SUPPLEMENTARY MATERIAL

A. Numerical illustration of the outcome variable construction

We use the PANSS score to illustrate the three types of MCID threshold and their equivalence. Let $\mathrm{PANSS}_{\mathrm{end}}$, and $\mathrm{PANSS}_{\mathrm{base}}$ be the endpoint and the baseline PANSS scores, respectively. Define τ to be the MCID threshold. Type I MCID threshold is defined where the successful event occurs if the endpoint PANSS score $\mathrm{PANSS}_{\mathrm{end}}$ reduces below some predetermined threshold τ (regardless of the baseline), for example, $\tau = 80$. This MCID threshold corresponds to improvement to a normal up to mildly ill symptom severity level.[1] In such a case, the outcome variable is $\mathrm{PANSS}_{\mathrm{end}}$, the MCID is 80, and the success is defined as a decrease in the outcome variable, i.e., $\mathrm{PANSS}_{\mathrm{end}} < 80$. Type II MCID threshold is defined where the outcome variable is the difference between the endpoint and the baseline PANSS score exceeds some predetermined threshold τ, for example, $\tau = 20$. This MCID threshold corresponds to the mean difference in the PANSS score of markedly ill patients.[2] In such a case, the outcome variable is $\mathrm{PANSS}_{\mathrm{end}} - \mathrm{PANSS}_{\mathrm{base}}$, the MCID is 20, and success is defined as an increase in the outcome variable, i.e., $\mathrm{PANSS}_{\mathrm{end}} - \mathrm{PANSS}_{\mathrm{base}} > 20$. Type III MCID threshold is defined by a relative decrease of the endpoint PANSS score with respect to the baseline score. In such a setting, the successful event occurs if the relative change in PANSS score exceeds some predetermined threshold. For example, if the minimal clinically important relative reduction is set to be 30%, which corresponds to an MCID threshold $\tau = 1 - 0.3 = 0.7$.[1] Namely, a successful event occurs if $\mathrm{PANSS}_{\mathrm{end}} < 0.7\mathrm{PANSS}_{\mathrm{base}}$. In such a case, the outcome variable is redefined as the difference between the endpoint PANSS score and 0.7 times the baseline PANSS score, namely, $\mathrm{PANSS}_{\mathrm{end}} - 0.7\mathrm{PANSS}_{\mathrm{base}}$. Thus the relevant MCID becomes zero, and the success is defined as a decrease in the outcome variable, i.e., $\mathrm{PANSS}_{\mathrm{end}} - 0.7\mathrm{PANSS}_{\mathrm{base}} < 0$. It is evident that, without loss generality, the three types of MCID threshold are equivalent as they are defined by an absolute change of a correctly constructed outcome variable.

B. Nonparametric and parametric estimation of the unadjusted Laupacis NNT

For the illustration of the nonparametric estimator of the unadjusted Laupacis NNT we use the simulated dataset `panss_unadjusted.csv`. The selected estimator was the Nonparametric MLE, the distribution field

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can be left blank or set to be Unknown, the MCID threshold was set to zero, and the success is defined as a decrease of the outcome variable. The results are presented in eTable 1.

eTable 1 The nonparametric estimator of the Laupacis NNT. The table presents the nonparametric maximum likelihood estimator (NNT L) with its corresponding Wald-based (WALD), delta-method-based (DL), and nonparametric-bootstrap-based (NBS) 95% CIs.

NNTL	CI WALD L	CI WALD U	CI DL L	CI DL U	CI NBS L	CI NBS U
3.23	2.66	4.09	2.54	3.91	2.63	4.11

NNT L; The Laupacis nonparametric maximum likelihood point estimator of the unadjusted NNT. CI WALD L; the lower limit of the 95% level Wald-based CI. CI WALD U; the upper limit of the 95% level Wald-based CI. CI DL L; the lower limit of the 95% level delta-method-based CI. CI DL U; the upper limit of the 95% level delta-method-based CI. CI NBS L; the lower limit of the 95% level nonparametric-bootstrap-based CI. CI BS U; the upper limit of the 95% level nonparametric-bootstrap-based CI.

For the illustration of the parametric estimator of the unadjusted Laupacis NNT, the selected estimator was the Parametric MLE, the selected distribution was Normal, the MCID threshold was set to zero, and the equal variance assumption checkbox was checked. The results are presented in eTable 2.

eTable 2 The parametric estimator of the Laupacis NNT. The table presents the parametric maximum likelihood estimator (NNT MLE) with its corresponding delta-method-based (DL) and nonparametric-bootstrap-based (NBS) 95% CIs.

NNT MLE	CI DL L	CI DL U	CI NBS L	CI NBS U
3.33	2.72	3.93	2.81	4.01

NNT MLE; The parametric maximum likelihood point estimator of the unadjusted NNT. CI DL L; the lower limit of the 95% level delta-method-based CI. CI DL U; the upper limit of the 95% level delta-method-based CI. CI NBS L; the lower limit of the 95% level nonparametric-bootstrap-based CI. CI BS U; the upper limit of the 95% level nonparametric-bootstrap-based CI.

C. Nonparametric and parametric estimation of the unadjusted Kraemer & Kupfer KK-NNT

For the KK-NNT, the available estimators are the nonparametric and the parametric maximum likelihood estimators. The available distribution of the outcome variable is normal, exponential, or unknown. Additional arguments include a checkbox on whether the success is defined as a decrease or an increase of the

outcome variable and a checkbox to indicate whether the variance equality assumption holds for normally distributed outcomes. No MCID threshold is required for the KK-NNT. If the chosen estimator is the parametric maximum likelihood, then the output consists of the parametric point estimator and two types of 95% CIs. To illustrate this function, we use the response variables of the simulated `pans_unadjusted.csv` dataset. We choose the normal distribution, with the parametric maximum likelihood estimators, and equal variances. The results are presented in eTable 3.

eTable 3 The output of the Kraemer & Kupfer KK-NNT parametric estimator, using the simulated dataset `panss_unadjusted.csv`. The table presents the parametric maximum likelihood estimator (KK-NNT) of the Kraemer & Kupfer KK-NNT in normally distributed outcomes with unequal variances, with its corresponding Cohens's-d-transformation-based (COHEN), delta-method-based (DL), and nonparametric-bootstrap-based (NBS) 95% CIs.

KK- NNT	CI COHEN L	CI COHEN U	CI DL L	CI DL U	CI NBS L	CI NBS U
2.02	1.75	2.42	1.69	2.34	1.76	2.37

KK-NNT; The parametric maximum likelihood point estimator of the Kraemer & Kupfer KK-NNT. CI COHEN L; the lower limit of the 95% level Cohens's-d-transformation-based CI. CI NBS U; the upper limit of the 95% level Cohens's-d-transformation-based CI. CI DL L; the lower limit of the 95% level delta-method-based CI. CI DL U; the upper limit of the 95% level delta-method-based CI. CI NBS L; the lower limit of the 95% level nonparametric-bootstrap-based CI. CI NBS U; the upper limit of the 95% level nonparametric-bootstrap-based CI.

The user may compare these results to the nonparametric maximum likelihood estimator of the KK-NNT, which can be obtained by changing the estimator to `Nonparametric MLE` and omitting the distribution specification and the variance equality arguments. The output is presented in eTable 4.

eTable 4 The output of the Kraemer & Kupfer KK-NNT nonparametric estimator, using the simulated dataset `panss_unadjusted.csv`. The table presents the nonparametric maximum likelihood estimator (KK-NNT) of the Kraemer & Kupfer KK-NNT with its corresponding nonparametric-bootstrap-based (NBS) 95% CIs.

KK-NNT	CI NBS L	CI NBS U
2.04	1.83	2.31

KK-NNT; The nonparametric maximum likelihood point estimator of the Kraemer & Kupfer KK-NNT. CI NBS L; the lower limit of the 95% level nonparametric-bootstrap-based CI. CI NBS U; the upper limit of the 95% level nonparametric-bootstrap-based CI.

There is no visible difference between the nonparametric, and the parametric estimators, and their CIs, which indicates a correct model specification and robust results.

D. Parametric estimation of the adjusted Laupacis NNT in the linear regression model

For the illustration of the linear regression model, we use the simulated dataset `panss_regression.csv`, where the dependent variable is set to be the relative change in PANSS score such that a reduction of 30% in the PANSS scored is defined as success. We choose the adjusted value of the baseline PANSS to be 100. The results are presented below in eTable 5.

eTable 5 Estimators of the Laupacis NNT in the linear regression model using the PANSS simulated dataset `panss_regression.csv`. The table presents the nonparametric maximum likelihood estimator (NNT L), the parametric maximum likelihood estimator (NNT MLE) of the marginal NNT, and the parametric maximum likelihood estimator of the adjusted NNT for baseline PANSS score of 100 (NNT(100)). Additionally, the table presents the corresponding transformation-based (TR), delta-method-based (DELTA), nonparametric-bootstrap-based (NBS), and parametric-bootstrap-based (PBS) 95% CIs for each one of the estimators.

	NNT	CI TR L	CI TR U	CI DL L	CI DL U	CI NBS L	CI NBS U	CI PBS L	CI PBS U
NNT L	3.33	2.74	4.26	2.61	4.06	2.78	4.29	NA	NA
NNT MLE	3.19	1.74	19.07	1.00	5.84	2.84	3.65	2.79	3.59
NNT(100)	2.56	1.18	Inf	1.00	5.55	2.25	2.97	2.22	2.90

NNT L; The Laupacis nonparametric maximum likelihood estimator of the unadjusted NNT. NNT MLE; linear-regression-based maximum likelihood estimator of the marginal NNT. NNT(100); linear-regression-based estimator of the adjusted NNT covariate value of 100.

NNT; point estimator of the NNT. CI TR L; the lower limit of the 95% level transformation-based CI. CI TR U; the upper limit of the 95% level transformation-based CI. CI DL L; the lower limit of the 95% level delta-method-based CI. CI DL U; the upper limit of the 95% level delta-method-based CI. CI NBS L; the lower limit of the 95% level nonparametric-bootstrap-based CI. CI NBS U; the upper limit of the 95% level nonparametric-bootstrap-based CI. CI PBS L; lower limit of the 95% level parametric-bootstrap-based CI. CI PBS U; the upper limit of the 95% level parametric-bootstrap-based CI.

E. Parametric estimation of the adjusted Laupacis NNT in the logistic regression model

For the illustration of the logistic regression model, we use the simulated dataset `panss_logistic.csv`, where we converted the nondichotomous outcomes of the PANSS relative change (outcome) to a binary outcome such that a reduction of 30% in the PANSS scored coded as 1 (otherwise, coded as 0). We choose the adjusted value to be 100. The results are presented below in eTable 6.

eTable 6 The output of the parametric estimator of the adjusted and marginal Laupacis NNT in logistic regression, using the PANSS simulated dataset `panss_logistic.csv` with a dichotomized outcome. The table presents point estimators of the unadjusted (NNT L), marginal (NNT MLE), and adjusted (NNT(100)) Laupacis type NNT for a logistic regression model with a logit link function, and the corresponding transformation-based (TR), delta-method-based (DL), nonparametric-bootstrap-based (NBS), and parametric-bootstrap-based (PBS) 95% CIs.

	NNT	CI TR L	CI TR U	CI DL L	CI DL U	CI NBS L	CI NBS U	CI PBS L	CI PBS U
NNT L	3.33	2.74	4.26	2.61	4.06	2.73	4.23	NA	NA
NNT MLE	3.32	1.00	Inf	1.00	20.91	2.79	4.07	2.67	3.97
NNT(100)	2.62	1.00	Inf	1.00	13.59	2.16	3.24	2.06	3.17

NNT L; The Laupacis nonparametric maximum likelihood estimator of the unadjusted NNT. NNT MLE; logistic-regression-based parametric maximum likelihood estimator of the marginal NNT. NNT(100); logistic-regression-based estimator of the adjusted NNT covariate value of 100.

NNT; point estimator of the NNT. CI TR L; the lower limit of the 95% level transformation-based CI. CI TR U; the upper limit of the 95% level transformation-based CI. CI DL L; the lower limit of the 95% level delta-method-based CI. CI DL U; the upper limit of the 95% level delta-method-based CI. CI NBS L; lower limit of the 95% level nonparametric-bootstrap-based CI. CI NBS U; the upper limit of the 95% level nonparametric-bootstrap-based CI. CI PBS L; the lower limit of the 95% level parametric-bootstrap-based CI. CI PBS U; the upper limit of the 95% level parametric-bootstrap-based CI.

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