Supplementary materials of “A non-inferiority framework for cost-effectiveness analysis” by Xuanqian Xie, Lindsey Falk, James M. Brophy, Hong Anh Tu, Jennifer Guo, Olga Gajic-Veljanoski, Nancy Sikich, Irfan A. Dhalla, Vivian Ng.

Supplement 1: Non-inferiority margin in clinical trials and fraction of effectiveness preserved in the economic model

We adapted the concept of non-inferiority trials and applied it to model-based economic evaluations.(1, 2) In non-inferiority trials, where we seek to determine if a new treatment is non-inferior to active control, a non-inferiority margin must be pre-specified. A fixed-margin method is recommended to determine the non-inferiority margin (1, 2) and requires two values. M1 represents the most conservative estimate of entire effect of the active control relative to the placebo control (typically the lower bound confidence interval [CI] of the effect estimate). This value is often based on previous trials or, when possible, a meta-analysis of previous trials. M2 reflects the largest clinically acceptable difference (effect loss) of the new intervention compared to the active control. For example, if we are willing to accept a maximum difference of 25% effect lost, the threshold of effect preserved by the new intervention is 75%. Non-inferiority trials use CI of effect estimate to compare with the pre-specified non-inferiority margin (M2) for testing non-inferiority.

In model-based economic evaluations with probabilistic sensitivity analysis (PSA) using Monte Carlo simulations, we can simultaneously examine the effectiveness of a new intervention, an active control, and a placebo control. Results of each simulation represent the estimates from a hypothetical three-arm clinical trial. We define M1 as the estimate of the active control’s effect size relative to the placebo control in each simulation. M2 is chosen as a fixed proportion of M1. It should be noted that our definition of M1 in a model-based economic evaluation is different than in non-inferiority trials. The value of M1 in our method varies in each simulation. We assumed that if the new intervention can preserve a certain fraction of the active control effectiveness (or, equivalently, tolerate a certain percentage of effectiveness loss), the new intervention would be non-inferior to the active control. We calculate the probability of non-inferiority of the new intervention (i.e., preserving the effectiveness over the pre-specific threshold) from the Monte Carlo simulations.

Section 2: Additional results from conventional cost-effectiveness analysis

Table S1: Summary of Results from Conventional Cost-Effectiveness Analysis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Strategy | Average Total Costs, $a | Incremental Cost, $a | Average Total QALYs | Incremental QALYs | Incremental Cost-Effectiveness Ratio |
|  | | | |  |  |
| ECT | 6,013 (409) | — | 0.3231 (0.0102) | — | — |
| rTMS | 5,275 (502) | −738 (228) | 0.3056 (0.0134) | −0.0175 (0.0092) | $42,193 |

Abbreviations: ECT, electroconvulsive therapy; QALY, quality-adjusted life-year; rTMS, repetitive transcranial magnetic stimulation.

Results were expressed in mean (standard deviation).

aAll costs are 2016 Canadian dollars.

Figure S1: Cost-effectiveness plane: the incremental cost and QALY gained of rTMS versus ECT

The triangle in the centre of the dots indicates the base case scenario. Each dot surrounding the triangle represents a single result from the simulation, presenting the incremental effects and incremental costs of rTMS versus ECT. The threshold line corresponds to an ICER of $50,000 per QALY gained.

Abbreviations: rTMS = repetitive transcranial magnetic stimulation, ECT = electroconvulsive therapy, QALY = quality-adjusted life-year.

Section 3: Additional results from New Non-Inferiority and Cost-Effectiveness Framework

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Figure S2: Modified cost-effectiveness acceptability curve: Probability of cost-effectiveness versus the threshold of effect preserved of rTMS. Cost-effectiveness was determined based on two criteria: meeting the threshold of effectiveness preserved and a positive net monetary benefit at a given WTP.

Note: When the WTP is $0, cost-effectiveness was determined using two criteria of: meeting the threshold of effect preserved and cost-saving for the new intervention.

Abbreviations: rTMS = repetitive transcranial magnetic stimulation, ECT = electroconvulsive therapy, WTP = willingness to pay, QALY = quality-adjusted life-year.

Table S2: Additional Results from New Non-Inferiority and Cost-Effectiveness Framework

|  |  |  |  |
| --- | --- | --- | --- |
| Threshold of effectiveness preserved (%) | Probability of ECT being cost-effective (%) | | |
| WTP = $0/QALY | WTP = $50,000/QALY | WTP = $100,000/QALY |
|  | | | |
| 50% | 70% | 37% | 14% |
| 75% | 23% | 21% | 13% |
| 90% | 7% | 7% | 7% |

Abbreviations: ECT, electroconvulsive therapy; QALY, quality-adjusted life-year; rTMS, repetitive transcranial magnetic stimulation.

Results were expressed in mean (standard deviation).

aAll costs are 2016 Canadian dollars.

*Two-way sensitivity analysis in the New Decision Framework*

The summary of the two-way sensitivity (WTP of $50,000 per QALY gained at the effectiveness preserved threshold of 75%) was presented in Table S3. When the odds ratios of response and remission for rTMS vs. ECT (uniform distribution [min, max]) were (0.65, 0.75), (0.75, 0.85) and (0.85, 0.95), the probabilities of being cost-effectiveness in rTMS group were 0.8740, 0.9959 and 0.9999, respectively. Note: besides the expected value, the variability of the parameters largely impacts the probability of being cost-effectiveness in PSA. In the sensitivity analysis, we assigned the narrow range of 0.1 of the uniform distributed odds ratios of response and remission in each analysis to compare rTMS versus ECT.

Table S3: Results of Two-way Sensitivity Analysis, Probability of Being Non-inferior And Cost-effective for rTMS Group at Willingness to Pay of $50,000 per QALY Gained and the Threshold of Effectiveness Preserved of 75%

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Uniform distribution (min, max) of odds ratio of response, rTMS vs. ECT\* | Uniform distribution (min, max) of odds ratio of remission, rTMS vs. ECT\* | | | | | | | | | |
| (0.25, 0.35) | (0.35, 0.45) | (0.45, 0.55) | (0.55, 0.65) | (0.65, 0.75) | (0.75, 0.85) | (0.85, 0.95) | (0.95, 1.05) | (1.05, 1.15) | (1.15, 1.25) |
| (0.25, 0.35) | 0 | 0 | 0 | 0 | 0.0003 | 0.0013 | 0.0037 | 0.009 | 0.0188 | 0.0214 |
| (0.35, 0.45) | 0 | 0 | 0 | 0 | 0.0026 | 0.016 | 0.0454 | 0.0888 | 0.1199 | 0.1645 |
| (0.45, 0.55) | 0 | 0 | 0 | 0.0045 | 0.0424 | 0.1535 | 0.2825 | 0.4076 | 0.47 | 0.5144 |
| (0.55, 0.65) | 0.0016 | 0.0073 | 0.0248 | 0.1125 | 0.3853 | 0.6296 | 0.7561 | 0.8073 | 0.8311 | 0.8426 |
| (0.65, 0.75) | 0.016 | 0.0624 | 0.2207 | 0.5814 | 0.874 | 0.9581 | 0.9799 | 0.9845 | 0.9902 | 0.9922 |
| (0.75, 0.85) | 0.0697 | 0.2252 | 0.5966 | 0.8951 | 0.9854 | 0.9959 | 0.9988 | 0.999 | 0.9997 | 0.9999 |
| (0.85, 0.95) | 0.1721 | 0.4733 | 0.8342 | 0.979 | 0.9985 | 0.9998 | 0.9999 | 0.9998 | 1 | 1 |
| (0.95, 1.05) | 0.2984 | 0.6481 | 0.93 | 0.994 | 0.9999 | 0.9999 | 1 | 1 | 1 | 1 |
| (1.05, 1.15) | 0.4036 | 0.7709 | 0.9665 | 0.9972 | 0.9999 | 1 | 1 | 1 | 1 | 1 |
| (1.15, 1.25) | 0.5015 | 0.8321 | 0.9803 | 0.9987 | 1 | 1 | 1 | 1 | 1 | 1 |

Abbreviations: ECT, electroconvulsive therapy; QALY, quality-adjusted life-year; rTMS, repetitive transcranial magnetic stimulation.

References:

1. The Food and Drug Administration of the United States. 2016. Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry. Available at: <https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf> (accessed 7 October 2017).

2. Wangge G, Roes KC, de Boer A, Hoes AW, Knol MJ. The challenges of determining noninferiority margins: a case study of noninferiority randomized controlled trials of novel oral anticoagulants. CMAJ. 2013;185(3):222-7.