Measuring change in IBM: clinical assessments versus imaging

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Abstract:

Sporadic inclusion body myositis (sIBM) is a heterogeneous progressive inflammatory muscle disease impacting skeletal muscles in the head, neck, and limbs. Use of valid, reliable, sensitive, and standardized clinical and paraclinical outcome assessments (COA) are critical to inform both proactive clinical care and clinical trial design. Here we review clinical and imaging methods used to quantify muscle strength, size, or function in sIBM, and discuss their application to clinical practice and use in clinical trials. Considerations for future work to validate measures in this population are also discussed.

Indexing terms: Inclusion body myositis; clinical outcome assessment; function; dysphagia; magnetic resonance imaging

Sporadic inclusion body myositis (sIBM) is the most common progressive inflammatory muscle disorder over the age of 50 years, affecting males predominantly over females at a ratio of 2:1 (1, 2). Diagnosis is made using both clinical and muscle histology findings and can be complicated by patients presenting with some but not all of the most common features of disease (3-5). Symptom onset is characterized by predominant weakness of the quadriceps and finger flexor muscles with progression to other muscle groups over time resulting in a median time to loss of ambulation of 7-10 years from symptom onset (6, 7). In addition, oropharyngeal and esophageal muscle weakness frequently result in progressive swallowing difficulties, which can impact a majority of patients with sIBM, and may be an under-reported symptom until severe swallowing difficulty is present (7).

To date there is no approved disease-modifying treatment available for patients with sIBM with many clinical trials failing to reach primary efficacy endpoints despite early research to suggest these treatments could be promising for patients with sIBM. The reason for this is likely multifaceted including the lack of a full understanding of disease pathophysiology, heterogeneity within sIBM study participants and their disease trajectories, lack of well-characterized disease biomarkers, treatment effect size, as well as considerations within the selected primary and secondary efficacy endpoints.

Use of valid, reliable, sensitive, and standardized clinical outcome assessments (COA) are critical to inform both proactive clinical care and clinical trial design. While there are several types of COA including patient-reported, observer-reported, clinician-reported, and performance based COA, the United States Food and Drug Administration (FDA) focuses COA on measures that report how a patient feels, functions, or survives (8). Natural history studies in sIBM provide a framework for counseling patients within a multidisciplinary clinic about average expectations for disease progression, differentiating disease-related and unrelated signs and symptoms, and

aid in identification of outlier performance or trajectories (9, 10). Similarly, standard use of COA within a clinical environment can guide patient counseling, as key factors impacting a particular skill can be identified, and equipment prescription, as time to loss of a particular skill can be anticipated (11). Skilled practitioners working within a multidisciplinary or interdisciplinary clinic should consider the International Classification of Functioning (ICF) model as a guide to evaluate the impact of sIBM on all of the patient's body structures and functions, activities, and participation in their home and community (12). In addition, use of clinician-administered, patient-reported, and/or other standardized testing (e.g., imaging) in isolation or in combination can drive clinical care and clinical trial design.

With these considerations in mind, here we describe and compare the utility of clinician-observed and patient-reported tools to available imaging techniques assessing limb and bulbar musculature in sIBM to guide clinical practice and inform future clinical trial design.

Limbs - Skeletal muscle: Clinical assessments

There have been several retrospective and prospective studies aiming to better understand and characterize disease progression in sIBM. Most frequently, strength testing across several muscles group has been assessed using manual muscle testing (MMT) (6, 10, 13-18), hand-held dynamometry (HHD) (9, 14-17, 19-21), and/or quantitative muscle testing (QMT) using a fixed system with force transducers and load cells (6, 10, 11, 22-24). While the exact muscle groups and methods of strength testing differ across studies, knee extensors and finger flexors, including pinch and hand grip, were most frequently assessed (6, 9-11, 13-24). In longitudinal studies, overall grouped strength declines ranged between 2-8% per year, whereas strength in individual muscle groups (i.e., quadriceps muscle strength) has been reported to decline as much as 17-27% in one year (6, 9-11, 14-16, 19, 24). These studies highlight that specific muscles are preferentially affected in patients with sIBM (e.g., quadriceps, finger flexors), thus

averaging muscle loss across a large number of groups has the potential to wash out the meaningfulness of change in a particular muscle. When considering future clinical trial design, it is important to carefully consider a proposed agent's treatment effect in a targeted muscle group versus systemically across the body to ensure appropriate selection of muscle groups to strength test and capture signs of treatment efficacy. Similarly, the method of strength testing is important to consider as MMT is likely to be less sensitive to small changes over time as sufficient strength is required to reach the threshold required to shift between grades. HHD and QMT may be more sensitive to small changes in strength over time, but meaningful change and relationship to function should be evaluated. Lastly, while strength testing is commonly included in natural history studies, inter-rater or test-retest reliability are rarely reported and are key to interpreting study findings or comparing results across cohorts.

Clinician-administered functional testing, such as timed tests and evaluator administered and scored motor composite scales, has been reported but much less frequently than strength testing in sIBM (11, 16, 21-23). While most reports were correlational in nature, there is a consistent but variable decline over time across all functional measures. More frequently, functional surveys such as the inclusion body myositis functional rating scale (IBMFRS) (25-27), Rivermead Mobility Index, and/or sIBM weakness composite index were described (2, 6, 9, 10, 13, 14, 16) due to their ease of administration and scoring and composite design provide a total score across all included constructs. While these composite scales have clinical utility and have been included in several clinical trials, it is important to note that an improvement, or stability, across multiple domains is required to demonstrate efficacy. Thus, for clinical trials with a targeted mechanism of action, any treatment effect can be washed out when totaling a score across the scale if all domains (i.e., swallowing, upper extremity function, and mobility) are not impacted by the investigational agent. Conversely, COA covering one specific construct (i.e.,

timed functional tests) may be more sensitive to efficacy signals if conducted in a standardized manner to reduce sources of variability on performance.

Lastly, patient-reported outcomes (PRO) are key to quantifying the patient's own perspective on disease progression and the impact on their independence with activities of daily living and quality of life. There is a renewed interest in incorporating the patient voice into clinical trials as both the United States FDA and European Medicines Agency (EMA) have issued guidance on the topic (28, 29). PRO can be health indices that evaluate a patient's perception of the disease impact on their own functional ability or be quality of life assessments which can quantify the effects of other external factors on their overall well-being (e.g., depression, anxiety). Most often health indices are included as exploratory endpoints as treatments are more likely to impact functional change and independence with activities than other external factors, such as depression, in patients with sIBM. The Sporadic Inclusion Body Myositis Functional Assessment (sIFA) is the only PRO specifically designed in accordance with the FDA PRO guidance with input from treating clinicians and patients with sIBM (30, 31). The sIFA is a composite PRO scale evaluating swallowing, lower extremity, and upper extremity functioning with established convergent and discriminative validity in validation cohorts of patients with sIBM (30, 31). While the sIFA has been included in few studies to date, authors did report a significant difference in sIFA score between the high dose cohort and placebo group in the RESILIENT trial of bimagrumab in sIBM (Hanna 2019) suggesting its potential sensitivity to change in response to treatment (32).

While there is a foundation of literature outlining the general natural history of sIBM disease progression, divergent trajectories, and inclusion of clinician-administered and patient-reported tools, there is an urgent need for prospective clinical trial readiness studies that shift the focus from characterization of disease to critical analysis of available COA and identification of any

gaps necessitating novel COA development for sIBM (Table 1). Valid, reliable, and sensitive COA with robust psychometric properties and standardized administration have the potential to enable proactive clinical care and hasten the translation of therapeutics through data-driven clinical trial design.

An initial step towards that goal was recently initiated. A prospective natural history study in sIBM is currently ongoing across 12 US sites and plans to enroll 150 patients fulfilling the European Neuromuscular Center (ENMC) 2011 criteria for IBM (NCT05046821). After baseline evaluation, participants will be followed up every 6 months for 2 years and will be tested for NT5c1A antibody status. In addition to investigating muscle and blood derived lymphocytes, this study will measure the rates of decline in IBMFRS score and TUG and will quantify decline in respiratory function (FVC [supine], MIP and MEP). Additional outcome measures assessing swallow function (Sydney Swallow Questionnaire (33) and Eating Assessment Tool (EAT-10) (34) are also employed, along with QOL using National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires (35, 36)) and the sIFA (30, 31).

Limbs - Skeletal muscle: Imaging

A variety of imaging techniques used to assess sIBM have been investigated (37, 38). Thus far, the modality of choice to image musculature in sIBM is magnetic resonance imaging (MRI). MRI provides a sensitive and non-invasive method of investigating musculature (39). MRI is useful in identifying optimal muscles for biopsy. Although not part of the formal ENMC criteria, muscle MRI has been used in clinical practice as a diagnostic tool to supplement examination findings and other investigations (such as creatinine kinase, electromyography and biopsy) (40). MRI may have utility in patients who cannot undergo biopsy or when histology is inconclusive. Muscle MRI is useful not only in the acute setting but also identifying chronic changes (Figure

1). In clinical practice, fat suppressed T2 sequences such as short tau inversion recovery (STIR) helps identify fluid accumulation in muscle; thereby detecting oedema reflective of active inflammation (41, 42). These changes appear as a hyperintense signal. STIR sequences are also helpful in recognition of necrosis and regeneration (41). T1 weighted images are more useful for detecting more progressive features such as fatty replacement of muscle and assessing atrophy (41). However, there are some disadvantages to MRI including costs and patient contraindications, such as claustrophobia, metal implants and certain cardiac devices. Oedema is present to a lesser extent in sIBM when compared to other idiopathic inflammatory myopathies (IIMs) and when it is present, it tends to be seen in distal muscles (37). Instead, there is a predilection for atrophy and fat deposition in the forearms and anterior compartment of the thighs. Muscles characteristically involved include the quadriceps muscles, flexor digitorum profundus (FDP) and medial gastrocnemius. The degree of atrophy tends to be more marked in the distal portion of the quadriceps (especially the vastus medialis and vastus intermedius) which gives a “melted appearance” (37). Of the quadriceps muscles, it is often reported that rectus femoris is relatively spared in sIBM. The atrophy of the vastus intermedius and lateralis, compared to the relatively unaffected fascia can often manifest as the ‘undulating fascia sign’ on MRI in sIBM patients (37, 42). However, it should be noted that this sign is not entirely specific to sIBM and can be seen in other IIMs (42). Despite MRI being often used to complement the diagnostic work up for sIBM, there are no standardized criteria for use of MRI in the diagnosis of sIBM, and the interpretation of images in everyday clinical practice remains subjective.

A variety of semi-quantitative scoring tools looking at MRI features such as muscle oedema, fascial oedema and fat accumulation have been developed for IIMs, but have yet to be developed for sIBM (43). Quantitative tools for assessing muscle using MRI have been developed for research purposes. The most frequently used parameters for measuring intramuscular fat accumulation include transverse relaxation fraction (T2), magnetization

transfer ratio (MTR) and fat fraction. MTR and T2 detect changes in water distribution and fat content (44, 45). MRI Dixon Fat water imaging is frequently used to measure fat fraction, which quantifies fat content on a 0-100% scale. In addition to assessing fat accumulation, quantitative MRI can be used to measure the size of the functioning muscle area also referred to as the remaining muscle area (RMA); which can be estimated by using the cross-sectional area. Morrow et al conducted a longitudinal study comparing the validity of quantitative MRI to other COAs in sIBM, Charcot-Marie-Tooth disease 1A (CMT1A) and healthy controls (46). The authors demonstrated a significant increase in fat fraction values in thigh and calf muscles of sIBM patients after a year. Thigh muscle fat fraction showed a strong negative correlation with Medical Research Council (MRC) Sum score, lower limb components of IBMFRS and 36-Item Short Form Health Survey questionnaire. Knee extension strength measured on myometry correlated with the RMA. Similar findings have been described in other studies, with fat fraction showing strong negative correlation with the IBMRFS, MRC sum scores and modified Rankin scores (47, 48). These studies provide support for the use of quantitative MRI as outcome measures in clinical trials. Lassche et al. demonstrated that fat accumulation measured by quantitative MRI T1 weighed images moderately correlated with semi-quantitative histopathology sum scores with the caveat that quantitative assessment of fatty infiltration is not be reliably assessed in Turbo Inversion Recovery Magnitude (TIRM) hyperintense muscles(49). Muscle oedema detected on TIRM also correlated with the degree of inflammation observed on histopathology. These observations suggest that quantitative MRI corroborates with changes in muscle composition in damaged muscles of sIBM patients and could potentially help track disease progression. Another MRI modality that has been studied in sIBM is MRI spectroscopy; however, its utility has yet to ascertained.

The role of using ultrasound (US) in evaluating muscle abnormalities sIBM has also been studied. Increased echogenicity within muscle is indicative of fat infiltration (48, 50, 51).

Increased echogenicity on US in FDP and medial gastrocnemius has the potential to differentiate sIBM from other myopathies (50, 51). Guimares et al. compared the use of US to whole body MRI in 12 sIBM patients (52). The accuracy and inter-reader reliability for detecting abnormalities between MRI and US was similar. However, further study with larger study populations and comparison to regional MRI is desirable. Although its diagnostic role has been assessed, any relationship between US findings and clinical features or COAs has yet to be elucidated.

Dual-energy x-ray absorptiometry (DEXA) has revealed reduced levels of lean body mass in sIBM, and DEXA has been used as secondary end point is some recent drug trials for sIBM (32, 53, 54).

Lastly, there have been a few studies that have investigated the use of positron emission tomography with computed tomography (PET-CT) in sIBM (55-57) These studies take advantage of the observation that beta amyloid is deposited in muscle fibers (58). Amyloid PET has already shown utility in clinical practice with respect to the diagnosis of Alzheimer's disease (59). Therefore, PET tracers that bind to beta amyloid have been explored in sIBM; Pittsburgh Compound B ([^{11}C]PIB) and [18F]florbetapir are the tracers that have been investigated in sIBM at the time of publication(55-57). Lilleker et al. noted [18F]florbetapir standardized uptake value ratios (SUVRs) to be significantly increased in sIBM in comparison to polymyositis (55). However total [18F]florbetapir SUVRs correlated poorly with clinical measures such as disease duration, MMT and IBMFRS. [^{11}C]PIB standardized uptake values (SUVs) were shown to be significantly increased in the gastrocnemius muscles of sIBM when compared to other controls with neuromuscular disease (57). Noto et al. found ([^{11}C]PIB SUVs to be significantly increased in all muscles of sIBM patients when compared with other types of IIMs (56). No correlation was noted between SUVs and clinical assessments (IBMFRS, MRC sum score and disease

duration). Again, the sample sizes of these studies appraising the clinical use of PET-CT have been small; further investigation into any clinical relationship and PET-CT is needed.

Head and Neck - Swallowing: Clinical assessments

Dysphagia (disordered swallowing) is extremely common in sIBM and can contribute to morbidity and mortality (60), although its pathophysiology remains poorly understood (61). Weakness in orofacial, pharyngeal, and esophageal musculature is hypothesized to contribute to the swallowing impairments observed in sIBM, subsequently impacting swallowing safety and efficiency. Common dysphagia symptomatology in sIBM includes globus sensation (likely secondary to cricopharyngeus muscle dysfunction), multiple swallows, reduced base of tongue retraction and pharyngeal constriction, and reduced hyolaryngeal excursion, which often result in unsafe and/or inefficient swallows (60, 62, 63). Unsafe swallowing results in ingested material entering the airway (i.e., aspiration), while inefficiency can lead to slowed bolus clearance and bolus collection (residue). Accumulation of residue may also result in subsequent aspiration of material, which can result in airway obstruction or pulmonary complications, such as aspiration pneumonia.

Alterations in swallowing function can be gradual and subtle in sIBM, thus the patient may not be overtly aware of such changes or may perceive such alterations as minor or attributable to another cause (e.g., ageing). As such, self-report measures alone are not sufficient, as swallowing difficulty is often underreported (62, 64). Routine monitoring of swallowing function is critical to document progression of dysfunction (if present) and to develop a targeted management plan. If there are swallowing concerns, a formal evaluation by a speech-language pathologist is warranted. Unfortunately, to date, we are not aware of any validated clinical measures of swallowing function specific to sIBM (Table 2). Therefore, at this time and until specific COAs measures are developed and validated, clinicians and researchers may adapt

and use a measure that has been validated in another patient population or included a heterogeneous patient sample with caution.

Screening questions and validated screening tools may identify “at-risk” individuals for aspiration/dysphagia and dysarthria as the outcome is pass or fail. These tools can be used by physicians, nurses, dietitians, and/or speech language pathologists depending on the environment and training. Validated screening measures often employ the patient to consume a large volume of water (65, 66), as silent aspiration has previously been observed to be volume-dependent (66), and at times also include quick simple observations of other signs of oropharyngeal difficulties (67). Other at-risk signs may include, but are not limited to, overt cranially innervated musculature dysfunction, onset of coughing during or immediately after eating, and unintentional weight loss. At-risk symptoms potentially reported by the patient may include, but also are not limited to, difficulty with foods once enjoyed, feeling of food “getting stuck” (globus sensation) or regurgitation of liquids/foods. An investigation by Cox and colleagues revealed two questions that reliably predicted the presence of dysphagia (identified on imaging as either repetitive swallowing, pharyngeal residue or cricopharyngeal dysfunction): the necessity of repeated swallowing and globus sensation (62). Patients failing the screen are considered “at-risk” and should be referred for a comprehensive swallowing assessment, which often includes imaging.

The aims of a comprehensive swallowing assessment are to determine the underlying neurophysiological and pathophysiological causes of dysphagia and guide treatment planning. This typically starts with a clinical (bedside) swallowing assessment (CSA). In addition to obtaining relevant medical/surgical and psychosocial history, a comprehensive clinical swallow assessment may include examination of cranial nerve integrity (V, VII, IX, X and XII, along with cervical and pharyngeal plexuses), PRO (e.g., EAT-10 (34)), and COA (e.g., Functional Oral

Intake Scale (FOIS) (68)). Both the EAT-10 and the FOIS scale have been used in limited studies with some sIBM patients (69, 70), although they have not yet been validated in this population. Frequently, swallow trials are also employed as part of the CSA and may range from various volumes of liquids to various food textures depending upon current patient status and functioning level. Clinicians typically make subjective observations based on these trials. Standardized and objective clinical measures of swallow trials can be added to contribute important quantified data to the CSA. Examples include the Timed Water Swallow Test (TWST (71)) and the Test of Masticating and Swallowing Solids (TOMASS (72)), which both provide normative data and are not yet validated in sIBM. Additional objective measurements that can provide valuable insights for treatment planning include measures of lingual strengthening (63) and respiratory/cough function. Lingual strength measurements are completed with a handheld oral manometry device including air-filled bulbs that are positioned inside the oral cavity (between the tongue and the hard palate). The patient is asked to press their tongue as hard as they can or perform a swallow, so that maximum isometric pressures or swallowing pressures can be obtained. Maximum lingual strength has been shown to decrease with time in one patient with sIBM and Sjogren's syndrome, while progressive lingual strengthening slowed the progression of this lingual strength loss and extended functional swallowing performance (63). Therefore, it could be another measure to monitor oral functioning, but large-scale study is needed.

Since respiratory weakness may also occur in sIBM (73), a measure of airway clearance capacity (e.g., voluntary cough testing) may provide clinically meaningful information to guide management decisions (74). Although diagnostic accuracy of voluntary cough testing performance for predicting aspiration has been reported in other progressive neurogenic populations (e.g., Parkinson's disease (75)), the authors are unaware of such a study in sIBM.

Although a comprehensive CSA can be very insightful and necessary part of a swallowing assessment, unfortunately, it does not adequately detail underlying biomechanical impairment(s) contributing to dysphagia, which makes it difficult to solely rely on the CSA to develop a thorough individualized and targeted management plan. Therefore, if a patient is identified as having difficulty swallowing, imaging should be used to confirm and detail the biomechanical pathophysiology to best inform patient care.

Head and Neck - Swallowing: Imaging

Imaging is considered the gold standard for definitively diagnosing dysphagia. The two most commonly employed instrumental procedures to assess swallowing function are flexible endoscopy and videofluoroscopy. Validated tools have been developed which can be employed with both methods to describe safety and efficiency, although these have not been specifically validated in sIBM. For example, the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) which was initially validated for use with videofluoroscopy has recently been validated for use with endoscopy (76). Although DIGEST was validated originally in the head and neck cancer population, it has been used in investigations with neurogenic populations, such as ALS (77). Flexible endoscopic evaluation of swallowing (FEES) uses a flexible endoscope to directly visualize the larynx and hypopharynx, allowing the clinician to evaluate laryngeal function (vocal fold mobility) and pharyngeal secretion management. Additional advantages are that it is a well-tolerated procedure employed at bedside, which allows for easy repeatability of the exam to document change, and can provide feedback to train therapeutic strategies deemed effective in promoting a safe and efficient swallow (78). Unfortunately, visualization may be temporarily obstructed (commonly referred to as the “white-out” period) due to tissue abutting against the camera during the pharyngeal swallow. Further, visualization of the oral and esophageal “phases” of swallowing are not feasible, and thus, impairments must be inferred based on pharyngeal observations before and after the swallow (e.g., regurgitation of material through the

cricopharyngeus/upper esophageal sphincter). Validated tools have been published to document swallow safety and efficiency observed during FEES, such as the Penetration-Aspiration Scale (PAS) (79), and the Yale Pharyngeal Residue Severity Rating Scale (80). A more recent standardized method combines safety and efficiency measures with FEES – the Visual Analysis of Swallowing Efficiency and Safety, which was validated using patients with unspecified neurodegenerative disease (81).

The videofluoroscopic swallow study (VFSS) is a radiographic procedure performed jointly by speech-language pathology and radiology that allows for visualization of the entire swallow mechanism (oral cavity to stomach) and uses contrast material (barium) to evaluate direction of bolus flow and if material remains (residue). The VFSS is also commonly known as a modified barium swallow study. Increasingly, the VFSS has also been recognized as being a useful method to screen for esophageal clearance issues (82). Swallow safety observed during VFSS is most commonly measured using the PAS (83) which remains a frequent outcome measure reported in swallowing-related investigations. Further, the PAS has also been used as an outcome variable in two treatment studies including patients with sIBM (63, 84). Because swallow safety is a consequence of swallowing function and biomechanics, other standardized tools have been developed to more accurately describe the underlying impairment contributing to impaired safety and efficiency. One such tool is the Modified Barium Swallow Impairment Profile, which quantifies swallowing impairment across 15 physiologic components across three functional domains (oral, pharyngeal and esophageal) and includes 2 additional components related to oral and pharyngeal residue (85).

More recently, high resolution manometry (HRM) has become increasingly employed in both clinical practice and research to investigate pharyngeal and upper esophageal pressures. Because cricopharyngeal dysfunction is a common impairment in this population (60), HRM

may guide management, particularly if surgery is being considered as a therapeutic option. Finally, new exciting imaging methods are now under optimization, such as dynamic MRI or simultaneous dynamic MRI and functional MRI (SimulScan) (86, 87). Such techniques, upon optimization and validation, can provide objective data on neuromuscular contributions, muscle performance, and brain activity during swallowing and other bulbar events and could prove to be valuable additional imaging tools for clinic and research. Olthoff et al. (87) examined the swallowing function in a cohort of sIBM patients using VFSS or FEES plus dynamic real time (RT)-MRI. Although, they found that dysphagia identification was feasible using both imaging modalities (VFSS/FEES and RT-MRI) and correlated well with a quality-of-life assessment related to dysphagia, differences in temporal resolution between imaging modalities should be considered. This, however, encourages continued efforts to optimize dynamic MRI as an additional imaging tool to evaluate dysphagia.

Dysphagia is a recognized, although often under-reported, symptom of sIBM. Previous investigations have detailed swallowing impairments observed in these patients (61). Standardization of assessment procedures, whether employing clinical or imaging procedures, will improve reliability of findings, allow for better documentation of disease progression, and enhance communication amongst team members, all of which will better inform patient management planning. Because standardized and validated tools do not yet exist to evaluate swallowing function in sIBM, we currently recommend a battery of tools, including use of published CSA and PRO tools validated in other neuromuscular populations, and imaging for comprehensive assessments.

Expert Commentary

While there has been a great foundation of work to date focused on characterizing sIBM disease, including enhanced understanding of general disease progression and underlying

pathophysiology, there remains an urgent need to critically appraise, validate, and develop objective, valid and reliable measures in order to achieve clinical trial readiness in sIBM. Natural history studies in sIBM have provided insight and enabled informed clinical counseling and care management, although most work has focused primarily on the impact of disease progression on motor function and its impacts on activities of daily living. Further research is needed to truly understand the prevalence, symptom onset, and the underlying pathophysiology of bulbar dysfunction (dysphagia and dysarthria) in sIBM. These learnings would promote rational recommendations for proactive management and would facilitate the development and validation of COAs that accurately quantify abilities and change over time. Various imaging techniques are available to better characterize underlying pathophysiology in sIBM in both limb muscles and bulbar musculature and function. Careful evaluation with validated COAs reliably measuring disease progression and its impact on abilities will inform future treatment plans and the development of more targeted disease-modifying therapeutics.

In preparation for future trials, it is critical to have validated and standardized COAs, which must relate to how a patient feels, functions, and survives (8). There is much work to be done to validate meaningful and responsive COAs in sIBM, as there is no one COA that will meet the needs of every future clinical trial. While systemic treatments resulting in amelioration of disease is the ultimate goal, the field must be prepared to measure change or slowed progression of disease in more targeted systems (e.g. swallowing, fine motor control, or walking speed) and identify early signals of treatment effect(s) that could warrant continued therapeutic development. Similarly, imaging methods may be useful to detect early changes in tissue function and quality or muscle size, which can serve as a surrogate endpoint measures. However demonstrating the eventual impact of imaging and its relationship to function will likely hasten acceptance of these methods by regulators. Well-designed, prospective clinical trial readiness studies are key to providing the supporting data to validate COAs for use in sIBM, to

ensure data consistency and reliability, to improve interpretability of trial results and to optimize detection of treatment effect if present.

Conclusions

COA selection is a multifaceted process requiring careful consideration of patient cohort characteristics, a thorough understanding of COA properties, while also understanding the unique needs of the clinic or trial including the proposed mechanism of action and anticipated treatment effect, among others. Rigorously designed prospective sIBM clinical trial readiness studies can inform clinical trial design and maximize interpretability of future trial results through a systematic critical analysis of COA validity, reliability, and sensitivity to change. Understanding of how a COA functions within a population can then inform the design of inclusion and exclusion criteria to address cohort heterogeneity, guide selection of study endpoints, and inform trial duration and visit schedule. Use of clinical and paraclinical COAs with robust psychometric properties can guide clinical care, reduce variability across a trial to ease interpretation of treatment efficacy and hasten translation of products to market.

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Table 1: Summary of select clinical outcome assessments (COAs) for limb strength and function and their use/validation status in sIBM

Assessment/Measurement obtained during clinical examination	**Type of assessment**	**Validated in sIBM patients**	**Not validated but used in sIBM patients per published research**	**Promising for future validation as clinical trial COA**
Strength testing: manual muscle testing, hand-held dynamometry, fixed system	Performance outcome	No	Yes	Potentially
6-minute walk test	Performance outcome	No	Yes	No
2-minute walk test	Performance outcome	No	Yes	Yes
Timed Up and Go	Performance outcome	No	Yes	Yes
4-stair climb	Performance outcome	No	Yes	Yes
sIBM weakness composite index	Performance outcome	No	Yes	Potentially
Sollerman hand function test	Performance outcome	No	Yes	Potentially
Purdue Pegboard	Performance outcome	No	Yes	Potentially

IBMFRS	Clinician-reported	No	Yes	Potentially
sIFA	Patient-reported	Yes	Yes	Yes
PROMIS	Patient-reported	No	Yes	Potentially
Rivermead Mobility Index	Observer- or Patient-reported	No	Yes	Potentially

Abbreviations: IBMFRS = Inclusion body myositis functional rating scale; sIFA = Sporadic inclusion body myositis physical functioning assessment; PROMIS = Patient-reported outcomes measurement information system

Table 2: Summary of select clinical outcome assessments (COAs) for swallowing function and their use/validation status in sIBM

Assessment/Measurement obtained during clinical examination	**Type of assessment**	**Validated in sIBM patients**	**Not validated but used in sIBM patients per published research**	**Promising for future validation**
EAT-10	Patient-reported	No	Yes	Yes
FOIS	Patient-reported or Observer (clinician)-reported	No	Yes	Yes
TWST	Observer-reported	No	No	Potentially
TOMASS	Observer-reported	No	No	Potentially
Lingual strength	Performance-based	No	Yes	Yes
Voluntary cough testing	Performance-based	No	Yes	Yes
Assessment/Measurement obtained during imaging (FEES or VFSS)	**Type of assessment**	**Validated in sIBM patients**	**Not validated but used in sIBM patients per**	**Promising for future validation**

			published research	
PAS	Observer-reported	No	Yes	Yes
MBSImP	Observer-reported	No	No	Yes
DIGEST	Observer-reported	No	No	Yes
Pharyngeal manometry values	Performance-based	No	Yes	Yes

Abbreviations: EAT-10 = Eating Assessment Tool; FOIS = Functional Oral Intake Scale; TWST = Timed Water Swallow Test; TOMASS = Test of Mastication and Swallowing of Solids; PAS = Penetration Aspiration Scale; MBSImP = Modified Barium Swallow Impairment Profile; DIGEST = Dynamic Imaging Grade of Swallowing Toxicity

Figure 1. MRI appearances in a patient with sIBM. Axial T1-weighted (A1) and STIR (A2) images of the thigh at baseline (A1 and A2), and axial T1-weighted (B1) and STIR (B2) images of the thigh of the same patient eight years later (B1 and B2). Images show significant progression of intramuscular fat accumulation; intramuscular fat accumulation is evident as hyperintensity on T1-weighted images while acute muscle inflammation is evident as hyperintensity on STIR images.