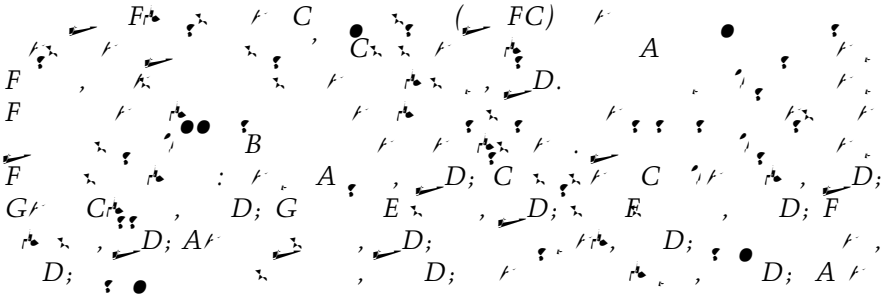
ACKNOWLEDGMENTS



arm/hand function; and cognitive function) met criteria for inclusion in a composite outcome measure. Three variables were recommended as primary measures in a Multiple Sclerosis Functional Composite (MSFC):1) Timed 25-Foot walk; 2) 9-Hole Peg Test (9-HPT); and 3) Paced Auditory Serial Addition Test (PASAT-3" version) (5,6).

Although components of the MSFC have been administered in a number of recent clinical trials, they have typically been administered by different study personnel, who vary in their experience and training in administering quantitative measures of performance. Ideally, a single examining technician should administer all three MSFC components following standardized procedures. This manual provides general instructions about the administration of quantitative functional measures to MS patients, and detailed instructions for administering each of the primary MSFC components. A self-assessment questionnaire is also provided so that examiners can assess their knowledge of key aspects of MSFC administration and scoring. Excellent reliability (both intra-rater and inter-rater) has been achieved when examining technicians are thoroughly trained in MSFC procedures (i.e., participate in a formal training session, practicing each of the measures at least five times prior to administering them to study patients) and strictly adhere to the instructions in this manual.

The manual also contains information on scoring methodology that can be used to create a single standardized score for each patient at each test session. Since the three variables are different in what they actually measure (time for the 9HPT and 25-Foot Timed Walk, but number of correct answers for the PASAT-3), it was necessary to identify a sensible way to use variables that inherently measure dimensions on different scales; that is, to define a common metric for these variables, and a Z-score was selected for this purpose. Thus, the results from each of these three tests are transformed into Z-sco

Many of those who will be administering the MSFC may not have had extensive experience with MS patients or with standardized testing procedures. The following instructions are provided to ensure that the MSFC is administered in a standardized in a manner, regardless of the examining technician's prior experience.

STANDARDIZING MSFC ADMINISTRATION

The MSFC should be administered as close to the beginning of a study visit as possible, but definitely before the patient does a distance walk. MSFC components should be administered in the following order:

1. Trial 1, Timed 25-Foot Walk
2. Trial 2, Timed 25-Foot Walk
3. Trial 1, Dominant Hand, 9-HPT
4. Trial 2, Dominant Hand, 9-HPT

TESTING ENVIRONMENT

TIMED 25-FOOT WALK

DESCRIPTION

The Timed 25-Foot Walk is a quantitative measure of lower extremity function. It is the first component of the MSFC administered at each visit. The patient is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The task is immediately administered again by having the patient walk back the same distance. Patients may use assistive devices when doing this task. In clinical trials, it is recommended that the treating neurologist select the appropriate assistive device for each patient.

MATERIALS NEEDED

Stopwatch, clipboard, Timed 25-Foot Walk Record Form, marked 25-foot distance in an unobstructed hallway, assistive device (if needed)

TIME LIMIT PER TRIAL

3 minutes (180 seconds) per trial.

DISCONTINUE RULES

1. If the patient cannot complete Trial 2 of the Timed Walk after a 5-minute rest period.
2. If the patient cannot complete a trial in 3 minutes.

ADMINISTRATION

Administration of the Timed 25-Foot Walk is demonstrated on the Training CD-ROM.

Trial 1

Make sure that the stopwatch is set to 0:00. For the Timed 25-Foot Walk, the subject should be directed to one end of a clearly marked 25-foot course (clearly defined on the floor or on the wall) and instructed to stand just behind the starting line. Point out where the 25-foot course ends, then instruct the patient as follows: **"I'd like you to walk 25**

QUESTIONS ABOUT THE

TIMED 25-FOOT WALK

D

A. As long as the style of the shoe is consistent for each patient from visit to visit, it does not matter what kind of shoes are worn. Encourage the patient to wear comfortable shoes and discourage patients from wearing, for example, high-heeled shoes one visit and running shoes the next.

25-

A. The patient should be encouraged to walk at a steady pace, one that he or she can sus-

.

A. A crutch extends under the axilla or supports the upper arm whereas the patient merely holds onto a cane.

.

A. Restart the trial and record the reason on the source document form.

.

A. Supply the patient with an accepted assistive device to use for the study visits. If it is a device unfamiliar to the patient, time should be allowed to practice with the device before the Timed 25-Foot Walk is administered.

DESCRIPTION

the pegs one at a time, using one hand only, and put them into the holes as quickly as you can in any order until all the holes are filled. Then, without pausing, remove the pegs one at a time and return them to the container as quickly as you can. We'll have you do this two (2) times with each hand. We'll start with your [DOMINANT] hand. You can hold the peg board steady with your [NON-DOMINANT] hand. If a peg falls onto the table, please retrieve it and continue with the task. If a peg falls on the floor, keep working on the task and I will retrieve it for you. See how fast you can put all of the pegs in and take them out again. Are you ready? Begin."

Start timing as soon as the patient touches the first peg, and stop timing when the last peg hits the container. If a peg drops on the floor, the examiner may retrieve it and put it back in the peg box. However, if a peg drops onto the table, allow the patient to retrieve it.

Record the patient's time under "Dominant hand—Trial 1." If the subject stops after having put all the pegs into the holes, prompt the subject to remove them as well by saying, **"And now remove them all."** If the subject begins to remove more than one peg at a time, correct him/her by saying, **"Pick up one peg at a time."**

Dominant Hand—Trial 2

After the first trial with the dominant hand, say, **"Good. Now, I'd like you to do the same thing again, once again using your [DOMINANT] hand. See how fast you can put all of the pegs in and take them out again. Ready? Begin."** Again, start timing as soon as the patient touches the first peg, and stop timing when the last peg hits the contain-

QUESTIONS ABOUT THE

9-HOLE PEG TEST

A. If a peg comes out of a hole and falls onto the table, let the patient retrieve it. If the peg comes out of a hole and falls onto the floor, you should retrieve it and place it in the container.

. 9-

A. Stop the trial. Reassemble the apparatus, repeat the instructions, and start the trial over. Encourage the patient to hold the pegboard steady with the hand he/she is not using, if possible. Note the incident in the appropriate section of the Record Form.

. 9-

A. If this happens on the enrollment visit (Day 1), the patient will not be able to enroll in the study. If this occurs once the patient is already enrolled in the study, indicate this in the appropriate section of the Record Form. Administer the 9-HPT at every visit, even if the patient was unable to complete it the visit before; the patient may be able to complete the test at subsequent visits.

. 9

A. No. The patient should progress directly from trial to trial, pausing only while you read the instructions for each subsequent trial.

.

A. If the stopwatch was not reset to 0:00 at the beginning of the trial, that trial will have to be repeated. Note on the Record Form which trial(s) [( ) -4 ((subeated.)-28 ([( ) -48 (repwh55 (.) -8 J ET BT 0.002 T4

INSTRUCTIONS FOR THE

PACED AUDITORY SERIAL ADDITION TEST

DESCRIPTION

Completing the PASAT Record Form

Circle all correct answers. Write in any incorrect responses in the space provided. Place a dash when no response is given. If the patient corrects him/herself after giving a response, count the amended answer as the response. The / response is the one that will be used in determining total correct, regardless of whether it was the correct or incorrect response. / / C' / / / - / / / / - .

Each section of the PASAT has a maximum of 60 correct answers (i.e. 61 digits are presented for each part). Count the total number correct (number of circled answers) for PASAT-3'' and record on the PASAT Record Form. Repeat the same scoring procedure for PASAT-2''. (Additional scores can also be computed to examine patterns of responses on the PASAT, but these are beyond the scope of this manual.)

QUESTIONS ABOUT THE

PACED AUDITORY SERIAL ADDITION TEST

. *C /CD A A ?*

A. No. You should always run the tape player/CD player on electric power to ensure that the rate of stimulus presentation is standardized.

. *A A ?*

A. If the patient has not made a response to any of the first five stimulus items, stop the practice trial and explain the task again. Remind the patient to state his/her answers aloud. Do not count the five "no responses" as one of the three practice trials. (This situation is likely to occur only on the patient's first visit, when the patient is not familiar

A. No. Observe the patient during the practice trials for this behavior. Instruct the patient that all calculations are to be done in his or her head and that "writing down" the numbers is not permitted.

A. No. Again, if this behavior is exhibited by the patient during the practice, explain that is not allowed and that all calculations must be done in the patient's head.

A. No. As the instructions indicate, once the PASAT test has begun, you cannot stop it even if the patient requests to do so. The only reasons that you would stop the PASAT test would be because of a major external disturbance, equipment failure/malfunction, or something of this nature.

A. The PASAT is a primary component of the MS Functional Composite. If a patient is

EXAMINING TECHNICIAN

SELF-ASSESSMENT

Examining technicians are encouraged to be thoroughly familiar with all of the MSFC components prior to administering these to a patient during a study visit. You should be able to answer each of the following questions without referring to the manual.

I. GENERAL OVERVIEW

1. Please number the following to indicate the correct sequence of tests (1–8):

____ PASAT-3''
____ 9-HPT (Dominant hand)—Trial 1
____ PASAT-2''
____ Timed 25-Foot Walk—Trial 1
____ 9-HPT (Non-dominant hand)—Trial 2
____ 9-HPT (Dominant hand)—Trial 2
____ Timed 25-Foot Walk—Trial 2
____ 9-HPT (Non-dominant hand)—Trial 1

4. What should the examining technician do before starting the next trial?

_____

5. When is the position of the 9-HPT apparatus changed? _____

_____

6. What should the examining technician do if a peg falls on the table?

_____

7. What should the examining technician do if a peg falls on the floor?

_____

8. What should the examining technician do if the patient pauses prior to removing the pegs from the pegboard? _____

_____

9. What should the examining technician do if the patient tries to pick up more than one peg at a time? _____

_____

10. When is the stopwatch stopped for this test? _____

_____

11. What should the examining technician do if during testing s/he realizes that the stopwatch was not set appropriately? _____

_____

12. What should the examining technician do if there is an external distraction during testing that affects the time the subject needs to complete the 9-HPT?

_____

13. For how long is the patient allowed to rest between trials on the 9-HPT?

_____

IV. PASAT

1. What equipment is needed for the PASAT? _____

_____

2. Who is responsible for ensuring that the correct PASAT form is used?

_____

_____

_____

3. Should the tape/CD player be operated on batteries for the PASAT?

   Yes _____ No _____

4. What is the [illegible] number of practice trials given before the PASAT-3'' or PASAT-2''? _____

   _____

5. What is the [illegible] number of practice trials given before the PASAT-3'' or PASAT-2''?

   _____

   _____

6. Which three conditions warrant stopping the practice trials prior to completion?

   _____

   _____

   _____

7. What is the correct way to record the patient's responses on the PASAT Record Form?

   Correct answers: _____

   Incorrect Answers: _____

   No Responses: _____

   Amended Responses: _____

8. What should the examining technician do if the patient indicates s/he wants to start the test over? _____

9. What is the minimum number of correct PASAT-3'' responses the patient must have during the randomization visit in order to be eligible for the study?

   _____

10. For how long is the patient allowed to rest between the PASAT-3'' and the PASAT-2''?

    _____

EXAMINING TECHNICIAN

SELF-ASSESSMENT TEST ANSWERS

I. GENERAL OVERVIEW

1. Please number the following to indicate the correct sequence of tests (1–8):

   __7__ PASAT-3''

   __3__ 9-HPT (Dominant hand)—Trial 1

   __8__ PASAT-2''

   __1__ Timed 25-Foot Walk—Trial 1

   __6__ 9-HPT (Non-dominant hand)—Trial 2

   __4__ 9-HPT (Dominant hand)—Trial 2

   __2__ Timed 25-Foot Walk—Trial 2

   __5__ 9-HPT (Non-dominant hand)—Trial 1

2. Why is it important to eliminate distractions during these tests?

   _____

   _____

3. Can the instructions for any of the tests be eliminated if the patient indicates that s/he remembers what to?

   Yes _____ No __X__

4. Should the patient be allowed to converse with the examiner while performing any of the MSFC tests?

   Yes _____ No __X__

II. TIMED 25-FOOT WALK

1. Who determines whether or not the patient will use an assistive device for this test throughout the course of the study?

2. When is the stopwatch started for this test?

3. Is a patient allowed to use a wall or other support other than the assistive device assigned by the treating physician?

   Yes _____ No __X__

4. When is the stopwatch stopped for this test?

5. What should the examining technician do before Trial 2?

6. What should the examining technician do if s/he realizes midway through testing that the stopwatch was not reset appropriately?

7. What should the examining technician do if there is an external distraction during testing that affects the time the subject needs to complete this test?

8. For how long is the patient allowed to rest between trials of the Timed 25- Foot Walk?

III. NINE-HOLE PEG TEST (9HPT)

1. What equipment is required for this test?

2. How is the 9-HPT board positioned in front of the subject?

3. When is the stopwatch started for this test?

4. What should the examining technician do before starting the next trial?

5. When is the position of the 9-HPT apparatus changed?

6. What should the examining technician do if a peg falls on the table?

LOWER EXTREMITY FUNCTION: TIMED 25-FOOT WALK

Subject ID Number

Day

UPPER EXTREMITY FUNCTION: NINE-HOLE PEG TEST (9-HPT)

Subject ID Number | Subject Initials | Visit Date: Day Month Year

9-HOLE PEG TEST

DOMINANT HAND *(Check one)*:

DOMINANT HAND

Trial 1

seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed

Unable to complete trial due to physical limitations ➡ Specify:

Other ➡

Trial 2

seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed

Unable to complete trial due to physical limitations ➡ Specify:

Other ➡

Did it take more than two attempts to get two sucessful trials? Yes No
If Yes, please specify reason(s) for more than two attempted trials:

NON-DOMINANT HAND

Trial 1

seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed

Unable to complete trial due to physical limitations ➡ Specify:

Other ➡

Trial 2

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed

Unable to complete trial due to physical limitations ➡ Specify:

Other ➡

Did it take more than two attempts to get two sucessful trials? Yes No
If Yes, please specify reason(s) for more than two attempted trials:

PASAT Practice Items

RATE #1
(3 sec.)

9 + 1 10 ____	3 4 ____	5 8 ____	2 7 ____	6 8 ____	4 10 ____	9 13 ____	7 16 ____	1 8 ____	4 5 ____

9 + 1 10 ____	3 4 ____	5 8 ____	2 7 ____	6 8 ____	4 10 ____	9 13 ____	7 16 ____	1 8 ____	4 5 ____

9 + 1 10 ____	3 4 ____	5 8 ____	2 7 ____	6 8 ____	4 10 ____	9 13 ____	7 16 ____	1 8 ____	4 5 ____

PASAT Practice Items

RATE #2
(2 sec.)

3 + 8 11 ____	2 10 ____	7 9 ____	9 16 ____	1 10 ____	8 9 ____	5 13 ____	2 7 ____	6 8 ____	4 10 ____

3 + 8 11 ____	2 10 ____	7 9 ____	9 16 ____	1 10 ____	8 9 ____	5 13 ____	2 7 ____	6 8 ____	4 10 ____

3 + 8 11 ____	2 10 ____	7 9 ____	9	1	8	5	2	6	4

COGNITIVE **F**UNCTION: **P**ASAT - **F**ORM A

Subject ID Number | Subject Initials | Visit Date: Day Month Year

RATE #1
(3 sec)

1 + 4 5____	8 12____	1 9____	5 6____	1 6____	3 4____	7 10____	2 9____	6 8____	9 15____
4 13____	7 11____	3 10____	5 8____	3 8____	6 9____	8 14____	2 10____	5 7____	1 6____
5 6____	4 9____	6 10____	3 9____	8 11____	1 9____	7 8____	4 11____	9 13____	3 12____
7 10____	2 9____	6 8____	9 15____	5 14____	2 7____	4 6____	8 12____	3 11____	1 4____
8 9____	5 13____	7 12____	1 8____	8 9____	2 10____	4 6____	9 13____	7 16____	9 16____
3 12____	1 4____	5 6____	7 12____	4 11____	8 12____	1 9____	3 4____	8 11____	2 10____

Total Correct (raw) = _____ Percent Correct = _____

RATE #2
(2 sec)

4 + 3 7____	7 10____	2 9____	5 7____	1 6____	8 9____	6 14____	9 15____	1 10____	7 8____
9 16____	4 13____	6 10____	3 9____	5 8____	8 13____	1 9____	6 7____	2 8____	7 9____
5 12____	9 14____	4 13____	5 9____	2 7____	6 8____	4 10____	8 12____	3 11____	5 8____
9 14____	7 16____	4 11____	2 6____	8 10____	5 13____	2 7____	1 3____	6 7____	4 10____
7 11____	3 10____	5 8____	9 14____	6 15____	4 10____	5 9____	3 8____	9 12____	4 13____
1 5____	8 9____	3 11____	1 4____	6 7____	8 14____	5 13____	4 9____	2 6____	6 8____

Total Correct (raw) = _____ Percent Correct = _____

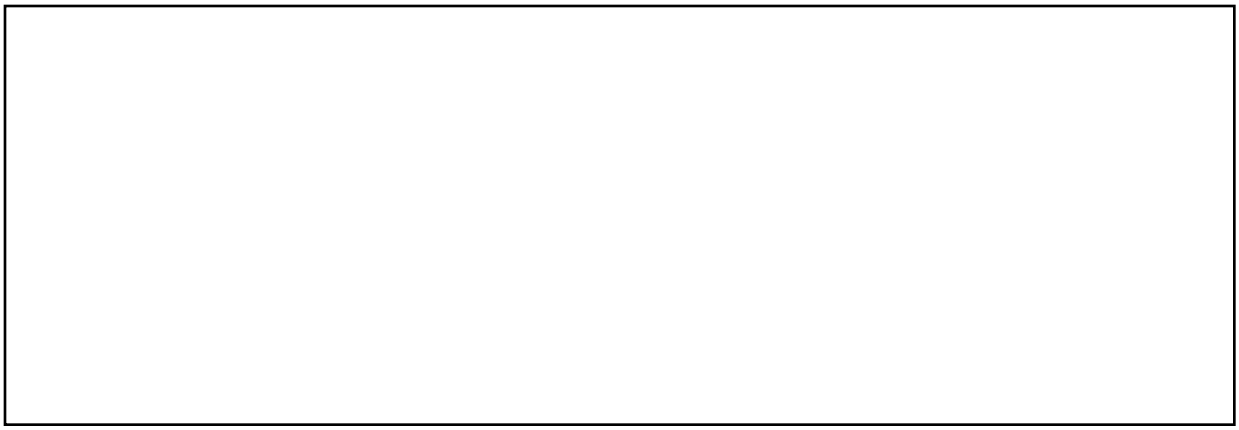
RATE #1
(3 sec)

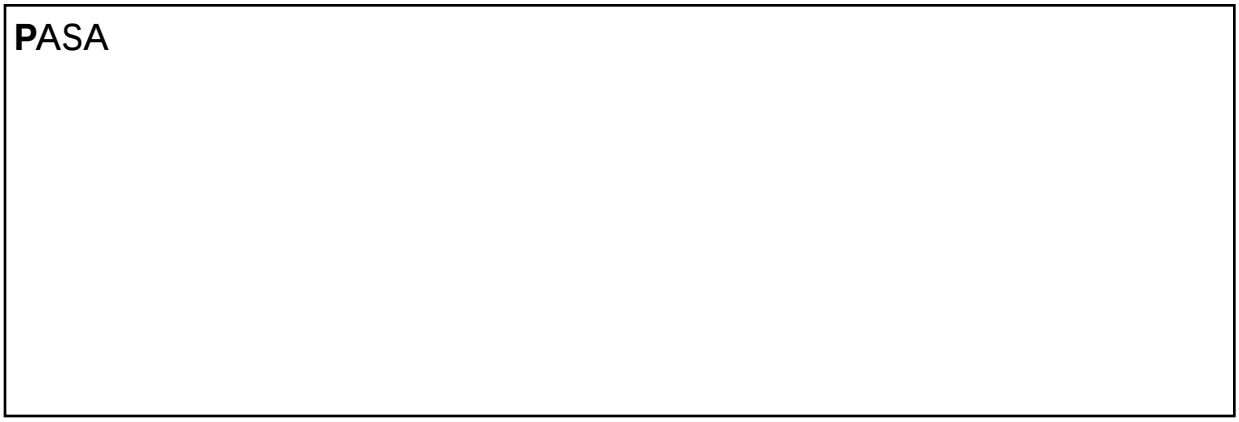
2 + 7 9____	5 12____	8 13____	2 10____	9 11____	6 15____	4 10____	1 5____	3 4____	6 9____
3 9____	6 9____	2 8____	8 10____	4 12____	9 13____	1 10____	6 7____	7 13____	2 9____
4 6____	1 5____	5 6____	7 12____	3 10____	9 12____	7 16____	2 9____	6 8____	8 14____
4 12____	2 6____	5 7____	8 13____	5 13____	9 14____	3 12____	7 10____	1 8____	4 5____
2 6____	4 6____	3 7____	6 9____	1 7____	7 8____	3 10____	8 11____	3 11____	9 12____
1 10____	3 4____	5 8____	2 7____	6 8____	4 10____	9 13____	7 16____	1 8____	4 5____

Total Correct (raw) = _____ Percent Correct = _____

7 + 8 15____	6 14____	3 9____	7 10____	5 12____	9 14____	1 10____	2 3____	6 8____	8 14____
3 11____	6 9____	2 8____	5 7____	9 14____	7 16____	1 8____	8 9____	3 11____	6 9____
7 13____	4 11____	2 6____	5 7____	3 8____	8 11____	6 14____	2 8____	3 5____	7 10____
3 10____	5 8____	2 7____	8 10____	5 13____	3 8____	7 10____	4 11____	1 5____	5 6____
2 7____	4 6____	1 5____	6 7____	3 9____	9 12____	7 16____	1 8____	8 9____	4 12____
6 10____	2 8____	5 7____	8 13____	1 9____	9 10____	7 16____	2 9____	8 10____	3 11____

Total Correct (raw) = _____ Percent Correct = _____ CorrT BT 12 0 0 12 4




PASA

SCORING INSTRUCTIONS FOR THE

MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE

In this section, instructions for creating a score from the MSFC component test results are provided. Detailed explanations and discussion are then given.

HOW TO CREATE THE MSFC SCORE

There are three components to the MSFC: (1) the average scores from the four trials on the 9-HPT (the two trials for each hand are averaged, converted to the reciprocals of the mean times for each hand and then the two reciprocals are averaged); (2) the average scores of two 25-Foot Timed Walk trials; (3) the number correct from the PASAT-3. The MSFC is based on the concept that scores for these three dimensions—arm, leg, and cognitive function are combined to create a single score (the MSFC) that can be used to detect change over time in a group of multiple sclerosis patients. This is done by creating Z-scores for each component of the MSFC, as explained below, and averaging them to create an overall composite score known as the MSFC score. Implicit in this approach is the idea that patients who deteriorate or improve on all three component measures will have an overall larger change than patients who change on only one of the three measures. Also, patients who deteriorate in one area but improve in another may show no change on the MSFC, because the MSFC represents the [illegible] change in the three tests. The general formula for creating the composite is given in Table 1. Detailed formulae that allow creation of the MSFC score are provided in Tables 2 and 3 and are further explained below.

Z-sco

line visit from all patients in a particular study cohort. The equation for this method is provided in Table 2. An alternative method is to use the results from a representative database with a broad spectrum of multiple sclerosis patients. The equation for this method, using data from the NMSS Task Force database, is shown in Table 3. This method allows a comparison of disease severity in patients participating in different studies because their scores are standardized against a common population. This method may not be the optimal method for demonstrating change in a particular population or for showing treatment effects.

TABLE 2

TABLE 3

Formula For Creating The MSFC Score Using The Task Force Database to Allow Comparison Between Studies

MSFC Score = { (Average (1/9-HPT) - 0.0439) / 0.0101
+ { - (Average 25-Foot Walk - 9.5353) / 11.4058}
+ (PASAT-3 - 45.0311) / 12.0771 } / 3.0

: "Average (1/9-HPT)" is the average of the inverse (reciprocal) for the mean time of the two trials on the right hand and reciprocal of the mean time of the two left hand trials from the test patient; 0.0439 and 0.0101 are the mean and standard deviation of the inverse of the 9-HPT for the reference population. "Average 25-Foot Walk" is the mean time from the two trials of the 25-foot timed walk; 9.5353 and 11.4058 are the mean and std dev of the reference population. "PASAT-3" is the score from the test patient; 45.0311 and 12.0771 are the mean and std dev of the reference population. These are discussed below.

The formula in Table 3 uses means and standard deviations derived from all patients in the Task Force dataset (4,5). Composite scores created using this formula should be comparable across different trials. The results from the formulae presented in Tables 2 and 3 will be similar but may not be identical, as discussed below.

Special consideration is given to handling missing scores or test results when the patient cannot perform the test because of disability. These important issues are discussed below.

with the following results for patients #1 to #5, respectively: 26, 26, 33, 34, and 43 seconds. Each of the five patients changed: patient #1 worsened by 6 seconds, #2 worsened by 1 second, #3 worsened by 3 seconds, #4 improved by 1 second, and #5 worsened by 3 seconds. Thus, the average change is 2.4 seconds with a standard deviation of the change of 2.608 seconds.

Table 6 illustrates the Z-score changes using different standard populations to create the scores.

While each of the individual changes is different, the ratio of the amount of change to the standard deviation of the change, shown as the t-value in the table, is constant. In actual seconds, for example, patient #1 changed 6 seconds; with reference to the baseline

Notice that this transformation has reversed the order of the relative times such that patient #1 now is the largest numerical z-score 1.474, indicating a performance better than the average.

TABLE 7

Creating Z-scores Using Inverse Test Values To Transform Scores (Same Patients As Table 4)

	F F - , 9-	- 9-
#1	(1/20 – .03528) / .009917	1.47
#2	(1/25 – .03538) / .009917	0.47
#3	(1/30 – .03538) / .009917	–0.21
#4	(1/35 – .03538) / .009917	–0.69
#5	(1/40 – .03538) / .009917	–1.05

Special Considerations

1.

In the event that a particular patient did not complete some of the tests (e.g., the patient was running late so only one trial of the 9-HPT per arm was completed), the available data can be used to calculate the MSFC. In this case, the MSFC is still the average of the 3 Z-scores as usual:

$$\text{MSFC Score} = [Z_{\text{arm, average}} + Z_{\text{leg, average}} + Z_{\text{cognitive}}] / 3.0$$

In the usual instance, the $Z_{\text{arm, average}}$ is computed as:

$$Z_{\text{arm, average}} = \{(1/\text{trial}_{\text{arm left}} + 1/\text{trial}_{\text{arm right}}) / 2.0 - \text{baseline mean (1/9-HPT)}\} / \text{Baseline Std Dev(1/9-HPT)}$$

where

$$1/\text{trial}_{\text{arm, left}} = (1/\text{average of the two times of the left arm trials})$$

and similarly for $1/\text{trial}_{\text{arm, right}}$.

In the absence of two trials for each arm for the 9-HPT, the $Z_{\text{arm, average}}$ would be computed based on the trials available, as follows:

$$Z_{\text{arm, average}} = \{(1/\text{trial}_{\text{arm, trial \#1, left}} + 1/\text{trial}_{\text{arm, trial \#1, right}}) / 2.0 - \text{Baseline mean (1/9-HPT)}\} / \text{Baseline Std Dev (1/9-HPT)}$$

2.

We recommend using data from patients who were unable to perform the test because of disability. For example, suppose an individual completed the 9-HPT in an average of 55 seconds at the beginning of the trial, but was unable to complete the 9-HPT at the end of the trial because of increasing disability. It is advantageous to capture the data in such

a way that it indicates worsening, rather than leaving the data point missing, which would provide no information about change.

9 : In most datasets used in the meta-analysis (3,4), the inability to perform the 9-HPT was coded as 777. Keeping that convention, 1/777 was arbitrarily

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REFERENCES