

**NINDS CDE Project**  
**Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)**  
**Autonomic Subgroup**

During the process of developing the ME/CFS Autonomic recommendations, the committee largely focused its deliberations on questionnaires that would ascertain for orthostatic intolerance. Because the need for supplemental measures of autonomic function would depend on the specific aims of a given study, the committee did not make recommendations about performing other physiologic maneuvers such as the cold pressor test, heart rate responses to deep breathing and the Valsalva maneuver, quantitative sudomotor axon reflex testing (QSART), blood volume measurement, or heart rate variability. Similarly, the committee did not recommend standing tests or tilt table testing in all studies. The need for such objective measures of orthostatic tolerance would depend on the study questions, as would decisions about whether to include catecholamine measures, end-tidal CO<sub>2</sub>, or transcranial Doppler ultrasounds during orthostatic stress.

The committee did suggest methods that would improve the consistency with which standing tests could be conducted, given that these are more practical to perform, and can be conducted in most clinical settings without specialized equipment.

To evaluate autonomic questionnaires, individual members of the committee reviewed published instruments and case report forms (CRFs) for their relevance to autonomic symptoms and orthostatic intolerance. Consensus was achieved during the telephone meetings. One important dilemma in adopting autonomic questionnaires for use in ME/CFS is that fatigue and cognitive dysfunction can be symptoms of orthostatic intolerance. For this reason, many of the existing autonomic questionnaires attribute these symptoms directly to the specific form of circulatory dysfunction under study. That is not always the correct attribution of these symptoms in ME/CFS.

The committee concluded that no published autonomic questionnaire offers a robust measure of autonomic or orthostatic intolerance symptoms in ME/CFS (see sections below). To address this gap, the committee drafted a new questionnaire by modifying the wording of the existing "Orthostatic Symptom Grading Scale," but this proposed questionnaire will need further validation.

We deferred questions on medical history and family history of specific orthostatic disorders to the general case report forms, which we expect will ask about the past history of fainting and about other medical problems that include orthostatic intolerance and autonomic dysfunction (for example, Ehlers Danlos syndrome). For similar reasons, we also did not include questions on prior diagnoses or on treatment of related conditions such as POTS, neutrally mediated hypotension, or orthostatic hypotension.

The following items were recommended as "Supplemental-Highly Recommended" by the subgroup:

- The 'COMPASS-31' instrument for assessing autonomic symptoms.
- The 'Beighton Score' for joint hypermobility as an important sub-grouping item in the evaluation of orthostatic intolerance.
- The 'Passive Standing Test' for objective measurement of heart rate, blood pressure, and symptomatic responses to standing for 10 minutes.

The following items were recommended as "Exploratory" by the subgroup:

- A 'Modified Orthostatic Symptom Grading Scale' to measure the frequency, severity, and impact of common orthostatic symptoms.

The committee also reviewed additional instruments, but did not feel that they were appropriate to this sub-working group. They are listed as follows:

1. Autonomic Symptom Profile
2. Orthostatic Grading Scale
3. Composite Autonomic Severity Scale (CASS)
4. Scale for Outcomes in Parkinson's Disease Autonomic (SCOPA-AUT)
5. Orthostatic Hypotension Questionnaire
6. Romberg test
7. DePaul Symptom Questionnaire
8. Functional Disability Inventory
9. PedsQL
10. Wood Mental Fatigue Inventory

None of the instruments recommended for measuring autonomic symptoms, such as the COMPASS 31 or the Modified Orthostatic Symptom Grading Scale, have been specifically studied in the pediatric population. The Beighton score has been studied in pediatric and adult ME/CFS populations. The COMPASS-31 instrument has been used in ages 8-79, however the younger children might have difficulty with some of the terms in the questionnaire, and it is unlikely that many young children were included in the study samples despite the claim it was valid and reliable down to age 8. In clinical practice, the passive standing test has been used in children ages 10 and older. The lower age range for the Modified Orthostatic Symptom Grading Scale is not clearly known at this time. The CRF is likely to be understood by older adolescents, however this will need to be confirmed in future studies.

**Below is a Table Summary of Recommendations for the Autonomic Subgroup:**

<b>Instrument / Scale / CRF Name</b> <i>Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs</i>	<b>Population</b>	<b>Classification</b> (e.g., Core, Supplemental - Highly Recommended, Supplemental, Exploratory)
COMPASS - 31	Adults and pediatrics (ages 8 and older)	Supplemental - Highly Recommended
Beighton Score CRF	Adults and pediatrics	Supplemental - Highly Recommended
Passive Standing Test CRF	Adults (Note: age ranges not clear for pediatric population, in clinical practice the test is normally well tolerated by children ages 10 or older)	Supplemental – Highly Recommended
Modified Orthostatic Symptom Grading Scale CRF	Adults and pediatric (Note: further study needed as the lower age limit is unknown)	Exploratory

Because fatigue and cognitive dysfunction are common symptoms of orthostatic intolerance, many of the existing autonomic questionnaires ask respondents to rate how much their difficulties thinking or their tiredness are due to their known circulatory condition. For example, the Orthostatic Hypotension Symptom Assessment asks the respondent to "Please tick the number on the scale that best rates how severe your symptoms **from low blood pressure** have been on the average over the past week" (emphasis added), with specific symptoms including weakness, fatigue, trouble concentrating, or head/neck discomfort.

Asking the questions in this manner would be problematic in ME/CFS for several reasons. ME/CFS patients might not be familiar with the term "orthostatic symptoms," might not have been diagnosed with a circulatory problem, or might have multiple causes for a given symptom. The committee chose to draft a new version of one of the published questionnaires in an attempt to derive a more appropriate measure of orthostatic intolerance symptom frequency, severity, and impact in ME/CFS. The modified questionnaire will need to be validated.

While the COMPASS 31 questionnaire has been validated and has been used in ME/CFS studies, it has a limited range of questions regarding orthostatic intolerance. It asks respondents only 4 questions about "feeling faint, dizzy, goofy, or having difficulty thinking soon after standing up from a sitting or lying position." In contrast, it asks 12 questions about gastrointestinal symptoms. The

presence or absence of lightheadedness is not ascertained, and there are no questions that address how long the respondent can stand without developing symptoms.

The DePaul questionnaire is similarly limited in the breadth of questions that address orthostatic tolerance, asking only about the frequency and severity of "Dizziness or fainting" and "Irregular heart beats". As these examples illustrate, greater precision in the wording is needed in order to improve ascertainment of orthostatic symptoms. Dizziness, for example, includes vertigo, which is caused by a process completely independent of orthostatic intolerance. Fainting certainly would indicate orthostatic intolerance at a single moment in time, but would not address whether chronic orthostatic intolerance is a problem.

Thus, there is a need to develop more relevant questionnaires for the ME/CFS population that ascertain the frequency and severity of the most common orthostatic symptoms (lightheadedness, fatigue, trouble thinking and concentrating, blurry vision) and to ask about those symptoms under specific orthostatic conditions such as with prolonged standing, or when exposed to heat. There is also a need to develop specific pediatric ME/CFS questionnaires that address orthostatic intolerance.