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Protocol for Psychometric Evaluation of the Amyotrophic Lateral Sclerosis – Bulbar Dysfunction Index (ALS-BDI)

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TITLE: Protocol for Psychometric Evaluation of the Amyotrophic Lateral Sclerosis – Bulbar Dysfunction Index (ALS-BDI)

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ABSTRACT

Introduction: Early detection and tracking of bulbar dysfunction in amyotrophic lateral sclerosis (ALS) are critical for directing management of the disease. Current clinical bulbar assessment tools are lacking, while existing physiological instrumental assessments are often inaccessible and cost-prohibitive for clinical application. The goal of our research is to develop and validate a brief and reliable, clinician-administered assessment tool - the ALS Bulbar Dysfunction Index (ALS-BDI). This publication describes the study protocol that has been established to ascertain the tools' psychometric properties.

Methods and analysis: The ALS-BDI's development closely follows guidelines outlined by the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN). Through the proposed study protocol, we expect to establish psychometric properties of both individual test items of the ALS-BDI as well as the final version of the entire tool, including test-retest and inter-rater reliability, construct validity using gold-standard assessment methods, and responsiveness.

Ethics and dissemination: This study has been reviewed and approved by research ethics boards at two data collection sites: Sunnybrook Health Science Centre, primary (Toronto, Canada; ID3080) and Mass General Brigham (#2013P001746, Boston, United States). Prior to participation in the study, the participants sign the informed consent in accordance with the Declaration of Helsinki. Once validated, the ALS-BDI will be disseminated to key stakeholders. Following validation, the ALS-BDI and any required training material will be implemented for clinical use in a context of a multidisciplinary ALS clinic and utilized as an outcome measure for clinical trials in ALS research.

KEY WORDS: Bulbar ALS, Assessment, Development, ALS-BDI, COSMIN

ARTICLE SUMMARY

Strengths and limitations of this study

- This project will yield the first clinician-administered tool (ALS Bulbar Dysfunction Index; ALS-BDI) that is specific to the assessment of bulbar dysfunction in patients with ALS and validated against gold-standard instrumental assessment methods.
- Initial development and design of the ALS-BDI has involved extensive consultation of projected end-users (i.e., neurologists, speech-language pathologists) to ensure that it is comprehensive, clinically feasible, and aligned with current practice goals and workflow.
- Repeated administrations of the ALS-BDI will establish test-retest and inter-rater reliability and responsiveness of each test item and the overall tool. Validation of the ALS-BDI will be completed relative to the established current physiological assessment methods and global measures of ALS related disability.
- Patient anchors will be used to inform interpretability and determine the clinical significance of ALS-BDI scores, including the minimal important difference (MID) and low activity disease states.
- Many individual items on the drafted ALS-BDI involve a subjective rating of severity (i.e., mild, moderate, severe), which may challenge inter-rater reliability. We will review the validity and reliability of individual item rating scales and their definitions, iteratively, to determine if any formal training or benchmarking is needed prior to clinical use.

INTRODUCTION

ALS is a fast-progressing disease with a lifespan post-diagnosis of 2-5 years.[1] The disease is characterized by the degeneration of motor neurons in the brain, brainstem, and spinal cord as well as extramotor (e.g., cognitive-linguistic) brain pathways.[2-4] The degeneration of motor neurons results in progressive muscle weakness, atrophy, and eventual paralysis. Nearly 90% of individuals diagnosed with ALS will experience speech and swallowing dysfunction either at the onset of the disease or when the disease spreads to the bulbar motor system, which controls muscles of the head and neck.[5] The presence of bulbar motor impairment is associated with a shorter survival (<2 years) and increases the risk of death by almost eightfold.[6, 7] The resulting speech impairment has been rated as the worse aspect of the disease by patients with ALS.[8] Despite the devastating consequences of bulbar dysfunction on the survival and quality of life, there are currently no validated tools for its assessment in a clinic. In the absence of a standardized assessment of bulbar motor dysfunction, current practices in ALS clinics are idiosyncratic, piecemeal, and rely primarily on symptom checklists.[9]

The overall aim of our work is to develop a reliable and psychometrically validated clinician-administered assessment tool of bulbar dysfunction, called the ALS-Bulbar Dysfunction Index (ALS-BDI), that is efficient, standardized, clinically feasible, comprehensive, and responsive to change over time. The ALS-BDI is currently being designed and validated for two diagnostic use cases: (1) to discriminate among patients with different severities of bulbar impairment (i.e., discriminative purpose); and (2) to evaluate the changes over time in a person or group (i.e., evaluative purpose).[10] This tool will have immediate implications for tracking disease progression and monitoring changes in ALS clinics or in clinical trials. In the future, it may serve as the core assessment that can be adapted for improving ALS diagnosis and

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3 prognosis; it could also eventually serve as a screening tool for determining the need for full
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5 dysphagia and speech assistive technology evaluations.
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7 Our process for developing the ALS-BDI adheres to established guidelines for
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9 developing a formative measure (COnsensus-based Standards for the selection of health
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11 Measurement INstruments, COSMIN). [11,12] Within a formative model, all items are
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13 considered relevant to represent the overall construct of interest and are not interchangeable;
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15 items may or not be correlated, and they may have different patterns of change when the
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17 construct changes. Formative measures, as opposed to reflective measures, are not assessed
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19 with respect to internal consistency or item-total correlations such as Cronbach's alpha, factor
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21 analysis, or the item response theory. The decision to retain or reduce items is primarily based
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23 on their clinical relevance in defining the construct (content and face validity), although reliability
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25 and responsiveness can also inform item retention.
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28 Our test development process is divided into three development cycles: Cycle 1 includes
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30 generation of the candidate item pool and demonstration of their content and face validity; Cycle
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32 2 is focused on establishing the item and overall tool's reliability; and Cycle 3 establishes the
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34 item and overall tool's construct validity in relation to well established instrumental and clinical
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36 measures, as well as responsiveness to change over time. The work in Cycle 1, which produced
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38 the first iteration of the ALS-BDI, has been now completed. The initial development steps have
39
40 been described in detail elsewhere.[13] Briefly, Cycle 1 involved convening a panel of experts to
41
42 identify key assessment domains for bulbar dysfunction. The panel met during a Northeastern
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44 ALS Consortium (NEALS) Bulbar Subcommittee meeting, members of which were experts in
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46 neurology, speech-language pathology (SLP), and measurement science.[14] Through
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48 consensus, the panel identified three core bulbar assessment domains: (1) Cranial Nerve Exam;
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50 (2) Auditory-Perceptual Assessment [of speech and voice]; and (3) Functional Assessment [of
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52 speech intelligibility, swallowing, chewing, and coughing]. Following the meeting, a literature
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54 review was conducted by our development team to generate candidate items for each domain.
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3 Expert surveys were then conducted to probe each item's face and content validity. Based on
4 this procedure, an initial draft of ALS-BDI was created. A group of speech-language pathologists
5 further vetted the testable draft of the instrument via pilot administration of the test draft and
6 completion of a cognitive interview with a member of our development team. As a result, a beta
7 of ALS-BDI has been prepared for its psychometric evaluation.
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14 The process for establishing psychometric properties of the ALS-BDI has been outlined in
15 the latest recommendations by the COSMIN group.[11] To our knowledge, no comprehensive
16 bulbar assessment tool has yet been developed and validated using this rigorous approach.[15]
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18 The key psychometric properties of the ALS-BDI that must be assessed under this framework
19 include inter-rater and test-retest reliability (Cycle 2 of the development), as well as the
20 construct validity against gold-standard measures of bulbar dysfunction in ALS and
21 responsiveness to change and minimal important difference (MID), minimal detectable change
22 (MDC) and low disease state of ALS-BDI to enhance interpretability of its scores (Cycle 3 of the
23 development). Here we present a detailed protocol for the psychometric evaluation of ALS-BDI
24 through Cycle 2 and 3.
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37 **METHODS AND ANALYSIS**

38 **Prospective study design**

39 A prospective longitudinal study design will be used to assess the ALS-BDI.
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45 **Participants & Recruitment**

46 Data for this study will be collected at the Bulbar Function Laboratory at the Sunnybrook
47 Health Sciences Centre in Toronto, Ontario, Canada and the Speech and Feeding Disorders
48 Lab at the MGH Institute for Health Professions in Boston, Massachusetts, USA. 100 adults
49 (≥18 years) diagnosed with possible, probable, or definite ALS as defined by the Revised El
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Escorial Criteria will be recruited consecutively at the ALS/MND Clinics in Toronto, Canada and Boston, USA.[16]

Individuals will be excluded if they have a history of other neurological conditions (e.g., stroke) or head and neck cancer; take medications known to affect speech production; are unable to comply with the study protocol due to significant cognitive impairment (i.e., Montreal Cognitive Assessment score <18);[17] or fail a hearing screen in both ears (i.e., 500-4000Hz, thresholds >40dB).

To ensure the ALS-BDI is tested across a broad sampling of disease severity, we will recruit an equal number of patients who fall within four categories of bulbar symptom severity, based on their ALSFRS-R bulbar subscore: normal bulbar function (i.e., score of 12/12); mild (9-11/12); moderate (6-8/12); or severe (1-5/12).[18]

1. Inter-rater and test-retest reliability

To estimate the inter-rater reliability of each candidate item, two SLPs will rate each patient's performance on the ALS-BDI on the same visit. The order of SLP raters will be randomized, and they will be blinded to each other's ratings. The first administration will be conducted at the beginning of the visit, and the second will take place at the very end. To minimize effects of fatigue, participants will be given sufficient time to rest before the second ALS-BDI assessment.

To determine test-retest reliability, each participant will be reassessed using the ALS-BDI, within one week after the initial visit. The second visit will be scheduled approximately at the same time of day as the first visit, to mitigate any daytime variability in fatigue. Given the natural history of ALS, it is unlikely that there will be significant clinical change in the period of two weeks. However, on the second visit, the participants will answer whether they think their bulbar function has changed compared to the first assessment (i.e., yes/no). Participants who report

any perceived differences in bulbar symptoms compared to the initial visit will be excluded from the test-retest reliability calculations.

We will calculate reliability statistics for each item on the ALS-BDI using weighted Kappa, because individual items were scored ordinally. Items with weighted Kappa <0.6 on either inter-rater or test-retest reliability will be flagged for reduction.[19] We will also calculate the overall reliability of the total score of the ALS-BDI (i.e., the sum of all items), using intra-class correlation coefficients (ICCs), considering raters as random effects (ICC formula 2,1).[20, 21] ICCs of ≥ 0.80 will be set as the minimal acceptable standard for evaluating groups of patients, whereas values of ≥ 0.90 will be required for individual patient use.[22] Item reduction based on reliability will be completed prior to construct validation of individual items and the full ALS-BDI.

Data from the first 50 consecutive individuals diagnosed with ALS and presenting with a range of bulbar impairment will be used for the reliability analyses. This exact sample size was estimated using the approach by Kraemer and Korner,[23] whereby for a minimum ICC of 0.8 and a lower 95% confidence interval (CI) of 0.7, 47 analyzable participants should be required. We will increase this number if some patients fail to attend the second visit (test-retest) within two weeks of the initial visit recording, or if they report a change in clinical status during this time interval.

2. Construct validity

Items remaining following reliability assessment will be evaluated for construct validity, relative to gold-standard instrumental physiological measures of bulbar dysfunction. For this phase of the study, data from 100 participants with ALS will be recorded. On the day of ALS-BDI administration, each patient will complete a battery of instrumental assessments and selected patient-reported outcomes (PRO) indicating overall ALS and bulbar-related disability, namely the ALSFRS-R and the Center for Neurologic Study Bulbar Function Scale (CNS-BFS).[18, 24]

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3 Table 1 shows the detailed mapping between individual items of ALS-BDI and specific
4 instrumental validators (i.e., tasks and measures). The entire session will be audio-recorded at
5 high resolution (44.1kHz, 16-bit) using a unidirectional lapel microphone, with a fixed mouth-to-
6 mic distance; the audio signal will be calibrated using a 1000Hz tone at the start of each session
7 to ensure accurate measures of signal intensity.[25] In addition to audio recordings of all speech
8 tasks, the Phonatory Aerodynamic System (Pentax Medical) will be used to measure nasal
9 airflow and oral pressure during speech and cough.[25, 26] Tongue and lip/facial muscle
10 strength will be measured using the Iowa Oral Performance Instrument (IOPI Medical LLC)
11 during maximum pressure generation tasks.[27, 28] Facial movements for speech and non-
12 speech (oro-motor) will be recorded using a three-dimensional video camera (Intel Real
13 Sense),[29] and tongue movement will be assessed using the Wave Speech System (NDI).[30,
14 31] To validate swallow tasks, each participant will undergo a standard videofluoroscopic
15 swallow study. The full validation protocol is estimated to take approximately two hours.
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37 All speech tasks will be analyzed using well-established spectral and timing measures (e.g.,
38 voice onset time, acoustic vowel space, segment durations; see Table 1 for examples).[25] The
39 standard passage reading will be analyzed using an automated Speech-Pause Analysis
40 algorithm, extracting measures of phrase and pause durations.[32] In addition, participants will
41 complete the Speech Intelligibility Test to quantify speech intelligibility (i.e., % words heard
42 correctly) and speaking rate (i.e., words per minute) in sentences.[33] Measures of swallow
43 safety (i.e., penetration/aspiration),[34] efficiency (i.e., residue),[35] and key physiological
44 events (e.g., pharyngeal constriction,[36, 37] chewing duration, laryngeal vestibule closure)[35]
45 will be obtained from a videofluoroscopic swallow study. Cough volume acceleration will be
46 measured from the Phonatory Aerodynamic System waveform of voluntary cough.[38, 39]
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3 We will study the validity of each reliable item, as determined in the reliability assessment
4 described above, in relation to its corresponding instrumental measure. All instrumental
5 measures for this study are continuous, so we will calculate the correlations (Pearson's or
6 Spearman's as appropriate) between each item and its instrumental equivalent. We have set an
7 *a priori* correlation cut point of ≥ 0.6 for criterion validity; items that correlate with instrumental
8 measures of > 0.6 will be flagged for inclusion.[40] Inter-item correlations will also be examined
9 for redundancy. In a formative model, while low or absent correlations between items are not an
10 issue, very high inter-item correlations (> 0.9) can indicate redundancy; pairs of items with
11 correlations > 0.9 will be assessed for potential reduction. If additional items are eliminated, we
12 will re-calculate the reliability coefficients for the final version of the ALS-BDI.
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Once we have the final version of the ALS-BDI, we will study the construct validity of the entire tool. We will test two hypotheses for construct validity: (1) the ALS-BDI total score will be highly correlated ($r \geq 0.7$) with ALSFRS-R bulbar sub-score and the CNS-BFS, which measures bulbar-specific disability; (2) the correlation will be weaker ($r = 0.4-0.6$) with the ALSFRS-R total score, which measures ALS disability as a whole and includes the effect of limb weakness and respiratory dysfunction. We will also compare the ALS-BDI scores between subgroups of patients divided by bulbar function severity. We will classify patients as having normal, mild, moderate, and severe bulbar dysfunction, based on their ALSFRS-R bulbar sub-scores.[18] We will compare the mean ALS-BDI scores on each bulbar severity group using ANOVAs. We hypothesize that the different severity groups will have statistically significant different mean ALS-BDI scores. Following the COSMIN guidelines, we will consider that the new scale has construct validity, if we confirm $\geq 75\%$ of the predefined hypotheses.[41]

3. Establishing responsiveness, minimal important difference (MID), minimal detectable change (MDC) and low disease state of ALS-BDI

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6 For this analysis, patients will have a second full assessment six months after the initial visit.
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8 On the second visit, patients will undergo the ALS-BDI, instrumental testing (as described
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10 above), as well as the ALSFRS-R and CNS-BFS. Patients will also answer a patient impression-
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12 of-change questionnaire (PIC), to indicate if their speech, voice, and/or swallowing have
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14 changed since the first assessment. The PIC will have 4 possible answers: 0=no change,
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16 1=minimally worse, 2=much worse, 3=very much worse; this is a modification from the method
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18 by Juniper, that used seven options for improvement or worsening.[42] Considering the natural
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20 history of ALS, we do not expect patients to report improvement. We will calculate the difference
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22 in ALS-BDI scores between visits 1 and 2, as well as the change scores for the instrumental
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24 measures, the ALSFRS-R and CNS-BFS. There is no single way to determine responsiveness,
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26 so current guidelines recommend using a range of methods to document sensitivity to change
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28 including (1) assessing statistically significant change—such as in a clinical trial—by comparing
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30 mean effects with a *t*-test, and (2) assessing change that is meaningful for patients.[41]
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33 We will estimate statistically significant change in four ways. First, we will compare the
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35 mean ALS-BDI scores at session 1 and session 2 through paired *t*-tests; we expect to see a
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37 statistically significant difference ($p < 0.05$), indicating worsening of bulbar function. Second, we
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39 will calculate the magnitude of change through the standardized response mean (SRM), which
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41 is the ratio between the mean change score to the standard deviation of said change score. We
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43 hypothesize that the SRM will be ≥ 0.3 . Third, we will study the correlations between the change
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45 in the ALS-BDI and the comparison measures, as a form of longitudinal validity.[43] We expect
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47 to find moderate correlations between the change scores ($r = 0.4-0.7$). Fourth, we will study the
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49 efficiency to detect statistically significant change of the ALS-BDI compared to the instrumental
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51 measures, the ALSFRS-R bulbar score and CNS-BFS. For this, we will calculate the ratio of the
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53 paired *t*-test statistics, as follows:
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(t -statistic_{ALS-BDI} / t -statistic_{comparison measure}).[44, 45]

A ratio >1 indicates that the ALS-BDI is more efficient than the comparison measure of interest; in other words, it is more sensitive with detecting a given effect size for the same sample size.

We hypothesize that the ALS-BDI will be more efficient than the ALSFRS-R bulbar score and the CNS-BFS; we expect that the ALS-BDI sub-scores will have equal or slightly lower efficiency than the corresponding instrumental measures.

We will determine if the ALS-BDI detects change that is meaningful to patients by using the PIC as an anchor. To be meaningful from the patients' perspective, the ALS-BDI change-scores should correlate with the PIC. For instance, patients reporting to be much worse should have a higher change in score than those reporting moderate, mild, or no change. We will use analysis of covariance to compare the mean change in scores among PIC groups, correcting for differences in baseline scores. We expect a significant difference in change scores across PIC groups, with larger change scores in those patients reporting to be much worse.

To enhance the interpretation of the change in scores, we will estimate the minimal important difference (MID) for worsening. This is the *smallest* change in score that is meaningful for patients, and we will use the PIC category of "a little worse" as the anchor of minimal worsening. This follows current recommendations of using anchor-based methods to determine the MID, as opposed to distribution-based methods.[46] We will estimate the MID at the individual level—that is, to classify one individual as having at least minimal worsening—using a receiver operator characteristic (ROC) curve. Patients who have at least minimal worsening will be classified as "changers." The MID at the individual level is the point of highest sensitivity and specificity. We will also estimate the MID at the group level—that is, the smallest mean change in scores that would be meaningful in a group, such as in a clinical trial. For this, we will calculate the mean change in ALS-BDI scores in the group of patients that reported being "a little worse";[42] we will also estimate the 75% percentile for potential misclassification bias. For

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3 the MID estimates to be interpretable, they should be above error of measurement. Therefore,
4 we will calculate the minimal detectable change (MDC), which is the smallest change between
5 assessments that is very likely above error of measurement. The MDC (with 95% CI) is
6 calculated using the test-retest reliability statistic as follows:
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$$1.96 \times \sqrt{2} \times (SD \times \sqrt{1 - ICC}),$$

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11 where *SD* is the standard deviation of the sample, and *ICC* is the test-retest reliability
12 coefficient.[46] For the MID scores to be meaningful, they should be above error; the MID
13 should be larger than the MDC.
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20 We will use the patient anchor to determine an ALS-BDI score threshold for the low disease
21 activity states.[47] This metric is similar to the patient acceptable symptom states (PASS), which
22 reflect the threshold on a patient-reported outcome where people feel generally well. At the
23 same time, it differs from the MID, described above, as it is not a measure of change. To
24 determine this threshold, we will ask patients on both visits, "Considering all the difficulties on
25 speaking and swallowing that you experience due to ALS, if you were to remain at this same
26 level of function for the following months, would you consider your speaking or swallowing
27 function satisfactory?" This is a modification of PASS/low disease state questions that have
28 been used in other diseases to help with interpretability of the scale scores.[47-50]
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41 **PATIENT AND PUBLIC INVOLVEMENT**

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45 We envision the end users of ALS-BDI to be clinicians delivering care to patients with ALS in the
46 context of a multidisciplinary ALS clinic. As such, patients have not been directly involved in the
47 development of the tool but were engaged in the trial assessments with the tool in Cycle 1 of its
48 development. Patients have not been directly involved in the design of the reliability or validation
49 studies presented here (Cycles 2 and 3). Patients were involved in the pilot of the validation
50 study to ensure that the study is well tolerated and optimized for the abilities of those patients
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3 with a more advanced presentation of ALS. Patient will be involved in conduct of the study. The
4 results will be disseminated to the patient participants through sharing study publications and
5 poster presentations with those who will express interest in receiving this information. The
6 results will also be presented to patient groups.
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11 12 13 **DISCUSSION**

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18 Bulbar motor dysfunction is among the most devastating consequences of amyotrophic
19 lateral sclerosis (ALS), a fast-progressing motor neuron disease. Although the assessment of
20 bulbar dysfunction is a core component of the ALS clinical exam, a well-designed, easy to
21 performed, and efficient tool for its assessment is lacking.[14,15] This work aims to fill this gap
22 by developing and validating a clinician-administered tool, the ALS-BDI, to serve as a primary
23 bulbar assessment tool in a clinic and in clinical trials. The innovation of this work is not only in
24 its uniqueness and methodological rigor, but the state-of-the-art instrumentation that will be
25 used for its validation.
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35 The ALS-BDI is being designed for speech-language pathologists (SLPs) because of their
36 specialized training in the assessment of voice, speech, and swallowing impairments. The tool's
37 administration is consistent with clinical assessment procedures used by SLPs, which are
38 based on clinician ratings of speech, swallowing, and oral structure and function. Although
39 clinician ratings are the foundation of an SLP assessment, the efficacy of these measures has
40 rarely been tested using rigorous experimental designs.[51]
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48 Because the tool will be based on the clinician's ratings, particular attention will be paid to
49 creating a training module for its standardized administration. Further, the tool's efficiency will
50 be addressed by careful evaluation and selection of the items. A useful bulbar assessment will
51 need to be brief, such that it can be administered from start to finish within 10 to 15 minutes,
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3 even for patients who are severely affected. A brief assessment will reduce the burden on the
4 patients, who are prone to fatigue and are frequently evaluated by multiple practitioners within a
5 single clinic visit. Standardization and efficiency will be achieved by developing a tool with a
6 minimal set of test items - removed based on reliability and validity/ responsiveness
7 evaluations - that selectively target key clinical characteristics associated with bulbar ALS, and
8 is accompanied by explicit instructions for administration.
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18 **NEXT STEPS AND IMPACT**

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23 The proposed study was placed on hold between March 2020 and March 2021 due to the
24 global COVID-19 pandemic. During this time, the tool was redesigned for an on-line/remote
25 administration, and the summary of the remote version of the tool is forthcoming. Meanwhile,
26 the return to in-person study administration outlined in the current protocol is in progress.
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31 To the best of our knowledge, the ALS-BDI will be the first standardized and
32 psychometrically validated clinician-administered bulbar assessment tool. The ALS-BDI aims to
33 meet the key requirements for the development of new clinical assessment tools: (1) supported
34 by the multidisciplinary ALS expert consensus; (2) developed with considerations of efficiency,
35 specificity, and standardization; and (3) established evidence of strong psychometric properties.
36
37 The long-term impacts of the ALS-BDI includes improving detection of bulbar ALS, expediting
38 diagnosis, improving clinical decision-making, and accelerating ALS clinical trials and drug
39 discovery. Because the tool is consistent with current assessment practices in SLP, which are
40 based on clinician ratings of speech, swallowing, and oral structure and function, it is likely to
41 have up-take within clinical practice settings focused on ALS.
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55 **ETHICS AND DISSEMINATION**

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5 This study has been reviewed and approved by research ethics boards at both data collection
6 sites: Sunnybrook Health Science Centre, primary (Toronto, Canada; ID3080) and Mass
7 General Brigham (Boston, United States; #2013P001746). Prior to participation in all elements
8 of the study, the participants sign the informed consent in accordance with the Declaration of
9 Helsinki. Once validated, the ALS-BDI will be disseminated to key stakeholders at clinical ALS
10 and speech-language pathology conferences (e.g., American Speech Hearing Association
11 (ASHA) Convention, International Symposium on ALS/MND). The tool and any relevant training
12 materials will be made publicly available to speech-language pathologists and neurologists who
13 provide ALS care. The ALS-BDI will also be launched as a validated outcome tool for clinical
14 research trials in ALS.
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50 **CONTRIBUTORS**

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2
3 The corresponding author attests that all listed authors meet authorship criteria and that no
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5 conceived the study and prepared the funding application. All authors contributed to the design
6 of the study protocol. AH and AW coordinated pilot testing of the validation protocol. All authors
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52 **COMPETING INTERESTS STATEMENT**

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Table 1. Validation procedures for each ALS-BDI item.

ALS-BDI Item(s)	Validation Method/ Instrumentation	Validation Task(s)	Measurement(s)
Items 1,2: Overall Severity of Dysarthria & Reduced Speech Intelligibility	Speech Intelligibility Test[33]	Audio-recorded sentence readings, at patient's comfortable speaking rate and loudness	Speech intelligibility (% words correct);[33, 53] Speaking rate (words per minute, WPM)[33, 53]
Items 3,7: Tongue Weakness and Fasciculations & Lip/Face Weakness	Iowa Oral Performance Instrument (IOPI Medical LLC)	Maximum isometric pressure at anterior and posterior tongue positions (3 repetitions each); Maximum isometric lip pressure (3 repetitions)[27, 28]	Peak pressure, in kilopascals (kPa)[27]
Items 5,6,8,9: Reduced Tongue Range of Motion (ROM); Slow Tongue Movement; & Reduced Lips Range of Motion Slow Lip Movement	3D video camera (Intel Real Sense) and Wave Speech System (NDI)	Same tasks as Cranial Nerve Exam items on ALS-BDI (e.g., maximum mouth opening, rapid movements of Smile-Pucker; tongue from side-to-side outside of the mouth)[54]	Kinematic measures of lip, jaw, and tongue movements, including range of motion and speed[31, 55-59]
Item 12: Nasal Emissions	Phonatory Aerodynamic System (Pentax Medical)	Syllable and sentence repetitions	Maximum nasal flow during pressure consonants[55, 60, 61]
Item 27: Hypernasality	Nasometer (Pentax Medical)	Oral – nasal sentence repetitions	Nasalance distance[62]
Items 13-18 (Phonatory subsystem): Strained Voice; Breathiness; Roughness; Voice Breaks;	Audio recording (44.1K, 16-bit resolution); Post-hoc analysis using Analysis of Dysphonia in Speech and Voice (Pentax Medical)	Sustained vowel phonation; CAPE-V30 sentences; Pitch glide	Cepstral peak prominence (CPP); [63] Low- to high-frequency spectral energy ratio (L/H ratio)[64];

Overall Dysphonia; & Inability to Elevate Pitch			Cepstral spectral index of dysphonia[25, 64]
Items 19-22 (Respiratory subsystem): Loudness Decay; Reduced Loudness; Short Phrases; & Effortful Breathing	Audio recording (44.1K, 16-bit resolution); Acoustic analysis using PRAAT and automatic Speech-Pause Analysis[65]	Standard passage reading[66]	Average intensity (mean dB SPL); Intensity range (min/max dB SPL); Intensity variability (standard deviation dB SPL); Tone unit ratio (speaking duration/#words in breath group) Average phrase duration;[32] Number of pauses[32, 55, 65, 66]
Items 23-26 (Prosody): Monopitch and/or Monoloudness; Excess and Equal Stress; Reduced Stress; & Overall Dysprosody	Audio recording (44.1K, 16-bit resolution); Post-hoc analysis using PRAAT	Standard passage reading[66]	Average fundamental frequency (mean F0);[25] Phonatory range (min/max F0);[67] Pitch variability (standard deviation F0)[25, 55]
Items 28-30 (Articulatory Subsystem): Imprecise Articulation; Slow Articulation Rate; & Reduced Overall Speaking Rate	Audio recording (as above); Post-hoc analysis Speech-Pause Analysis[65]	Standard passage reading[66]	Acoustic vowel space; [25] Vowel and fricative durations;[25] Voice onset time;[25] Speaking rate (words per minute, WPM)[36, 53]
Items 31-34: Slow DDK Rate; Irregular DDK Rhythm; Slow /pataka/ Rate; & Irregular /pataka/ Rhythm	Audio recording (as above); Post-hoc analysis using a validated in-house algorithm[68]	Syllable repetitions (i.e., “puh”, “tuh”, “kuh”, “pataka”)[69]	DDK rate (syllables/second);[56, 69-72] DDK regularity (standard deviation of syllable duration)[72]
Item 35: Impaired Voluntary Cough	Phonatory Aerodynamic	Voluntary cough	Cough volume acceleration[38]

	System (Pentax Medical)		
Items 36-37: Swallowing Difficulties 3oz Water Swallow; Increased Chewing Time	Videofluoroscopic Swallow Study, Toshiba Ultimix System MDX-8000A at 30 pulses per second; uncompressed image captured with TIMS 2000 DICOM system (Forest Imaging)	Swallows of standardized barium mixtures (Varibar® 40% weight-to-volume) of the following order/texture: 2x 5-ml thin liquid; 2x natural sip thin liquid; 2x sequential sip thin liquid; 2x 5-ml extremely thick liquid; 1 bite size cookie	Penetration-Aspiration Scale (8-point);[34] Pharyngeal constriction;[35-37] Pharyngeal residue;[35, 73, 74] Time-to laryngeal vestibule closure;[35, 75] Degree of laryngeal vestibule closure[35, 75]
Items 4, 11: Tongue Atrophy & Jaw Jerk			Cannot be instrumentally assessed/validated

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Protocol for Psychometric Evaluation of the Amyotrophic Lateral Sclerosis – Bulbar Dysfunction Index (ALS-BDI): A prospective longitudinal study

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TITLE: Protocol for Psychometric Evaluation of the Amyotrophic Lateral Sclerosis – Bulbar Dysfunction Index (ALS-BDI): A prospective longitudinal study

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ABSTRACT

Introduction: Early detection and tracking of bulbar dysfunction in amyotrophic lateral sclerosis (ALS) are critical for directing management of the disease. Current clinical bulbar assessment tools are lacking, while existing physiological instrumental assessments are often inaccessible and cost-prohibitive for clinical application. The goal of our research is to develop and validate a brief and reliable, clinician-administered assessment tool - the ALS Bulbar Dysfunction Index (ALS-BDI). This publication describes the study protocol that has been established to ascertain the tools' psychometric properties.

Methods and analysis: The ALS-BDI's development closely follows guidelines outlined by the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN). Through the proposed study protocol, we expect to establish psychometric properties of both individual test items of the ALS-BDI as well as the final version of the entire tool, including test-retest and inter-rater reliability, construct validity using gold-standard assessment methods, and responsiveness.

Ethics and dissemination: This study has been reviewed and approved by research ethics boards at two data collection sites: Sunnybrook Health Science Centre, primary (Toronto, Canada; ID3080) and Mass General Brigham (#2013P001746, Boston, United States). Prior to participation in the study, the participants sign the informed consent in accordance with the Declaration of Helsinki. Once validated, the ALS-BDI will be disseminated to key stakeholders. Following validation, the ALS-BDI and any required training material will be implemented for clinical use in a context of a multidisciplinary ALS clinic and utilized as an outcome measure for clinical trials in ALS research.

KEY WORDS: Bulbar ALS, Assessment, Development, ALS-BDI, COSMIN

ARTICLE SUMMARY

Strengths and limitations of this study

- The ALS-BDI development process adheres to the established methodological guidelines for developing a formative assessment measure - Consensus-based Standards for the selection of health Measurement Instruments (COSMIN).
- Initial development and design of the ALS-BDI has involved extensive consultation of projected end-users (i.e., neurologists, speech-language pathologists) to ensure that it is comprehensive, clinically feasible, and aligned with current practice goals and workflow.
- Psychometric evaluation of the ALS-BDI will include test-retest and inter-rater reliability, construct validity and responsiveness of each test item and the overall tool.
- Patient anchors will be used to inform interpretability and determine the clinical significance of ALS-BDI scores, including the minimal important difference (MID) and low activity disease states.
- Many individual items on the drafted ALS-BDI involve a subjective rating of severity (i.e., mild, moderate, severe), which may challenge inter-rater reliability.

INTRODUCTION

ALS is a fast-progressing disease with a lifespan post-diagnosis of 2-5 years.[1] The disease is characterized by the degeneration of motor neurons in the brain, brainstem, and spinal cord as well as extramotor (e.g., cognitive-linguistic) brain pathways.[2-4] The degeneration of motor neurons results in progressive muscle weakness, atrophy, and eventual paralysis. Nearly 90% of individuals diagnosed with ALS will experience speech and swallowing dysfunction either at the onset of the disease or when the disease spreads to the bulbar motor system, which controls muscles of the head and neck.[5] The presence of bulbar motor impairment is associated with a shorter survival (<2 years) and increases the risk of death by almost eightfold.[6, 7] The resulting speech impairment has been rated as the worse aspect of the disease by patients with ALS.[8] Despite the devastating consequences of bulbar dysfunction on the survival and quality of life, there are currently no validated tools for its assessment in a clinic. In the absence of a standardized assessment of bulbar motor dysfunction, current practices in ALS clinics are idiosyncratic, piecemeal, and rely primarily on symptom checklists.[9]

The overall aim of our work is to develop a reliable and psychometrically validated clinician-administered assessment tool of bulbar dysfunction, called the ALS-Bulbar Dysfunction Index (ALS-BDI), that is efficient, standardized, clinically feasible, comprehensive, and responsive to change over time. The ALS-BDI is currently being designed and validated for two diagnostic use cases: (1) to discriminate among patients with different severities of bulbar impairment (i.e., discriminative purpose); and (2) to evaluate the changes over time in a person or group (i.e., evaluative purpose).[10] This tool will have immediate implications for tracking disease progression and monitoring changes in ALS clinics or in clinical trials. In the future, it may serve as the core assessment that can be adapted for improving ALS diagnosis and

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3 prognosis; it could also eventually serve as a screening tool for determining the need for full
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5 dysphagia and speech assistive technology evaluations.
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7 Our process for developing the ALS-BDI adheres to established guidelines for
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9 developing a formative measure (COnsensus-based Standards for the selection of health
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11 Measurement INstruments, COSMIN).[11,12] Within a formative model, all items are considered
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13 relevant to represent the overall construct of interest and are not interchangeable; items may or
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15 not be correlated, and they may have different patterns of change when the construct changes.
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17 Formative measures, as opposed to reflective measures, are not assessed with respect to
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19 internal consistency or item-total correlations such as Cronbach's alpha, factor analysis, or the
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21 item response theory. The decision to retain or reduce items is primarily based on their clinical
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23 relevance in defining the construct (content and face validity), although reliability and
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25 responsiveness can also inform item retention.
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28 Our test development process is divided into three development cycles: Cycle 1 includes
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30 generation of the candidate item pool and demonstration of their content and face validity; Cycle
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32 2 is focused on establishing the item and overall tool's reliability; and Cycle 3 establishes the
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34 item and overall tool's construct validity in relation to well established instrumental and clinical
35
36 measures, as well as responsiveness to change over time. The work in Cycle 1, which produced
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38 the first iteration of the ALS-BDI, has been now completed. The initial development steps have
39
40 been described in detail elsewhere.[13] Briefly, Cycle 1 involved convening a panel of experts to
41
42 identify key assessment domains for bulbar dysfunction. The panel met during a Northeastern
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44 ALS Consortium (NEALS) Bulbar Subcommittee meeting, members of which were experts in
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46 neurology, speech-language pathology (SLP), and measurement science.[14] Through
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48 consensus, the panel identified three core bulbar assessment domains: (1) Cranial Nerve Exam;
49
50 (2) Auditory-Perceptual Assessment [of speech and voice]; and (3) Functional Assessment [of
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52 speech intelligibility, swallowing, chewing, and coughing]. Following the meeting, a literature
53
54 review was conducted by our development team to generate candidate items for each domain.
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3 Expert surveys were then conducted to probe each item's face and content validity. Based on
4 this procedure, an initial draft of ALS-BDI was created. A group of speech-language pathologists
5 further vetted the testable draft of the instrument via pilot administration of the test draft and
6 completion of a cognitive interview with a member of our development team. As a result, a beta
7 of ALS-BDI has been prepared for its psychometric evaluation.
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14 The process for establishing psychometric properties of the ALS-BDI has been outlined in
15 the latest recommendations by the COSMIN group.[11] To our knowledge, no comprehensive
16 bulbar assessment tool has yet been developed and validated using this rigorous approach.[15]
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18 The key psychometric properties of the ALS-BDI that must be assessed under this framework
19 include inter-rater and test-retest reliability (Cycle 2 of the development), as well as the
20 construct validity against gold-standard measures of bulbar dysfunction in ALS and
21 responsiveness to change and minimal important difference (MID), minimal detectable change
22 (MDC), and low disease state of ALS-BDI to enhance interpretability of its scores (Cycle 3 of the
23 development). Here we present a detailed protocol for the psychometric evaluation of ALS-BDI
24 through Cycle 2 and 3.
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37 **METHODS AND ANALYSIS**

38 **Prospective study design**

39 A prospective longitudinal study design will be used to assess the ALS-BDI.
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45 **Participants & Recruitment**

46 Data for this study will be collected at the Bulbar Function Laboratory at the Sunnybrook
47 Health Sciences Centre in Toronto, Ontario, Canada and the Speech and Feeding Disorders
48 Lab at the MGH Institute for Health Professions in Boston, Massachusetts, USA. The study has
49 been initiated in May 2021 with anticipated completion by June 2023.
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3 100 adults (≥ 18 years) diagnosed with possible, probable, or definite ALS as defined by the
4 Revised El Escorial Criteria will be recruited consecutively at the ALS/MND Clinics in Toronto,
5 Canada and Boston, USA.[16] Individuals will be excluded if they have a history of other
6 neurological conditions (e.g., stroke) or head and neck cancer; take medications known to affect
7 speech production; are unable to comply with the study protocol due to significant cognitive
8 impairment (i.e., Montreal Cognitive Assessment score < 18);[17] or fail a hearing screen in both
9 ears (i.e., 500-4000Hz, thresholds > 40 dB).
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17 To ensure the ALS-BDI is tested across a broad sampling of disease severity, we will recruit
18 an equal number of patients who fall within four categories of bulbar symptom severity, based
19 on their ALSFRS-R bulbar subscore: normal bulbar function (i.e., score of 12/12); mild (9-
20 11/12); moderate (6-8/12); or severe (1-5/12).[18]
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28 **1. Inter-rater and test-retest reliability**

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31 To estimate the inter-rater reliability of each candidate item, two SLPs will rate each
32 patient's performance on the ALS-BDI on the same visit. The order of SLP raters will be
33 randomized, and they will be blinded to each other's ratings. The first administration will be
34 conducted at the beginning of the visit, and the second will take place at the very end. To
35 minimize effects of fatigue, participants will be given sufficient time to rest before the second
36 ALS-BDI assessment.
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45 To determine test-retest reliability, each participant will be reassessed using the ALS-BDI,
46 within one week after the initial visit. The second visit will be scheduled approximately at the
47 same time of day as the first visit, to mitigate any daytime variability in fatigue. Given the natural
48 history of ALS, it is unlikely that there will be significant clinical change in the period of two
49 weeks. However, on the second visit, the participants will answer whether they think their bulbar
50 function has changed compared to the first assessment (i.e., yes/no). Participants who report
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any perceived differences in bulbar symptoms compared to the initial visit will be excluded from the test-retest reliability calculations.

We will calculate reliability statistics for each item on the ALS-BDI using weighted Kappa, because individual items were scored ordinally. Items with weighted Kappa <0.6 on either inter-rater or test-retest reliability will be flagged for reduction.[19] We will also calculate the overall reliability of the total score of the ALS-BDI (i.e., the sum of all items), using intra-class correlation coefficients (ICCs), considering raters as random effects (ICC formula 2,1).[20, 21] ICCs of ≥ 0.80 will be set as the minimal acceptable standard for evaluating groups of patients, whereas values of ≥ 0.90 will be required for individual patient use.[22] Item reduction based on reliability will be completed prior to construct validation of individual items and the full ALS-BDI.

Data from the first 50 consecutive individuals diagnosed with ALS and presenting with a range of bulbar impairment will be used for the reliability analyses. This exact sample size was estimated using the approach by Kraemer and Korner,[23] whereby for a minimum ICC of 0.8 and a lower 95% confidence interval (CI) of 0.7, 47 analyzable participants should be required. We will increase this number if some patients fail to attend the second visit (test-retest) within two weeks of the initial visit recording, or if they report a change in clinical status during this time interval.

2. Construct validity

Items remaining following reliability assessment will be evaluated for construct validity, relative to gold-standard instrumental physiological measures of bulbar dysfunction. For this phase of the study, data from 100 participants with ALS will be recorded. On the day of ALS-BDI administration, each patient will complete a battery of instrumental assessments and selected patient-reported outcomes (PRO) indicating overall ALS and bulbar-related disability, namely the ALSFRS-R and the Center for Neurologic Study Bulbar Function Scale (CNS-BFS).[18, 24]

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3 Table 1 shows the detailed mapping between individual items of ALS-BDI and specific
4 instrumental validators (i.e., tasks and measures). The entire session will be audio-recorded at
5 high resolution (44.1kHz, 16-bit) using a unidirectional lapel microphone, with a fixed mouth-to-
6 mic distance; the audio signal will be calibrated using a 1000Hz tone at the start of each session
7 to ensure accurate measures of signal intensity.[25] In addition to audio recordings of all speech
8 tasks, the Phonatory Aerodynamic System (Pentax Medical) will be used to measure nasal
9 airflow and oral pressure during speech and cough.[25, 26] Tongue and lip/facial muscle
10 strength will be measured using the Iowa Oral Performance Instrument (IOPI Medical LLC)
11 during maximum pressure generation tasks.[27, 28] Facial movements for speech and non-
12 speech (oro-motor) will be recorded using a three-dimensional video camera (Intel Real
13 Sense),[29] and tongue movement will be assessed using the Wave Speech System (NDI).[30,
14 31] To validate swallow tasks, each participant will undergo a standard videofluoroscopic
15 swallow study. The full validation protocol is estimated to take approximately two hours.
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32 [Insert Table 1 about here]
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37 All speech tasks will be analyzed using well-established spectral and timing measures (e.g.,
38 voice onset time, acoustic vowel space, segment durations; see Table 1 for examples).[25] The
39 standard passage reading will be analyzed using an automated Speech-Pause Analysis
40 algorithm, extracting measures of phrase and pause durations.[32] In addition, participants will
41 complete the Speech Intelligibility Test to quantify speech intelligibility (i.e., % words heard
42 correctly) and speaking rate (i.e., words per minute) in sentences.[33] Measures of swallow
43 safety (i.e., penetration/aspiration),[34] efficiency (i.e., residue),[35] and key physiological
44 events (e.g., pharyngeal constriction,[36, 37] chewing duration, laryngeal vestibule closure)[35]
45 will be obtained from a videofluoroscopic swallow study. Cough volume acceleration will be
46 measured from the Phonatory Aerodynamic System waveform of voluntary cough.[38, 39]
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3 We will study the validity of each reliable item, as determined in the reliability assessment
4 described above, in relation to its corresponding instrumental measure. All instrumental
5 measures for this study are continuous, so we will calculate the correlations (Pearson's or
6 Spearman's as appropriate) between each item and its instrumental equivalent. We have set an
7 *a priori* correlation cut point of ≥ 0.6 for criterion validity; items that correlate with instrumental
8 measures of > 0.6 will be flagged for inclusion.[40] Inter-item correlations will also be examined
9 for redundancy. In a formative model, while low or absent correlations between items are not an
10 issue, very high inter-item correlations (> 0.9) can indicate redundancy; pairs of items with
11 correlations > 0.9 will be assessed for potential reduction. If additional items are eliminated, we
12 will re-calculate the reliability coefficients for the final version of the ALS-BDI.
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Once we have the final version of the ALS-BDI, we will study the construct validity of the entire tool. We will test two hypotheses for construct validity: (1) the ALS-BDI total score will be highly correlated ($r \geq 0.7$) with ALSFRS-R bulbar sub-score and the CNS-BFS, which measures bulbar-specific disability; (2) the correlation will be weaker ($r = 0.4-0.6$) with the ALSFRS-R total score, which measures ALS disability as a whole and includes the effect of limb weakness and respiratory dysfunction. We will also compare the ALS-BDI scores between subgroups of patients divided by bulbar function severity. We will classify patients as having normal, mild, moderate, and severe bulbar dysfunction, based on their ALSFRS-R bulbar sub-scores.[18] We will compare the mean ALS-BDI scores on each bulbar severity group using ANOVAs. We hypothesize that the different severity groups will have statistically significant different mean ALS-BDI scores. Following the COSMIN guidelines, we will consider that the new scale has construct validity, if we confirm $\geq 75\%$ of the predefined hypotheses.[41]

3. Establishing responsiveness, minimal important difference (MID), minimal detectable change (MDC) and low disease state of ALS-BDI

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6 For this analysis, patients will have a second full assessment six months after the initial visit.
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8 On the second visit, patients will undergo the ALS-BDI, instrumental testing (as described
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10 above), as well as the ALSFRS-R and CNS-BFS. Patients will also answer a patient impression-
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12 of-change questionnaire (PIC), to indicate if their speech, voice, and/or swallowing have
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14 changed since the first assessment. The PIC will have 4 possible answers: 0=no change,
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16 1=minimally worse, 2=much worse, 3=very much worse; this is a modification from the method
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18 by Juniper, that used seven options for improvement or worsening.[42] Considering the natural
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20 history of ALS, we do not expect patients to report improvement. We will calculate the difference
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22 in ALS-BDI scores between visits 1 and 2, as well as the change scores for the instrumental
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24 measures, the ALSFRS-R and CNS-BFS. There is no single way to determine responsiveness,
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26 so current guidelines recommend using a range of methods to document sensitivity to change
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28 including (1) assessing statistically significant change—such as in a clinical trial—by comparing
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30 mean effects with a *t*-test, and (2) assessing change that is meaningful for patients.[41]
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33 We will estimate statistically significant change in four ways. First, we will compare the
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35 mean ALS-BDI scores at session 1 and session 2 through paired *t*-tests; we expect to see a
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37 statistically significant difference ($p < 0.05$), indicating worsening of bulbar function. Second, we
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39 will calculate the magnitude of change through the standardized response mean (SRM), which
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41 is the ratio between the mean change score to the standard deviation of said change score. We
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43 hypothesize that the SRM will be ≥ 0.3 . Third, we will study the correlations between the change
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45 in the ALS-BDI and the comparison measures, as a form of longitudinal validity.[43] We expect
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47 to find moderate correlations between the change scores ($r = 0.4-0.7$). Fourth, we will study the
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49 efficiency to detect statistically significant change of the ALS-BDI compared to the instrumental
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51 measures, the ALSFRS-R bulbar score, and CNS-BFS. For this, we will calculate the ratio of the
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53 paired *t*-test statistics, as follows:
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(t -statistic_{ALS-BDI} / t -statistic_{comparison measure}).[44, 45]

A ratio >1 indicates that the ALS-BDI is more efficient than the comparison measure of interest; in other words, it is more sensitive with detecting a given effect size for the same sample size.

We hypothesize that the ALS-BDI will be more efficient than the ALSFRS-R bulbar score and the CNS-BFS; we expect that the ALS-BDI sub-scores will have equal or slightly lower efficiency than the corresponding instrumental measures.

We will determine if the ALS-BDI detects change that is meaningful to patients by using the PIC as an anchor. To be meaningful from the patients' perspective, the ALS-BDI change-scores should correlate with the PIC. For instance, patients reporting to be much worse should have a higher change in score than those reporting moderate, mild, or no change. We will use analysis of covariance to compare the mean change in scores among PIC groups, correcting for differences in baseline scores. We expect a significant difference in change scores across PIC groups, with larger change scores in those patients reporting to be much worse.

To enhance the interpretation of the change in scores, we will estimate the minimal important difference (MID) for worsening. This is the *smallest* change in score that is meaningful for patients, and we will use the PIC category of "a little worse" as the anchor of minimal worsening. This follows current recommendations of using anchor-based methods to determine the MID, as opposed to distribution-based methods.[46] We will estimate the MID at the individual level—that is, to classify one individual as having at least minimal worsening—using a receiver operator characteristic (ROC) curve. Patients who have at least minimal worsening will be classified as "changers." The MID at the individual level is the point of highest sensitivity and specificity. We will also estimate the MID at the group level—that is, the smallest mean change in scores that would be meaningful in a group, such as in a clinical trial. For this, we will calculate the mean change in ALS-BDI scores in the group of patients that reported being "a little worse";[42] we will also estimate the 75% percentile for potential misclassification bias. For the MID estimates to be interpretable, they should be above error of measurement. Therefore,

we will calculate the minimal detectable change (MDC), which is the smallest change between assessments that is very likely above error of measurement. The MDC (with 95% CI) is calculated using the test-retest reliability statistic as follows:

$$1.96 \times \sqrt{2} \times (SD \times \sqrt{1 - ICC}),$$

where *SD* is the standard deviation of the sample, and *ICC* is the test-retest reliability coefficient.[46] For the MID scores to be meaningful, they should be above error; the MID should be larger than the MDC.

We will use the patient anchor to determine an ALS-BDI score threshold for the low disease activity states.[47] This metric is similar to the patient acceptable symptom states (PASS), which reflect the threshold on a patient-reported outcome where people feel generally well. At the same time, it differs from the MID, described above, as it is not a measure of change. To determine this threshold, we will ask patients on both visits, "Considering all the difficulties on speaking and swallowing that you experience due to ALS, if you were to remain at this same level of function for the following months, would you consider your speaking or swallowing function satisfactory?" This is a modification of PASS/low disease state questions that have been used in other diseases to help with interpretability of the scale scores.[47-50]

PATIENT AND PUBLIC INVOLVEMENT

We envision the end users of ALS-BDI to be clinicians delivering care to patients with ALS in the context of a multidisciplinary ALS clinic. As such, patients have not been directly involved in the development of the tool but were engaged in the trial assessments with the tool in Cycle 1 of its development. Patients have not been directly involved in the design of the reliability or validation studies presented here (Cycles 2 and 3). Patients were involved in the pilot of the validation study to ensure that the study is well tolerated and optimized for the abilities of those patients with a more advanced presentation of ALS. Patients will be involved in

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3 conduct of the study. The results will be disseminated to the patient participants through sharing
4 study publications and poster presentations with those who will express interest in receiving this
5 information. The results will also be presented to patient groups.
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10 11 **DISCUSSION**

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16 Bulbar motor dysfunction is among the most devastating consequences of amyotrophic
17 lateral sclerosis (ALS), a fast-progressing motor neuron disease. Although the assessment of
18 bulbar dysfunction is a core component of the ALS clinical exam, a well-designed, easy to
19 performed, and efficient tool for its assessment is lacking.[14,15] This work aims to fill this gap
20 by developing and validating a clinician-administered tool, the ALS-BDI, to serve as a primary
21 bulbar assessment tool in a clinic and in clinical trials. The innovation of this work is not only in
22 its uniqueness and methodological rigor, but the state-of-the-art instrumentation that will be
23 used for its validation.
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33 The ALS-BDI is being designed for speech-language pathologists (SLPs) because of their
34 specialized training in the assessment of voice, speech, and swallowing impairments. The tool's
35 administration is consistent with clinical assessment procedures used by SLPs, which are
36 based on clinician ratings of speech, swallowing, and oral structure and function. Although
37 clinician ratings are the foundation of an SLP assessment, the efficacy of these measures has
38 rarely been tested using rigorous experimental designs.[51]
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46 Because the tool will be based on the clinician's ratings, particular attention will be paid to
47 creating a training module for its standardized administration. Further, the tool's efficiency will
48 be addressed by careful evaluation and selection of the items. A useful bulbar assessment will
49 need to be brief, such that it can be administered from start to finish within 10 to 15 minutes,
50 even for patients who are severely affected. A brief assessment will reduce the burden on the
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3 patients, who are prone to fatigue and are frequently evaluated by multiple practitioners within a
4 single clinic visit. Standardization and efficiency will be achieved by developing a tool with a
5 minimal set of test items – removed based on reliability, validity, and responsiveness
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7 evaluations – that selectively target key clinical characteristics associated with bulbar ALS and
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9 is accompanied by explicit instructions for administration.
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16 **NEXT STEPS AND IMPACT**

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20 The proposed study was placed on hold between March 2020 and March 2021 due to the
21 global COVID-19 pandemic. During this time, the tool was redesigned for an on-line/remote
22 administration, and the summary of the remote version of the tool is forthcoming. Meanwhile,
23 the return to in-person study administration outlined in the current protocol is in progress.
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29 To the best of our knowledge, the ALS-BDI will be the first standardized and
30 psychometrically validated clinician-administered bulbar assessment tool. The ALS-BDI aims to
31 meet the key requirements for the development of new clinical assessment tools: (1) supported
32 by the multidisciplinary ALS expert consensus; (2) developed with considerations of efficiency,
33 specificity, and standardization; and (3) established evidence of strong psychometric properties.
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35 The long-term impacts of the ALS-BDI includes improving detection of bulbar ALS, expediting
36 diagnosis, improving clinical decision-making, and accelerating ALS clinical trials and drug
37 discovery. Because the tool is consistent with current assessment practices in SLP, which are
38 based on clinician ratings of speech, swallowing, and oral structure and function, it is likely to
39 have up-take within clinical practice settings focused on ALS.
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52 **ETHICS AND DISSEMINATION**

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3 This study has been reviewed and approved by research ethics boards at both data collection
4 sites: Sunnybrook Health Science Centre, primary (Toronto, Canada; ID3080) and Mass
5 General Brigham (Boston, United States; #2013P001746). Prior to participation in all elements
6 of the study, the participants sign the informed consent in accordance with the Declaration of
7 Helsinki. Once validated, the ALS-BDI will be disseminated to key stakeholders at clinical ALS
8 and speech-language pathology conferences (e.g., American Speech Hearing Association
9 (ASHA) Convention, International Symposium on ALS/MND). The tool and any relevant training
10 materials will be made publicly available to speech-language pathologists and neurologists who
11 provide ALS care. The ALS-BDI will also be launched as a validated outcome tool for clinical
12 research trials in ALS.
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48 **CONTRIBUTORS**

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52 The corresponding author attests that all listed authors meet authorship criteria and that no
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3 conceived the study and prepared the funding application. All authors contributed to the design
4 of the study protocol. AH and AW coordinated pilot testing of the validation protocol. All authors
5 reviewed feedback and came to consensus on tool design. YY, AW, CBT, and JG wrote the
6 manuscript. All authors read, edited, and approved the final manuscript.
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Table 1. Validation procedures for ALS-BDI items.

ALS-BDI Item(s)	Validation Method/ Instrumentation	Validation Task(s)	Measurement(s)
Items 1,2: Overall Severity of Dysarthria & Reduced Speech Intelligibility	Audio recordings (44.1K, 16-bit resolution) Speech Intelligibility Test [33]	Sentences	Speech intelligibility (%words correct);[33, 52]; Speaking rate (words per minute, WPM)[33, 52]
Items 3,7: Tongue Weakness and Fasciculations & Lip/Face Weakness	Iowa Oral Performance Instrument (IOPPI Medical LLC)	Max isometric pressure of tongue; Max isometric lip pressure[27, 28]	Peak pressure, in kilopascals (kPa)[27]
Items 5,6,8,9: Reduced Tongue Range of Motion (ROM) & Slow Movement; Reduced Lips ROM & Slow Movement	3D video camera (Intel Real Sense) and Wave Speech System (NDI)	Max mouth opening, rapid movements of Smile-Pucker; tongue from side-to-side outside of the mouth)[53]	Kinematic measures of lip, jaw, and tongue movements, including range of motion and speed[31, 54-58]
Item 12: Nasal Emissions	Phonatory Aerodynamic System, PAS (KayPentax)	Syllable and sentence repetitions	Max nasal flow during pressure consonants [54, 59, 60]
Item 27: Hypernasality	Nasometer (KayPentax)	Oral – nasal sentences	Nasalance distance[61]
Items 13-18 (Phonatory): Strained Voice; Breathiness; Roughness; Voice Breaks; Overall Dysphonia; & Inability to Elevate Pitch	Audio recordings (as above); Analysis of Dysphonia in Speech and Voice (KayPentax)	Sustained phonation; CAPE-V[62] sentences; Pitch glide	Cepstral peak prominence (CPP); [63]; Spectral energy ratio (L/H ratio)[64]; Cepstral spectral index of dysphonia[25, 64]
Items 19-22 (Respiratory): Loudness Decay; Reduced Loudness; Short Phrases; & Effortful Breathing	Audio recordings; Acoustic analysis using PRAAT and automatic Speech-Pause Analysis[65]	Standard passage reading[66]	Intensity (dB SPL) mean, range, variability; Tone unit ratio; Mean phrase duration;[32] # of pauses[32, 54, 65, 66]
Items 23-26 (Prosody): Monopitch and/or Monoloudness; Excess and Equal Stress; Reduced Stress; & Overall Dysprosody	Audio recording (44.1K, 16-bit resolution); Post-hoc analysis using PRAAT	Standard passage reading[66]	Mean fundamental frequency;[25] Phonatory range (min/max F0);[67] Pitch variability (standard deviation F0)[25, 54]

Items 28-30 (Articulatory): Imprecise Articulation; Slow Articulation Rate; & Reduced Overall Speaking Rate	Audio recording (as above); Post-hoc analysis Speech-Pause Analysis[65]	Standard passage reading[66]	Acoustic vowel space; [25] Vowel and fricative durations;[25] Voice onset time;[25] Speaking rate (WPM)[36, 53]
Items 31-34: Slow DDK Rate; Irregular DDK Rhythm; Slow /pataka/ Rate; & Irregular /pataka/ Rhythm	Audio recording (as above); Post-hoc analysis using a validated in-house algorithm[68]	Syllable repetitions (i.e., “puh”, “tuh”, “kuh”, “pataka”)[69]	DDK rate (syl/second);[55, 69-72]; DDK regularity (standard deviation of syllable duration)[72]
Item 35: Impaired Voluntary Cough	PAS (KayPentax)	Voluntary cough[38]	Cough volume acceleration[38]
Items 36-37: Swallowing Difficulties 3oz Water Swallow; Increased Chewing Time	Videofluoroscopic Swallow Study, Toshiba Ultimix System MDX-8000A at 30 pulses per second; uncompressed image captured with TIMS 2000 DICOM system (Forest Imaging)	Swallows of standardized barium mixtures (Varibar® 40% weight-to-volume) of the following order/texture: 2x 5-ml thin liquid; 2x natural sip thin liquid; 2x sequential sip thin liquid; 2x 5-ml extremely thick liquid; 1 bite size cookie	Penetration-Aspiration Scale (8-point);[34] Pharyngeal constriction;[35-37] Residue;[35, 73, 74] Time-to laryngeal vestibule closure;[35, 75]; Degree of laryngeal vestibule closure[35, 75]
Items 4, 11: Tongue Atrophy & Jaw Jerk			Cannot be instrumentally assessed/validated

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