# NINDS CDE (Common Data Elements) Task Group

# on Neurological Outcomes and Endpoints

# for Spinal Cord Injury (SCI)

Final Report to NINDS (March 7, 2014)

## Preamble:

 Only one of the assessment tools listed below might be considered as a Core tool and this is the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI).

 The rest of the listed neurological measurement tools are recommended as SUPPLEMENTAL or EXPLORATORY outcomes or endpoints during an SCI clinical study and/or experimental human study. They are not required assessments as other outcome measures may be more appropriate (study/trial) endpoints depending on: 1) the therapeutic intervention, 2) the target of the experimental treatment, 3) the desired ICF domain for the outcome to be achieved, 4) the time since initial SCI, and/or 5) specific phase of the clinical trial.

 The "core" data set of the NINDS and/or the International SCI data sets ([International Spinal Cord Society Data Sets](http://www.iscos.org.uk/international-sci-data-sets)) are very useful when tracking an individual from an early time point after SCI. However, some of the requested data in the core data worksheets may not be known or available if the experimental study is being conducted during a later, more chronic, time period.

## CNS Sensorimotor Impairment (or Preservation)

Traumatic and non-traumatic SCI often occurs at a specific spinal cord segment or within a few adjacent cord segments. Such CNS damage requires characterization and classification in terms of the segmental level of injury, as well as the severity of the neurological impairment.

### Instrument:

 International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI or International Standards)

### ICF Domain:

 Body structure or function

### Assessment Focus:

 Impairment (or preservation) of CNS sensory and motor function

### Recommended Use:

 CORE assessment for all acute clinical studies, regardless of therapy. SUPPLEMENTAL at later survival times (> 6-12 months). See comments below.

Psychometric Properties: [International Standards for Neurological Classification of Spinal Cord Injury](http://www.rehabmeasures.org/Lists/RehabMeasures/PrintView.aspx?ID=956)

### Comments:

 As mentioned in the preamble, the ISNCSCI (or International Standards) is one tool that has gained widespread acceptance and has become the current worldwide standard for the examination and classification of neurological sensorimotor impairment after SCI. The ISNCSCI is a classification scheme that combines elements of sensory and motor examination with classification of the neurological level and severity (completeness) of injury. Completion of the latest version of the ISNCSCI worksheet ([INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY Worksheet](http://www.asia-spinalinjury.org/elearning/ASIA_ISCOS_high.pdf)) provides an assessment of the integrity of somatosensory perception (light touch and pin prick) by an individual at each spinal cord segment along the neuraxis. Using the Manual Muscle Test (MMT), ISNCSCI also provides an assessment of 5 'key' muscles or muscle groups (bilaterally) that are associated with specific cervical spinal cord segments and 5 'key' muscles or muscle groups (bilaterally) associated with specific lumbosacral cord segments. Note: MMT was derived from and is synonymous with the Oxford muscle assessment.

 ISNCSCI also includes a method for determining the most caudal segmental cord levels for sensory and motor function, as well as a single neurological level, which is the most caudal spinal cord level with bilateral intact sensory perception and intact anti-gravity motor function (all rostral spinal cord segments being normal). The American Spinal Injury Association (ASIA) Impairment Scale (AIS A-E) is part of the International Standards or ISNCSCI and is a simple grading of the severity of SCI. Note: AIS grades were derived from Frankel grades, which use slightly different criteria. Thus Frankel grades are not synonymous with AIS grades.

 ISNCSCI is an involved physical assessment procedure that requires little equipment, but does require standardized training and practice. Due to the intrinsic variability in the acute medical status and treatment of an individual after SCI, the ISNCSCI assessment may be difficult to complete in a totally accurate manner within the first few days after SCI. While acute trials with very short treatment initiation windows will need to obtain baseline ISNCSCI measurement within the first few hours after SCI, the inherent reliability challenges for such early assessments will add to the variability in outcomes and hence the necessary number of enrolled subjects. The ISNCSCI examination can also be a most useful tool for monitoring and tracking the neurological safety of a therapeutic. Online training is available from the ASIA learning center ([ASIA Learning Center Login Website](http://lms3.learnshare.com/home.aspx)).

 Varying degrees of improvement (recovery) in both neurological and functional (activity) outcomes are known to occur spontaneously over the first few months after SCI, even with just standard clinical and rehabilitation care. Furthermore, the correlation between neurological recovery and improvement in functional activities can diminish with time after SCI. Thus activity outcomes can continue to improve at later stages without a change in neurological impairment as measured by ISNCSCI. Even when SCI trials utilize endpoints in other measurement domains utilization of the ISNCSCI is recommended since the neurological characterization of the study cohort is commonly an independent variable of interest. The incorporation of ISNCSCI outcomes will also serve a useful and common reference point for comparisons between studies. Note: Other sensory and motor functional outcomes can be found in the electrophysiological or functional outcomes sections of this NINDS CDE document.

## Change in ISNCSCI Motor Score or Motor Level (as a study endpoint)

 In the past, an improvement of 2 AIS grades (e.g. AIS-A to AIS-C) was suggested and evaluated as a simple trial endpoint (response criterion). However, no experimental treatment has ever been shown to be effective using this endpoint. With standard clinical care and rehabilitation, a one AIS grade improvement occurs at too high a spontaneous rate, thus an impractically large sample size would be required for any study. Thus, a 2 AIS grade change is thought to be too insensitive to detect a subtle treatment effect for early phase clinical trials and, conversely, sometimes a 2 grade change can be accomplished with an improvement that will not be widely meaningful (e.g. recovery of only a slight anal sphincter contraction could reclassify a participant from AIS-A to AIS-C).

 Nevertheless, the recovery of any amount of useful motor function is likely to contribute to the overall recovery of functional activity and increased independence by an individual living with SCI. Thus, in comparison to appropriate controls, a therapeutic-induced improvement in ISNCSCI motor score has been suggested to be a trial endpoint that could be useful. Because of the ordinal nature of the ISNCSCI motor scores and the inability of the classification scheme to precisely define the distribution of motor function, the use of motor score improvement thresholds as a trial endpoint may not provide evidence of clinically meaningful change. While the exact delta value and the segmental distribution for any meaningful change in motor points remains to be determined, interest in the use of motor scores as the most direct clinical measure of neurological change has prompted ongoing efforts to correlate this data with measures of functional activity.

Ideally, any change in motor score should be correlated with a meaningful change within the ICF activity domain. Based on an evaluation of spontaneous recovery within two detailed SCI datasets, some motor function values might be useful for one SCI sub-population, specifically cervical sensorimotor complete (AIS-A) participants with a level of injury between C4-C7 (see below)

### Instrument:

 2 motor level improvement (either side), but ONLY for cervical sensorimotor complete (AIS-A) participants (Kramer et al., 2012)

### ICF Domain:

 Body structure or function

### Assessment Focus:

 In comparison to appropriate control participants, a recovery of 2 motor levels (as defined by ISNCSCI) within the cervical spinal cord after sensorimotor complete SCI.

### Recommended Use:

 EXPLORATORY only (requires further validation in a clinical trial setting)

### Psychometric Properties:

 [International Standards for Neurological Classification of Spinal Cord Injury (ASIA Impairment Scale)](http://www.rehabmeasures.org/Lists/RehabMeasures/PrintView.aspx?ID=956)

 Kramer JL, et al. 2012. Relationship between motor recovery and independence after sensorimotor-complete cervical spinal cord injury. *Neurorehabil Neural Repair* 26(9):1064-71.

### Comments:

 The initial motor level for cervical sensorimotor complete participants did not significantly influence the total UEMS recovered or number of motor levels recovered. SCIM self-care sub-score recovery was significantly greater for those individuals regaining 2 motor levels compared with those recovering only 1 or 0 motor levels. Thus, a 2 motor-level improvement indicates a potentially clinically meaningful change and might be considered a primary outcome in acute and subacute interventional trials enrolling individuals with cervical sensorimotor-complete (AIS-A) SCI. This endpoint was further explored in a review [Steeves JD, et al. 2012. *Topics Spinal Cord Injury Rehabil* 18(1):1-14]. Note: As defined by ISNCSCI, motor level is determined after assessment of segmental motor function using the MMT and equates to the cervical spinal cord segment obtaining at least 3/5 in the MMT score for the associated key muscle, providing the key muscles for all the above cord segments score as intact (5/5). The motor level can be different for the right and left side of the body.

## Spinal Reflexes

 Reflex testing can help differentiate some specific aspects of SCI, including the degree to which lower motoneuron damage may be contributing to the neurological impairment. Thus reflex testing is valuable to the accurate diagnosis and classification of the neurological impairment after a suspected SCI, including the detection of damage at the level of the spinal cord (i.e. cervical cord damage with severe motoneuron damage) and at the level of conus medullaris or cauda equina. Reflex testing may be used as an indicator of underlying pathophysiology, distinguishing weakness caused by loss of supraspinal drive (weak motor exam with associated hyperreflexia) from that caused by segmental injury to motor efferents (weak motor exam with associated hyporeflexia).

### Instrument:

 NINDS Myotatic Reflex Scale [Hallett, M. 1993. *Neurology* 43(12): 2723]

### ICF Domain:

 Body structure or function

### Assessment Focus:

 Deep tendon reflexes to assess the underlying pathophysiology of SCI related weakness.

### Recommended Use:

 It is suggested as an EXPLORATORY assessment after SCI, at any time after primary injury, although areflexia is commonly noted in acute injury. However, for therapeutic interventions directed to the CNS, it might be considered a valuable SUPPLEMENTAL assessment, especially to determine whether there is concomitant lower (alpha) motoneuron damage accompanying incomplete SCI which could be an eligibility consideration in some trials. Depending on the study, lower motoneuron damage may alter achievement of the desired clinical endpoint.

### Psychometric Properties:

 Variable reports about psychometric properties, but most recent study (Dafkin et al. 2013. Muscle Nerve 47(1): 81-8) suggests that the subjective evaluation has very good intra- and inter-rater reliability.

### Comments:

 Tendon reflex testing allows the investigator to detect a major alpha-motoneuron injury (often characterized by a hyporeflexive response) at the level of spinal damage. However, below the level of lesion the observed increased reflex responses after the sub-acute stage of SCI (after resolution of spinal shock) indicates changes in the excitability of the motor neuron pool. Hyperreflexia often depends on the severity of CNS injury with hyperreflexive responses being the least with either mild or most severe types of SCI and the strongest with moderate levels of SCI severity. Hyperreflexia can be associated with increased muscle tone (and eventually lead to stiffness of fibro-elastic properties of muscles-tendons-joint capsules) in an individual and depending on the trial clinical endpoint might be a criterion for exclusion from a study. Finally, tendon reflexes can be absent (areflexia) in severe sensorimotor complete SCI or during very acute stages of SCI (often referred to as “spinal shock").

 Tendon reflexes that can be tested, with the corresponding spinal cord segment, include: Pectoral – C4/5, Biceps – C5/6, Triceps – C7/8, Hip Adductors (brevis, longus and magnus) – L3/4, Quadriceps (patellar tendon) – L3/4, and Achilles – S1/2. The classical deep tendon reflex is the Quadriceps or patellar tendon reflex. Scoring of the reflexes is in categorical values where: absent = 0, reduced = 1, normal = 2, increased = 3, and elicitation of clonus (a form of spasticity) is sometimes scored as "4".

### Instrument:

 Pathological Reflex Tests

### ICF Domain:

 Body structure or function

### Assessment Focus:

 Presence of Hoffman or Babinski sign and absence of Bulbocavernosus reflex

### Recommended Use:

 EXPLORATORY assessment after SCI at any time after primary injury

### Psychometrics Properties:

Not extensively reported and when clinicians undertake these reflex tests, most have little difficulty in performing and accurately assessing these tests

### Comments:

 The Hoffman sign is associated with upper extremity function. The Hoffmann sign is elicited by a downward flicking the nail of the middle finger. Any flexion of the ipsilateral thumb and/or index finger is considered pathological and indicative of possible damage above the cervical cord. The Babinski sign (plantar reflex) is elicited by stroking the lateral plantar surface (L5 dermatome) of the foot with a blunt instrument and considered pathological if there is an upward deflection of the hallux (big toe) and/or fanning of the toes. Both the Hoffman and Babinski signs can be either unilateral or bilateral and thought to be suprasegmental corticospinal tract dysfunction. Thus a unilateral or bilateral presentation can provide some knowledge of the laterality and completeness of SCI. Note: in the absence of other clinical findings, it is of limited utility and thus is listed as exploratory.

 The bulbocavernosus reflex is a normal reflex elicited by manipulation of the glans penis or clitoris (or bladder neck afferents which can be activated by gently pulling on an indwelling catheter) and monitoring a reflex contraction of the anal sphincter. It involves the sacral cord segments (S2-S4). The absence of such a reflex is often indicative of general spinal hyporeflexia or areflexia due to injury at those sacral levels OR the presence of “spinal shock”. After SCI above the conus medullaris, the bulbocavernosus reflex is usually initially absent but re-emerges within a few days and indicates the earliest recovery of reflex excitability within the spinal cord. Note: in the absence of other clinical findings, it is of limited utility and thus is listed as exploratory.

## Spasticity

 Spasticity is a common clinical term for the Upper Motor Neuron Syndrome which includes hypereflexia, hypertonia, spasms (flexor, extensor, adductor), clonus, co-activations during movement, and pathological reflexes (see above). Spasticity represents motor control generated by an altered balance between supraspinal and sensory afferent input to spinal neural circuits. Several clinical scales have been developed to characterize aspects of the UMN syndrome.

### Instrument:

 Modified Ashworth Scale

### ICF Domain:

 Body structure or function

### Assessment Focus:

 Examines muscle resistance (tone) to passive movement about a joint with varying degrees of stretch velocity

### Recommended Use:

 SUPPLEMENTAL assessment after SCI at any time after primary injury

### Psychometrics Properties:

 [Modified Ashworth Scale Link](http://www.rehabmeasures.org/Lists/RehabMeasures/PrintView.aspx?ID=902)

### Comments:

 The Modified Ashworth Scale is the most widely used measure of the hyperreflexia of "spasticity". As such, it is likely to be used as an outcome measure primarily in studies that are intended directly to address muscle tone. The Modified Ashworth is relatively simple to perform and does not require special equipment or extensive training. It measures only one aspect of spasticity, and can be markedly affected by the clinical setting, the positioning of the subject, timing of the examination with reference to antispasticity medication dosing and other variables that might influence afferent sensory input to the spinal cord. The use of this clinical scale is thus limited by the episodic, complex and variable nature of the condition, which limits its ability to objectively and reliably measure the 'real world' spasticity phenomenon. Nonetheless, the test has been used successfully as a clinical endpoint in registration trials of anti-spasticity drugs (tizanidine, intrathecal baclofen, nabiximols), hence its recommendation as a Supplemental assessment.

### Instrument:

 Tardieu Scale

### ICF Domain:

 Body structure or function

### Assessment Focus:

 A more elaborate examination of muscle resistance (tone) and hyperreflexia than Modified Ashworth

### Recommended Use:

 EXPLORATORY assessment after SCI at any time after primary injury

### Psychometrics Properties:

 no specific data for SCI, but data is available for stroke, cerebral palsy and traumatic brain injury (TBI)

### Comments:

 The Tardieu Scale involves a more elaborate examination of hyperreflexia than any of the other test, employing three different speeds of movement, and also measures range of motion. Hence it requires more training, more time to administer, and the use of a goniometer. The analysis of the outcome is potentially quite complex, given the multi-dimensional nature of the measurement. It has been explored more widely in other conditions, such as stroke, traumatic brain injury and cerebral palsy. There is relatively little experience in SCI studies. As a more complete measure of the phenomenon of spasticity it may be scientifically useful, though perhaps more detailed than is really necessary or appropriate in a clinical trial for an anti-spasticity medication. Like the simpler Modified Ashworth Scale, it suffers from the limitation of a measurement applied in an "artificial" clinical setting to a condition that can show large temporal and situational variability in the real world, where its medical significance lies.

### Instrument:

 Spinal Cord Assessment Tool for Spastic Reflexes (SCATS)

### ICF Domain:

 Body structure or function

### Assessment Focus:

 Assesses three types of spastic motor behaviors in SCI patients - clonus, flexor spasms, and extensor spasms.

### Recommended Use:

 EXPLORATORY assessment after SCI at any time after primary injury

### Psychometrics Properties:

 [Spinal Cord Assessment Tool for Spastic Reflexes Link](http://www.rehabmeasures.org/Lists/RehabMeasures/PrintView.aspx?ID=961)

### Comments:

 The SCATS scale measures 3 distinct components of lower extremity spasticity: 1 Ankle clonus; 2 Flexor reflex spasm; 3 Extensor reflex spasm. As such, it can in some ways be considered an extension of the Modified Ashworth Scale in that it goes beyond the measurement of velocity dependent reflex twitch to the self-sustaining spasm aspect of hyper-excitability of the central motor system. It requires no specialized equipment and little specific training for a clinician to administer. Although there is relatively little experience with application to clinical trial outcomes, it could be reasonably explored as an addition to the limitation of the Modified Ashworth Scale.

### Instrument:

 Penn Spasm Frequency Scale

### ICF Domain:

 Body structure or function

### Assessment Focus:

 A participant self-report measure that assess an individual's perception of spasticity frequency and severity

### Recommended Use:

 EXPLORATORY assessment after SCI at any time after primary injury

### Psychometrics Properties:

 [Penn Spasm Frequency Scale Link](http://www.rehabmeasures.org/Lists/RehabMeasures/PrintView.aspx?ID=971)

### Comments:

 The Penn Spasm Frequency Scale is a self-report assessment that includes elements of frequency and severity of muscle spasms, which form major aspects of the spasticity experience, besides muscle "stiffness" that is the focus of the Modified Ashworth Scale. The subjectivity in determining frequency and severity can confound interpretation of the score and make it somewhat difficult to compare between individuals or groups. However, it can be considered as a potentially useful adjunct to the Modified Ashworth Scale. Both instruments provide essentially ordered categorical elements that do not lend themselves well to accurate quantitative analysis. This scale is what we have currently in the realm of a self-report outcome for spasticity.

The scale has been used in studies of spasticity for many years, but it seems possible and desirable to improve on it. Two more recent efforts at developing a Patient Reported Outcomes for spasticity that utilize modern measurement technique are the Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET, Adams et at., 2007, *Arch Phys Med Rehabil* 88: 1185-1192) and the Patient Reported Impact of Spasticity Measure (PRISM, Cook et al., 2007 *J Rehabil Res Dev* 44(3): 363-371). Both questionnaire based tools address the negative and positive effects of spasticity on quality of life and are beginning to be used in combination with the older, symptom-based scales.

### Instrument:

 Pendulum Test

### ICF Domain:

 Body structure or function

### Assessment Focus:

 Spasticity of the Quadriceps femoris (knee extensor) muscle can be quantified using the pendulum test.

### Recommended Use:

 EXPLORATORY assessment after SCI at any time after primary injury

### Psychometrics Properties:

 [Pendulum Test (Wartenberg) Link](http://www.scireproject.com/outcome-measures-new/pendulum-test-wartenberg)

### Comments:

The Pendulum (Wartenburg) Test is an instrumented test of the velocity-dependent hyperreflexia aspect of spasticity. Like all the tests listed above, the Pendulum Test is limited by the episodic, complex and variable nature of spasticity. It is mainly useful in testing the knee extensors but has also been used for the upper extremity. It has been used in studies of spasticity in SCI, but has been more extensively used for studies involving stroke participants.

It has the advantage of providing a 'quantitative' measure, as compared to the more qualitative Modified Ashworth Score. However, the quantitative output of the test is not readily interpretable in terms of the clinical meaning and the test requires specialized equipment and analysis methods. It is only a truly continuous measure within a certain range of hyperreflexia. It is likely more valuable when combined with electromyographic (EMG) recordings from the involved muscles (see Figure 2 from Hofstoetter U, et al. 2014. *J Spinal Cord Med* 37(2):202-211). It is difficult to say whether it provides additional practical value to the Modified Ashworth Score, which is a simpler test that can be applied to a wider range of muscle groups. However, the Pendulum Test was used as a supplemental measure in a registration trial of tizanidine.