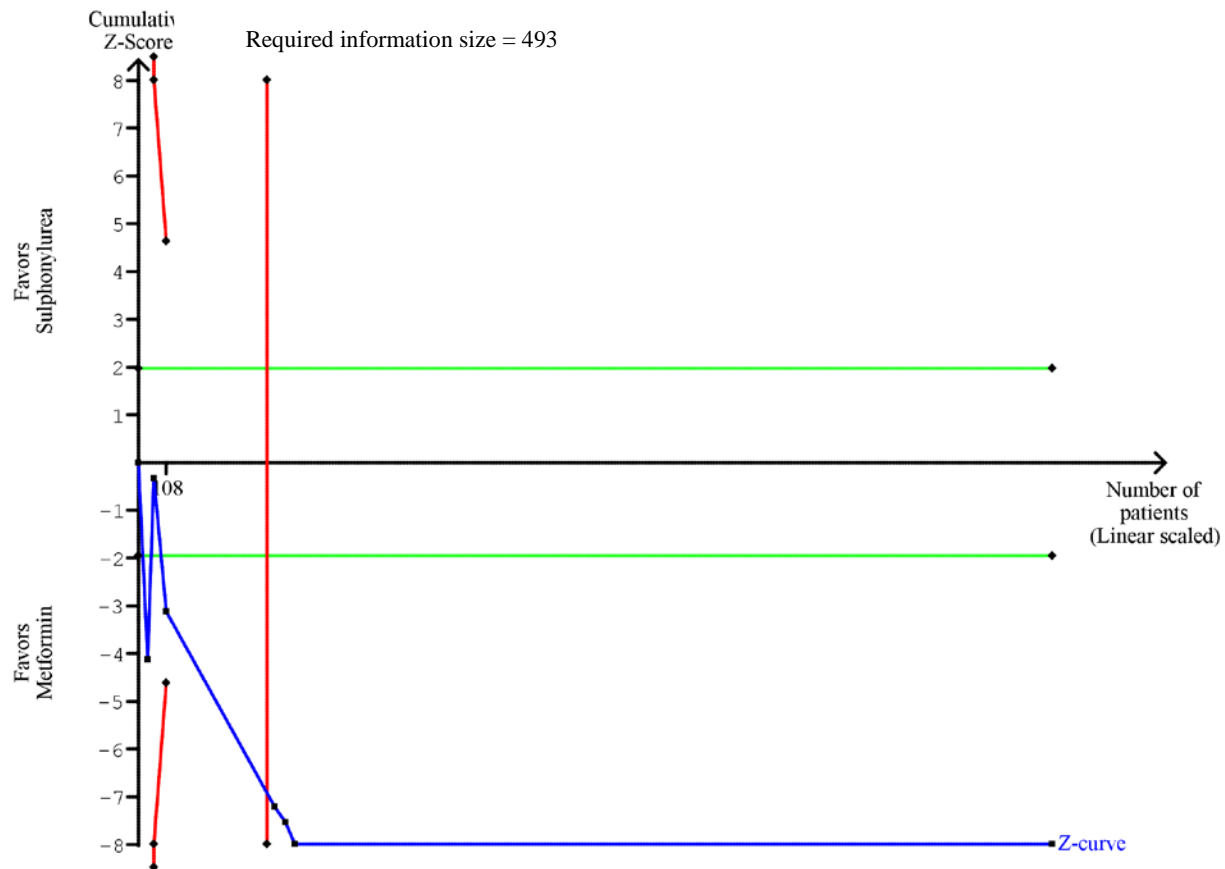
## Appendix 5 (as supplied by the authors): Trial sequential analyses



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  $\alpha = 5\%$ , 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 cross 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 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  $\alpha = 5\%$ , 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 cross 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  $\alpha = 5\%$  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 ( $p = 0.05$ )