# Summary Statement for the ALS Outcomes Subgroup

This summary is the companion document to the NINDS ALS CDE Working Group – Outcomes CDE Tables.

The goal of the NINDS ALS outcomes subgroup is to recommend clinical outcomes that can be readily used in data collection for clinical trials that are as broad as possible and applicable to all stages of ALS. The objective is to create greater standardization among human ALS trials to facilitate comparisons of study results across clinical trials and independent of geographic or time factors. In the following sections, the ALS outcomes subgroup has assessed published outcomes that should be considered for use in ALS clinical trials, including those outcomes the subgroup deemed core or essential to the clinical manifestations of ALS. The list was generated following a comprehensive literature review and the individual measures were weighted by their prevalence of use and the strength or their validation.

The subgroup realized that not all clinical trials have identical goals. Therefore, no one outcome measure or set of outcome measures could be recommended as preferred. However four principal domains were identified, representing different aspects of motor dysfunction (cognitive dysfunction was handled by a separate subgroup) in ALS. These domains included measures of functional status, measures of pulmonary performance, measures of muscle strength and other clinical manifestations, and measures of quality of life. Within each domain, we attempted to provide a hierarchy of outcome measures, including clinical relevance, level of validation, and acceptance within the medical/scientific community.

Each measure or scale identified was judged to be a Core clinical outcome measure, a supplemental clinical outcome measure or an exploratory clinical outcome measure. Core measures are those outcomes felt to be central to the pathophysiology and clinical manifestations of ALS and that assess disease status in ALS and facilitate comparisons between trials and across time. Core measures are thus those that have been widely used in ALS clinical studies, and that have been formally validated and are well-accepted by dinput of widespread and longstanding use. To identify the core measures the inclusion criteria included the following: the measure was required to be directly relevant to the pathophysiology of ALS, the measure had to reflect a clinically meaningful outcome, the measure had to validated, and the measure must show a consistent pattern of use in ALS clinical research. One or more core measures was identified in each domain.

Supplemental measures were defined as measures designed to assess a more focused clinical manifestation. To be denoted as supplemental the outcome measure must first measure clinically relevant features of ALS and be validated for use in the ALS population. These measures may focus on discrete clinical questions and may not be as broad in scope as the core measures but may provide very meaningful information for a carefully designed research question. Alternatively, a broader scale or outcome may be deemed supplemental if it has been well validated in ALS clinical trial and has been applied as an outcome measure in some, but not most ALS human clinical research.

Finally, exploratory measures are those measures that are yet to be validated in ALS or have been used in infrequent or isolated studies. In these circumstances, it is yet to be determined what role these scales and measures may have in assessing outcome in ALS human research studies.

In making these recommendations, it was not the subgroup’s intention to restrict innovation in ALS clinical trial research. To the contrary, this exercise more clearly identifies the areas were innovation and advancement are still needed. As with any well designed clinical research study, the outcomes utilized should be directly reflective of the questions and hypotheses being tested. The subcommittee is hopeful that the present document will help facilitate that process while keeping ALS research uniform for the benefit of all ALS research and ultimately our ALS patients.

Please note: The timing of Outcome Measures should be appropriate to what is known about the PK/ PD relationships of the drug under study. Additionally, studies should have manuals to define how specific measurements (e.g., Pulmonary Function elements) should be performed.

## Appendix: NINDS Amyotrophic Lateral Sclerosis (ALS) Common Data Element (CDE) Project

### Recommendations from the ALS Outcomes Subgroup

The NINDS ALS Outcomes Subgroup has reviewed literature, CRFs, etc. and has made the following recommendations for use in data collection for clinical research project. These recommendations are as broad as possible and applicable to all stages of ALS. In the following sections (pages 2-6), the Outcomes group has endeavored to provide an objective assessment of scales, measurements, and variables that may be used in clinical research. The decision to provide recommendations at a more global level are two-fold: (1) for domains such as pulmonary function and muscle strength which are considered core domains in which something should be collected there is no “gold standard” so investigators are provided an option of choices, but one measure should be included; and, (2) many other domains are considered secondary and again with no “gold standard” a list of measures are available of consideration.

CORE– at a minimum these components should be included in an ALS clinical research study:

Functional Status: Amyotrophic Lateral Sclerosis Functional Rating Scale- Revised (ALSFRS-R)

Pulmonary Function/ Respiratory Status (choose 1)

Muscle Strength (choose 1)

Quality of Life (choose 1)

Upper Motor Neuron Signs/ Neuromuscular Excitability (choose 1)

Core Recommendation Functional Status Data Table

| Subdomain | Forms |
| --- | --- |
| Overall | Amyotrophic Lateral Sclerosis Functional Rating Scale- Revised (ALSRFS-R) |
| Milestones/Events | Survival – Data of Death |

Supplemental Recommendation Functional Status Data Table

| Subdomain | Forms |
| --- | --- |
| Clinical | Amyotrophic Lateral Sclerosis Severity Scale (Hillel Scale)  Appel ALS Scale (AALS)  Barthel Index  Norris Scale  Schwab and England Activities of Daily Living |
| Milestones/Events | Loss of speech  Loss of ambulation  PEG/ Feeding Tube  Tracheostomy  Incidence of falls |
| Speech and Swallowing | SWAL QOL |
| Timed Tests | The Six Minute Walk Test (6MWT)  Timed Up-and–Go (TUG)  Twenty- five foot walk test (25FWT) |

Exploratory Recommendation Functional Status Data Table

| Subdomain | Forms |
| --- | --- |
| Clinical | Epworth Sleepiness Scale (sleep scale & somnolence)  Center for Neurologic Study Bulbar Function Scale (CNS-BFS)  Dynamic Gait Index (DGI)  Edmonton Symptom Assessment System (ESAS)  EQ-5D rating scale  Performance-oriented mobility assessment (POMA-B) balance  Sensory Organization Test (SOT) equilibrium scores |
| Milestones/Events | Non-invasive ventilation  Incidence of falls  Number, severity and duration of cramps |
| Speech and Swallowing | ALS Swallowing Severity Score from the Amyotrophic Lateral Sclerosis Severity Scale (Hillel Scale) |
| Timed Tests | Timed Motor Function Test/Madrid Scale |
| Muscle Fatigue | Hand grip fatigue Maximal  Hand grip fatigue Sub Maximal  Shoulder Flexion Fatigue |
| General Fatigue | Fatigue Severity Scale (FSS)  Modified Fatigue Impact Scale  Checklist for Individual Strength – Fatigue (CIS) |

Investigators should select one or more of the following measures in this domain: Forced Vital Capacity (FVC) or Slow Vital Capacity (SVC). Additional measures may be considered depending on the study; these measures are defined as supplemental or exploratory.

Core Pulmonary Function Testing/Respiratory Status Data Table

| Subdomain | Measure |
| --- | --- |
| Expiratory and Inspiratory Function | Slow Vital Capacity (sVC)[[1]](#footnote-1)  Forced Vital Capacity (FVC)\* |

Supplemental Pulmonary Function Testing/Respiratory Status Data Table

| Subdomain | Measure |
| --- | --- |
| Expiratory and Inspiratory Function | Maximum Expiratory Pressure (MEP)  Peak Expiratory Flow (PEF)  Forced Expiratory Volume in 1 second (FEV1) |
| Bellows Lung Function | Maximal Voluntary Ventilation (MVV) |
| Dyspnea Rating Scales | Borg Dyspnea Scale |

Exploratory Pulmonary Function Testing/Respiratory Status Data Table

| Subdomain | Measure |
| --- | --- |
| Expiratory and Inspiratory Function | Maximal Inspiratory Pressure (MIP)- Sniff Nasal Inspiratory Pressure (SNIP) or Maximal Voluntary Ventilation (MVV) |
| Respiratory Measures | Myocardial Oxygen Consumption (MVO2)  Gas Exchange  Nocturnal Oximetry |
| Dyspnea Rating Scales | Baseline Dyspnea Index  Transition Dyspnea Index |

Investigators should use either a Manual Muscle Test or Quantitative Dynamometry to measure muscle strength. If a Manual Muscle Test is selected the MMT/MCR is the recommended element. If Quantitative Dynamometry is used, there are several to choose from depending on what is most appropriate for the study being conducted. No one test is superior, thus the ALS study should include at least one test from this subdomain.

Core Recommendation Muscle Strength Testing Data Table

| Subdomain | Measure |
| --- | --- |
| Manual Muscle Testing or Quantitative Dynamometry | See possible measures listed below[[2]](#footnote-2) |

Supplemental Recommendation Muscle Strength Testing Data Table

| Subdomain | Measure |
| --- | --- |
| Manual Muscle Testing | Manual Muscle Testing (MMT)/ Muscle Research Council Scale for Muscle Strength (MRC) |
| Quantitative Dynamometry | Maximum Voluntary Isometric Contraction (MVIC)  Fixed Dynamometry [e.g. Accurate Test of Limb Isometric Strength (ATLIS)]  Grip Strength Testing and Grip Strength Fatigue Testing  Hand Held Dynamometry |

Quality of Life should be a Core measure; several available validated instruments are available for consideration depending on the clinical research project.

Core Recommendation Quality of Life Data Table

| Subdomain | Measure |
| --- | --- |
| Quality of Life | (intentionally left blank) [[3]](#footnote-3) |

Supplemental Recommendation Quality of Life Data Table

| Subdomain | Measure |
| --- | --- |
| Quality of Life | Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALS-AQ40)  McGill Quality of Life Questionnaire  SF-36 |

Exploratory Recommendation Quality of Life Data Table

| Subdomain | Measure |
| --- | --- |
| Quality of Life | EuroQol VAS  Self- evaluation Quality of Life- Direct Weighting (SEQOL-DW)  Sickness Impact Profile  Neuro-QOL |

Core Recommendation Upper Motor Neuron Signs/Neuromuscular Excitability Data Table

| Subdomain | Measure |
| --- | --- |
| N/A | Modified Ashworth Scale[[4]](#footnote-4)  Tardieu Rating Scale[[5]](#footnote-5) |

Supplemental Recommendation Upper Motor Neuron Signs/Neuromuscular Excitability Data Table

| Subdomain | Measure |
| --- | --- |
| N/A | NINDS Reflex Rating Scale |

Exploratory Recommendation Upper Motor Neuron Signs/Neuromuscular Excitability Data Table

| Subdomain | Measure |
| --- | --- |
| N/A | Adductor Tone Scale  Spasm Frequency Scale |

Exploratory Recommendation Subjective Assessments/Patient and Caregiver Reported Outcomes Data Table

| Subdomain | Measure |
| --- | --- |
| Patient | Clinical Global Impression – Improvement Scale (CGI-I)[[6]](#footnote-6)  Clinical Global Impression – Severity Scale (CGI-S)\* |
| Caregiver | CareGiver Burden Scale (CGBS)  SF-8  Zarit Caregiver Burden Scale |

1. Choose either Forced Vital Capacity or Slow Vital Capacity as core measure. [↑](#footnote-ref-1)
2. MMT or Quantitative Dynamometry- Select Manual Muscle Test/ Medical Research Councul or a Quantitative Dynamometry Instrument [↑](#footnote-ref-2)
3. Choose one Quality of Life Measure [↑](#footnote-ref-3)
4. Choose Modified Ashworth Scale or Tardieu Rating Scale [↑](#footnote-ref-4)
5. Choose Modified Ashworth Scale or Tardieu Rating Scale [↑](#footnote-ref-5)
6. This can be done by either the patient or the clinician to the patient [↑](#footnote-ref-6)