A Simple, Assumption-Free, and Clinically Interpretable Approach for Analysis of Modified Rankin Outcomes

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Background and Purpose—There is debate regarding the approach for analysis of modified Rankin scale scores, the most common functional outcome scale used in acute stroke trials.

Methods—We propose to use tests to assess treatment differences addressing the metric, “if a patient is chosen at random from each treatment group and if they have different outcomes, what is the chance the patient who received the investigational treatment will have a better outcome than will the patient receiving the standard treatment?” This approach has an associated statement of treatment efficacy easily understood by patients and clinicians, and leads to statistical testing of treatment differences by tests closely related to the Mann-Whitney U test (Wilcoxon Rank-Sum test), which can be tested precisely by permutation tests (randomization tests).

Results—We show that a permutation test is as powerful as are other approaches assessing ordinal outcomes of the modified Rankin scores, and we provide data from several examples contrasting alternative approaches.

Discussion—Whereas many approaches to analysis of modified Rankin scores outcomes have generally similar statistical performance, this proposed approach: captures information from the ordinal scale, provides a powerful clinical interpretation understood by both patients and clinicians, has power at least equivalent to other ordinal approaches, avoids assumptions in the parameterization, and provides an interpretable parameter based on the same foundation as the calculation of the probability value. (Stroke. 2012;43:664-669.)

Key Words: ordinal analysis • modified Rankin score

See editorial, p 621.

The stroke community is in the midst of a spirited discussion regarding optimal approaches to the analysis and interpretation of the modified Rankin (mRS) score, which is commonly used as an outcome in acute stroke clinical trials.1–5 The mRS is a 7-point scale ranging from 0 (no symptoms) to 6 (dead; Table 1). The most severe scores, representing severe disability (mRS = 5) and death (mRS = 6), are frequently pooled, as these outcomes are considered equivalently bad. Two general approaches for analyzing mRS outcomes have been employed:

Categorical Statistical Approach Where the mRS Is Dichotomized

Most studies have taken the approach of either dichotomizing the scale at a fixed point (as in the Albumin in Acute Stroke [ALIAS] I trial7), or of using a sliding dichotomy, where a good outcome is defined as a function of baseline severity (as in the The Paracetamol (Acetaminophen) In Stroke [PAIS] trial8). This approach has the advantage of simplicity of clinical interpretation (and has been strongly encouraged by the U.S. Food and Drug Administration), but the disadvantage of failing to harness information from the entire spectrum of mRS outcomes. Analysis of the mRS dichotomous groups has been generally implemented by χ² testing or by logistic regression.

Ordinal Statistical Approaches of the Distribution Across the Entire mRS

Two analytic ordinal approaches have been employed, both having the advantage of increased statistical power provided by using information from the entire mRS and by capturing...
The Proportional Odds Model

The Proportional Odds Model (POM) is a straightforward generalization of logistic regression where the OR is calculated for each cut-point across the mRS (for example, 0 versus 1–6, then 0–1 versus 2–6, and so on), and then a generalized of logistic regression where the OR is calculated for each cut-point across the mRS (for example, 0 versus 1–6, then 0–1 versus 2–6, and so on), and then a

The Proportional Odds Model (POM) is a straightforward generalization of logistic regression where the OR is calculated for each cut-point across the mRS (for example, 0 versus 1–6, then 0–1 versus 2–6, and so on), and then a summary OR is calculated from the individual ORs, under the assumption that the individual ORs are the same. This approach has the advantage of providing a clinically interpretable parameter (the estimated summary OR), but the disadvantage of requiring the assumption that the individual ORs are the same (the proportional odds assumption). A second disadvantage is the potential for misinterpretation of the summary OR for two reasons. First, odds ratios and relative risk are frequently inappropriately interpreted to be identical. Specifically “odds” are the number of people with a condition divided by the number without the condition. For example, if there are 10 people with a positive outcome and 5 people without the outcome, then the odds for the group is 2.0 (10/5). In contrast, the “risk” is proportion with the outcome, in the example 10/(10 + 5) = 0.67. While both the odds ratio and relative risk compare two groups, they are considering the differences for different measures of risk, and are only similar in magnitude if the outcome is rare (generally not the case for analysis of mRS outcomes). In addition, the odds ratio provided by POM does not reflect a “simple” odds ratio, but rather an average across multiple thresholds of classification of the outcome, and as such should not be interpreted as a simple odds ratio.

The Cochrane-Mantel-Haenszel Test

The Cochrane-Mantel-Haenszel (CMH) is a test of the similarity of the mean rank (across the mRS) for 2 groups. The CMH test has the advantage of requiring virtually no assumptions for calculation of the probability value, but the disadvantage of not providing a clinically interpretable parameter.

In the analysis of the ordinal outcome, some studies (such as SAINT-1) used the CMH test treatment differences, and once significance was established, used the POM to provide a clinically interpretable parameter. Although this approach is generally acceptable, it does have the disadvantage of basing the assessment of the significance on a different approach (different metric) than does the estimation of the magnitude of the effect, as the 2 approaches can potentially give disparate results.

Thus, commonly used current approaches require the choice between the easily interpretable dichotomous analyses that fail to capture the information across the entire mRS spectrum, versus ordinal analyses that either provide no measures of clinical efficacy or provide measures that are commonly misinterpreted.

An Alternative Approach

We set out to find an alternative approach that: captures information from the ordinal scale, provides a powerful and easily understood clinical interpretation, has statistical power at least equivalent to the CMH or POM, avoids assumptions in parameterization, and has the clinically interpretable parameter based on the same foundation as the calculation of the probability value. This process began by attempting to state simply the treatment effects in terms that patients and clinicians would understand, and we suggest that the simple statement, “if a patient is chosen at random from each treatment group and if they have different mRS outcomes, what is the chance that the patient who received the investigational treatment will have a better outcome than will the patient receiving the standard treatment?” captures the essential information necessary for clinical decision making. This statistical statement of treatment efficacy can be rephrased to be understood easily by both patients and treating clinicians. For example, the findings of the National Institute of Neurological Disorders and Stroke Tissue Plasminogen Activator trial would be explained as, “Of 100 patients treated with tissue-type plasminogen activator (tPA) instead of placebo, 48 patients will be better with tPA, whereas 31 patients will be better with placebo. Twenty one (21) patients appear the same with either treatment.” We suggest this simple statement provides the information patients value by focusing on the chance that they will do better with a particular treatment. We are also confident that this statement can be
further refined with future experience working with patients with the interpretation of results.

This approach was initially proposed more than 60 years ago as an approach now referred to as the Mann-Whitney U test (MWU). This idea of whether a randomly chosen person from 1 group has better outcome (ie, lower mRS) than does a randomly chosen person from the other group has been shown to be mathematically equivalent to a ranking approach proposed 2 years earlier (the Wilcoxon Rank-Sum test). Both tests were developed for a continuous outcome where ties are impossible (or at least very rare), but this is not the case in the analysis of mRS outcomes. Approaches to handle the ties, however, have been subsequently proposed and are now very well-accepted. Although these 2 tests are among the most commonly used nonparametric tests, normally the focus is on the probability value, with little emphasis on the real-life, patient-centric description of the magnitude of the clinical effect. However, it is this description of the effect magnitude that was the impetus for the proposed alternative approach.

Because our alternative approach arose from discussions with clinicians to develop a statement of clinical effect, it differs slightly from the MWU on the accounting for tied scores. Specifically, the MWU assumes that half the pairs with tied scores are superior for 1 treatment and half are superior for the other (ie, half the tied scores had a lower mRS score for the patient assigned to investigational treatment, and half had lower mRS score for the standard-treatment patient). Although this approach is mathematically attractive, it leads to an awkward clinical statement of treatment differences—perhaps, “if a patient is chosen at random from each treatment group, and we assume that half the pairs of patients who have the same mRS score did in fact have a better outcome in the investigational-treatment group and half had a better outcome in the standard-treatment group, then what is the chance that the patients receiving the investigational treatment will have a better outcome than will the patient with standard treatment?” We consider this statement awkward to the point that understanding and explaining the clinical effect is a barrier.

Hence, our approach differs from the MWU in how it accounts for the tied values, where we consider only untied pairs of patients and the MWU assumes half to be superior in each group. Therefore, the MWU does not precisely test our proposed clinical statement; however, this can be accomplished by a permutation test (ie, randomization test). The permutation test first calculates a test statistic for the observed data. In this case, we used how far the observed proportion of non-tied pairs was from the null hypothesis of 50%. The permutation test randomly assigns treatments to individuals, ensuring no association between treatment and the test statistic (guaranteeing the null hypothesis is true). This process is repeated many times and the distribution of the test statistic under the null hypothesis is estimated. Whether the observed test statistic is unusual under the null hypothesis (that is, the probability value) is simply the location of the observed test statistic in distribution of test statistics under the null hypothesis. For example, if 234 of 1000 test statistics calculated under the null hypothesis are greater than the observed test statistic, then the probability value is 0.234. Although the construction details of the test are slightly complex and performing this test does require a bit of computer programming, we provide SAS code for the calculations in the Supplemental Data. This concept of permutation test is also not new, but was proposed by Fisher in 1935 as part of the pivotal Lady Tasting Tea experiment; the approach was generalized to randomization test (ie, rerandomization test) when the sample size is large and complete enumeration of all outcomes is impractical. Finally, the correlation between probability values from the permutation test and the MWU in the simulations considered for this report was 0.989; and although this estimated correlation will change with the distribution of mRS scores, this high correlation suggests that the MWU provides an approximate probability value for the more correct permutation test.

The calculations underlying our approach can be demonstrated using data from the National Institute of Neurological Disorders and Stroke tPA trial. Here, the distribution of the mRS in the tPA-treated patients is shown in rows, whereas the mRS scores for placebo-treated patients are shown in columns (Table 2). The first patient from the first group is matched up with each patient in the second group, the second patient in the first group with each patient in the second group, and so on to the last patient in the first group matched up with each patient in the second group; hence, the number of pairs of patients is simply the product of the number of patients in each combination. For example, there were 29 tPA-treated patients with a mRS of 3, and 30 placebo-treated patients with a mRS of 2; hence, there are $29 \times 30 = 870$ pairs of patients with this combination of scores. Altogether, there are 30 178 pairs of patients with higher (worse) mRS for placebo, 46 016 pairs of patients with lower (better) scores for tPA, and 19 596 pairs of patients with a tie between placebo and tPA. As such, 48% of pairs of patients (46 016 of 95 790) had lower (better) scores for tPA, 20% had tied scores (19 896 of 95 790), and 31% had lower (better) scores for placebo (30 178 of 95 790). Hence, these data support the statement, “Of 100 patients given tPA instead of placebo, 48 patients will be better with tPA, whereas 31 patients will be better with placebo. Twenty one (21) patients appear the same with either treatment.”

The approach is also flexible. For example, if the primary hypothesis requires stratification by a covariate (for example, stroke severity), the analysis can be adjusted by totaling the number of pairs of patients that are better, worse, or tied within each stratum of the covariate, and then by summing across the covariate strata. Importantly, this statistic is calculated by summing the pairs as higher/lower within each strata, then summing across strata, and only then calculating the statistic. Because the statistic is not calculated within the strata, but rather across all strata, the approach does not require a large sample size within each stratum to meet asymptomatic distribution assumptions for each strata. Hence, the approach does not require large sample size and does allow for the simultaneous adjustment multiple covariates. In addition, the potential for effect modification (interaction with treatment) within a trial can be assessed by calculating the proportion with better outcomes within each stratum, and by using a
permutation test testing if there is a large difference between
strata.

Not surprisingly, the statistical power to detect treatment
effects using this approach is equivalent to that of the CMH
or POM. As demonstrated in Table 3, we assumed a standard
treatment mRS distribution of the placebo-treated patients in
the National Institute of Neurological Disorders and Stroke
tPA study, then created a distribution for patients treated with
the investigational drug by shifting an increasingly larger
proportion of individuals to lower mRS strata (details of the
approach for shifting is provided in Supplemental Material).
The power of our approach is indistinguishable from the
power of the POM, both of which are generally marginally
more powerful than is the CMH test. We stress that it is
possible also to specify distributions where the CMH will be
marginally more powerful than are either this proposed
approach or the POM, and it is also possible to specify more
extreme distributions where the dichotomous analysis is most
powerful.

Finally, Table 4 provides a comparison of the alternative
ordinal approaches for 4 recently reported studies. As ex-
pected, the statistical test evaluating treatment effects is
concordant among the 3 approaches.

Discussion

Our analytic approach meets all the goals we established to
achieve in defining a statistical approach, specifically: it
captures information from the ordinal scale, it provides a
clinical interpretation that is easily understood, it has power at
least equivalent to that of the CMH or POM, it avoids
assumptions in the calculation of the significance of treatment
differences, and the clinically interpretable parameter is based
on the same foundation as the calculation of the probability
value. We suggest that this approach is:

- Superior to the dichotomous approach, as it captures the
  entire spectrum of the mRS, and therefore will be generally
  more powerful.
- Superior to the CMH test, as it provides an easily interpre-
  table index of treatment efficacy that is based on the same
  metric as is the significance test (ie, does not require the

Table 2. Distribution of mRS for the NINDS-tPA Trial3 Showing the Number of Pairs of Patients With
Each Combination of mRS

<table>
<thead>
<tr>
<th>mRS for tPA-Treated Patients</th>
<th>mRS for Placebo-Treated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n=23)</td>
</tr>
<tr>
<td>0 (n=49)</td>
<td>1127</td>
</tr>
<tr>
<td>1 (n=52)</td>
<td>1196</td>
</tr>
<tr>
<td>2 (n=26)</td>
<td>598</td>
</tr>
<tr>
<td>3 (n=29)</td>
<td>667</td>
</tr>
<tr>
<td>4 (n=68)</td>
<td>1564</td>
</tr>
<tr>
<td>5 or 6 (n=86)</td>
<td>1978</td>
</tr>
</tbody>
</table>

There were 29 tPA-treated patients with a mRS of 3, and 30 placebo-treated patients with a mRS of 2; hence, there are
29×30=870 pairs of patients with this combination of scores.
Numbers above the higher line represent pairs of patients with higher score for placebo than tPA: 46,016 pairs.
Numbers in the boxes down the diagonal represent pairs of patients with tied scores for placebo and tPA: 19,596 pairs.
Number below the lower line represent pairs of patients with lower scores for placebo than tPA: 30,178 pairs.

Table 3. Statistical Power to Detect Differences Between a Standard and Investigational Treatment as a Function of the Difference
Between Treatment Groups (Shift) and Sample Size

<table>
<thead>
<tr>
<th>Shift</th>
<th>MWU</th>
<th>POM</th>
<th>CMH</th>
<th>MWU</th>
<th>POM</th>
<th>CMH</th>
<th>MWU</th>
<th>POM</th>
<th>CMH</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>8.9</td>
<td>8.9</td>
<td>8.3</td>
<td>10.8</td>
<td>10.8</td>
<td>9.2</td>
<td>15.3</td>
<td>15.3</td>
<td>12.1</td>
</tr>
<tr>
<td>15</td>
<td>10.2</td>
<td>10.2</td>
<td>9.9</td>
<td>18.2</td>
<td>18.2</td>
<td>14.5</td>
<td>27.0</td>
<td>27.0</td>
<td>21.4</td>
</tr>
<tr>
<td>20</td>
<td>20.2</td>
<td>20.2</td>
<td>17.6</td>
<td>31.1</td>
<td>31.2</td>
<td>25.9</td>
<td>43.5</td>
<td>43.5</td>
<td>35.9</td>
</tr>
<tr>
<td>25</td>
<td>24.5</td>
<td>24.5</td>
<td>20.1</td>
<td>44.6</td>
<td>44.7</td>
<td>36.8</td>
<td>62.4</td>
<td>62.4</td>
<td>52.0</td>
</tr>
<tr>
<td>30</td>
<td>34.4</td>
<td>34.6</td>
<td>28.5</td>
<td>57.6</td>
<td>57.6</td>
<td>49.2</td>
<td>76.0</td>
<td>76.1</td>
<td>66.7</td>
</tr>
<tr>
<td>35</td>
<td>41.7</td>
<td>41.7</td>
<td>35.1</td>
<td>72.1</td>
<td>72.1</td>
<td>62.8</td>
<td>89.0</td>
<td>89.0</td>
<td>82.4</td>
</tr>
<tr>
<td>40</td>
<td>53.5</td>
<td>53.6</td>
<td>45.1</td>
<td>84.3</td>
<td>84.3</td>
<td>73.1</td>
<td>95.7</td>
<td>95.7</td>
<td>90.2</td>
</tr>
<tr>
<td>45</td>
<td>63.4</td>
<td>63.4</td>
<td>54.2</td>
<td>90.6</td>
<td>90.6</td>
<td>82.4</td>
<td>98.5</td>
<td>98.5</td>
<td>94.9</td>
</tr>
<tr>
<td>50</td>
<td>73.7</td>
<td>73.7</td>
<td>64.2</td>
<td>96.1</td>
<td>96.1</td>
<td>92.9</td>
<td>99.5</td>
<td>99.5</td>
<td>98.5</td>
</tr>
</tbody>
</table>

This table represents multiple replications where within each replication multiple permutations are required. We note that for this table, we used the MWU
approximation to the proposed test.

MWU indicates Mann-Whitney U test; POM, proportional odds model; CMH, Cochran-Mantel-Haenszel test.
Table 4. Performance of the Dichotomous Analysis (Dichotomized at 0–1 Versus 2–6), the Cochran-Mantel-Haenszel (CMH) Test, Proportional Odds Model (POM), and Proposed Model

<table>
<thead>
<tr>
<th>Dichotomous Outcome</th>
<th>Ordinal Outcome Approach</th>
<th>Proportional Odds Test</th>
<th>Propensity Approach (With Permutation/Randomization Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMH Test</td>
<td>Proportional Odds</td>
<td>Proportion of Changes Better for Active Treatment (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Test of Proportional</td>
<td>Worse (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Odd Assumption</td>
<td>Same (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Difference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS Score of 0/1</td>
<td>CMH Test P</td>
<td>Test of Proportional</td>
<td>Proportion of Changes Better for Active Treatment (%)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td>Odd Assumption P</td>
<td>Worse (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment Difference P</td>
<td>Same (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPA17</td>
<td>A: 33% P: 17%</td>
<td>&lt;0.0001</td>
<td>48.0</td>
</tr>
<tr>
<td>(n=619)</td>
<td></td>
<td>0.14</td>
<td>31.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.0002</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.69 (1.28–2.25)</td>
<td>60.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>SAINT 112</td>
<td>A: 33% P: 31%</td>
<td>0.28</td>
<td>43.1</td>
</tr>
<tr>
<td>(n=1699)</td>
<td></td>
<td>0.138</td>
<td>39.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.059</td>
<td>17.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.13 (0.96–1.34)</td>
<td>52.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.151</td>
</tr>
<tr>
<td>Alias 17</td>
<td>A: 28% P: 37%</td>
<td>0.16</td>
<td>43.4</td>
</tr>
<tr>
<td>(n=257)</td>
<td></td>
<td>0.654</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.43</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.11 (0.72–1.71)</td>
<td>52.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.626</td>
</tr>
<tr>
<td>Minocycline Trial10</td>
<td>A: 80% P: 25%</td>
<td>&lt;0.0001</td>
<td>76.7</td>
</tr>
<tr>
<td>(n=151)</td>
<td></td>
<td>0.78</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.16 (6.54–27.03)</td>
<td>89.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
</tbody>
</table>

For dichotomous analyses, A, active treatment (investigational treatment); P, placebo.

For the proportional odds model, the test of proportional odds is the probability that the assumption of proportional odds is met in the study.

mRS indicates modified Rankin scores; CMH, Cochran-Mantel-Haenszel; TPA, tissue-type plasminogen activator; SAINT, Stroke-Acute Ischemic NXY Treatment.

Perhaps the greatest among these are the advantages of computational ease and the implementation of the test in all major statistical packages, including the computation of confidence bounds for effects and adjustment for covariates. Although we offer the program for calculation of the index and probability value (Supplemental Appendix), these extensions of the technique will both require modest additional programming and will be more computationally intensive (noting, however, that computational burden is becoming less of an issue). Others, including coauthors of this work (V.W.R.), are developing methods for re-expression of measures of association from the MWU to include NNT and measures of effect; however, we hope that the measure of association of the proposed approach, the POM, and the CMH are primarily a matter of personal preference; it should focus on the benefit of having the basis for the measure of the association and probability value arising from the same metric versus the additional computational burden of the proposed approach.

One could easily (and perhaps correctly) argue that because the proposed approach, the POM, and the CMH are generally concordant, the choice among them is not a major study design issue. However, the discussion in the neurological community regarding the strengths and weaknesses of the analytic approach for the mRS outcome seems to be a never-ending spirited debate. We do not claim that our approach is universally more powerful than the others are, but rather that it is generally as powerful, yet superior, because it avoids the pitfalls present in other approaches.

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Disclosures

None.
References

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Supplemental Material

SAS code to perform the re-randomization test for treatment differences in mRS scores (or other ordinal outcomes)
/* this program calculates the indices for treatment difference for the mRS and performs a
permutation test of treatment differences. It assumes that data will include two variables:
1) TRT which is a 0/1 indicator variable for treatment, and 2) MRS which is the modified
Rankin Score. It would be wise to create a dataset that only contains these two variables
(reduces the chance that a variable name in the dataset would be the same as a variable
that was used in the program. */

/* the data step calculates the percent that is better */
data perm;
  set tmp end=last; /* data set with the data is inserted here */
  retain
    a0 a1 a2 a3 a4 a5
    b0 b1 b2 b3 b4 b5 num_g0 ;
  array a a0 a1 a2 a3 a4 a5;
  array b b0 b1 b2 b3 b4 b5;
  if _n_ = 1 then do;
    a0=0; a1=0; a2=0; a3=0; a4=0; a5=0;
    b0=0; b1=0; b2=0; b3=0; b4=0; b5=0;
    num_g0=0;
  end;
  if trt=0 then num_g0=num_g0+1;
  if trt=0 then a[mrs+1]=a[mrs+1]+1;
    else b[mrs+1]=b[mrs+1]+1;
  if last=1 then do;
    atot=a0+a1+a2+a3+a4+a5;
    btot=b0+b1+b2+b3+b4+b5;
    better =
      a0*b1 + a0*b2 + a0*b3 + a0*b4 + a0*b5 +
      a1*b2 + a1*b3 + a1*b4 + a1*b5 +
      a2*b3 + a2*b4 + a2*b5 +
      a3*b4 + a3*b5 +
      a4*b5 ;
    worse =
      b0*a1 + b0*a2 + b0*a3 + b0*a4 + b0*a5 +
      b1*a2 + b1*a3 + b1*a4 + b1*a5 +
      b2*a3 + b2*a4 + b2*a5 +
      b3*a4 + b3*a5 +
      b4*a5 ;
    same = a0*b0 + a1*b1 + a2*b2 + a3*b3 + a4*b4 + a5*b5;
    ratio=better/(better+worse);
    dif_ratio=abs(ratio-.5);
    m=1;
    pct_better=better/(better+same+worse);
    pct_same=same/(better+same+worse);
    pct_worse=worse/(better+same+worse);
    format pct_better pct_same pct_worse nlpct5.2;
  output;
  end;
  keep a0-a5 b0-b5 atot btot better same worse pct_better pct_same pct_worse ratio
dif_ratio num_g0 m;
run;

proc print data=perm;
  var a0-a5 b0-b5 better same worse pct_better pct_same pct_worse ratio num_g0;
  title 'Listing of the number of people in each mRS category for treatment 0 (A0-A5),';
  title2 'treatment 1 (B0-B5), the number of pairs that are better (BETTER) and worse
(WORSE),';
/* now re-randomize */

/* assign a random number for ordering */
data reran;
  set tmp;
  length trt mrs reran_rep t 4;
  keep trt mrs reran_rep t m;
  m=1;

  /* this is the "random" seed. This can be any large number. If it is set
to zero, the program will create a randomly selected number. The advantage of
this is runs of the program are independent. The disadvantage is that
running the program on the same data set will provide slightly different answers
(not the case if a large number is entered, which will provide completely identical
estimates */
  retain seed 8382732;
  do reran_rep=1 to 10000; /* number of replications of the re-randomzation. Should be
      at least 5000 */
    t=ranuni(seed);
    output;
  end;
run;

/* randomly order the observations */
proc sort data=reran;
  by reran_rep t;
run;

/* now merge in the PERM file to get the number treated with TRT=0 */
data reran2;
  merge reran perm;
  by m;
  keep trt mrs reran_rep num_g0;
run;

/* now randomly assign treatments */
data reran3;
  set reran2;
  by reran_rep;
  keep reran_rep trt mrs;
  length reran_rep trt mrs 4;
  retain nobs;
  if first.reran_rep then nobs=0;
  nobs=nobs+1;

  /* now randomly assign treatment */
  if nobs<=num_g0 then trt=0; else trt=1;
run;

/* now get ratios from each of the reran_reps */
data perm2;
  set reran3;
  by reran_rep;
  retain a0 a1 a2 a3 a4 a5
b0 b1 b2 b3 b4 b5;

array a a0 a1 a2 a3 a4 a5;
array b b0 b1 b2 b3 b4 b5;

if first.reran_rep then do;
a0=0; a1=0; a2=0; a3=0; a4=0; a5=0;
b0=0; b1=0; b2=0; b3=0; b4=0; b5=0;
end;

if trt=0 then a[mrs+1]=a[mrs+1]+1;
else b[mrs+1]=b[mrs+1]+1;

if last.reran_rep then do;
atot=a0+a1+a2+a3+a4+a5;
btot=b0+b1+b2+b3+b4+b5;
better =
a0*b1 + a0*b2 + a0*b3 + a0*b4 + a0*b5 +
a1*b2 + a1*b3 + a1*b4 + a1*b5 +
a2*b3 + a2*b4 + a2*b5 +
a3*b4 + a3*b5 +
a4*b5;

worse =
b0*a1 + b0*a2 + b0*a3 + b0*a4 + b0*a5 +
b1*a2 + b1*a3 + b1*a4 + b1*a5 +
b2*a3 + b2*a4 + b2*a5 +
b3*a4 + b3*a5 +
b4*a5;

reran_ratio=better/(better+worse);
diff_rr_ratio = abs(reran_ratio -.5);

m=1;

output;
end;

length reran_rep reran_ratio diff_rr_ratio 4;
keep reran_rep reran_ratio diff_rr_ratio m;
run;

proc chart data=perm_both;
  hbar reran_ratio diff_rr_ratio;
  title 'Distribution of the score under the null';
run;

/* now get the number with bigger deviations */
data perm_both;
merge perm perm2;
by m;
if dif_ratio>diff_rr_ratio then bigger=0; else bigger=1;
run;

/* now get p-value */
proc means data=perm_both mean;
  var bigger;
  title 'the p-value is the proportion with bigger';
  output mean=pr_perm out=perm_test;
run;