**Supplemental Digital Content 1. Derivation of harm and benefit constraints.**

 (To generalize to unequal group sizes, replace 2 with (r+1)/r and change the degrees of freedom to (r+1)n-2, where r is the ratio of the larger to the smaller group.)

n = per group sample size

To be “implementable,” two constraints must be met: a constraint on harm and a constraint on benefit.

Constraint on harm: Take a specific example for illustration. If the maximum risk of harm is 0.5%, then the following condition must be met:

LCL99>

LCL99 =

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This can be generalized by replacing with =

Constraint on benefit: If the minimum chance of benefit = 25%, then the following condition must be met:

UCL50

UCL50 =

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This can be generalized by replacing with

For some minimum chances of benefit, the lower confidence limit comes into play. For example, if minimum chance of benefit=75%, then the following condition must be met:

LCL50

LCL50 =

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This can be rewritten as:

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This can again be generalized by replacing with

Thus, to be “implementable”, the following two conditions must be met:

1. 🡪