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Regular article

Therapy development for the mucopolysaccharidoses: Updated consensus recommendations for neuropsychological endpoints

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ABSTRACT

Neurological dysfunction represents a significant clinical component of many of the mucopolysaccharidoses (also known as MPS disorders). The accurate and consistent assessment of neuropsychological function is essential to gain a greater understanding of the precise natural history of these conditions and to design effective clinical trials to evaluate the impact of therapies on the brain. In 2017, an International MPS Consensus Panel published recommendations for best practice in the design and conduct of clinical studies investigating the effects of therapies on cognitive function and adaptive behavior in patients with neuronopathic mucopolysaccharidoses. Based on an International MPS Consensus Conference held in February 2020, this article provides updated consensus recommendations and expands the objectives to include approaches for assessing behavioral and social-emotional state, caregiver burden and quality of life in patients with all mucopolysaccharidoses.

1. Introduction

The mucopolysaccharidoses (also known as MPS disorders) are inborn errors of metabolism characterized by the progressive accumulation of glycosaminoglycans in tissues throughout the body [1]. There are currently 11 known MPS disorders, each caused by a different lysosomal enzyme deficiency. They vary in their prevalence, presentation and natural history, although all begin in early life. Some patients experience progressive somatic involvement only, while others develop marked and sometimes progressive central nervous system (CNS) dysfunction as well as somatic involvement. There is considerable clinical heterogeneity even within each MPS disorder.

The progressive somatic manifestations of MPS disorders vary, but can include coarse facies, hepatosplenomegaly, skeletal and joint abnormalities and cardiorespiratory disease [1]. CNS functional involvement includes progressive cognitive impairment (in MPS I, II, III and

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VII), behavioral abnormalities, sleep problems and/or seizures [1–9]. These progressive and lethal MPS disorders are described as 'neuronopathic'. MPS IV and VI, as well attenuated forms of MPS I, II and, rarely, MPS III, are described as 'non-neuronopathic'. In addition to severe somatic symptoms, neuropsychological abnormalities without progression have been found in attenuated forms of MPS I and II and in MPS IV and MPS VI [10–14]. The clinical burden of disease manifestations is considerable, and they also take a toll on the psychological health of caregivers and family members. Effective treatments for MPS disorders must aim to prevent or halt the development of both somatic and CNS manifestations and alleviate the psychological burden on patients and their families.

Current US Food and Drug Administration (FDA) guidance for industry suggests that clinical trials should include assessments of disease manifestations that are meaningful to the patient as an integral component of the evaluation of a drug's effectiveness [15]. The guidance also states that studies need to demonstrate substantial evidence of clinical benefit for regulatory approval to be given. Clinical benefit may be defined as improvements in how a patient feels, functions or survives. Therefore, prospective clinical trials should include somatic, cognitive, behavioral, social-emotional and quality of life (QoL) endpoints if they are to provide a sufficiently broad characterization of the treatment effect; although improvements in any one of those areas would likely represent significant benefit to patients and their families.

Numerous studies have demonstrated a beneficial effect of existing treatments on the somatic features of MPS disorders[16-29], but detecting functional CNS benefit is more difficult. Obtaining reliable and accurate longitudinal neurocognitive, behavioral and psychological assessment data can be a challenge in patients with MPS disorders due to dementia or very low cognitive functioning, as well as disruptive, non-cooperative behavior and/or physical/sensory disabilities. The rarity of MPS disorders poses an additional challenge, as clinical studies must often recruit patients from several countries to achieve statistical power, bringing in a diversity of testing languages and cultures. Pragmatic and user-friendly disease-specific approaches are needed to accurately evaluate disease progression and, ultimately, treatment outcomes, in patients with these conditions.

To address these challenges, a second International MPS Consensus Conference for Neuropsychological Endpoints took place on 9 February 2020, organized by the National MPS Society and supported by the pharmaceutical industry. This meeting was an update to the consensus conference held in London, UK, in 2016. During the meeting, an international panel of experts was convened to review and revise previously developed guidance on approaches to evaluate cognitive function and adaptive behavior in patients with MPS disorders [30]; taking into account feedback from multiple stakeholders and recent revisions and/or updates to some of the tests that had been recommended. The panel also discussed potential approaches to assess behavioral and social-emotional state, caregiver burden and QoL in individuals with these conditions. The goal was to achieve consensus on best practices for the design and conduct of clinical studies to investigate therapies for MPS disorders, with a focus on neuropsychological outcomes measures. The outcomes from the consensus panel discussion are reported here.

2. Methods

A modified Delphi technique was used to reach consensus on best practices to determine and measure appropriate neuropsychological endpoints in patients with MPS disorders. This methodology, developed by the Rand Corporation/University of California, Los Angeles (UCLA), CA, USA [31], is based on the original Delphi process [32], which has been widely used to achieve consensus on a specific issue and is increasingly used for the development of clinical guidelines where empirical evidence is limited [30,33–35]. An overview of the consensus process is shown in Fig. 1.

To identify priority areas for discussion, a survey was sent to members of the expert panel that participated in the development of the previous consensus recommendations for cognitive endpoints for therapy development for neuronopathic mucopolysaccharidoses [30], asking them to rank 10 topics according to their importance. The survey was also sent to expert clinicians who attended the 2016 consensus meeting, but who were not panel members. Responses to the survey provided the basis for the agenda for a subsequent Delphi consensus process.

Representatives of pharmaceutical companies with planned or ongoing clinical trials in patients with MPS disorders were also provided with an opportunity to inform the agenda. In a survey separate from that completed by expert clinicians and panel members, industry representatives were asked to rank challenges influencing trial design and to indicate whether the previous consensus recommendations as outlined in van der Lee *et al.* 2017 were useful [30].

In consultation with the National MPS Society, a 15-member expert panel was formed to participate in the consensus process. Participants included some panel members from the 2016 consensus meeting, plus additional experts. The final composition of the expert panel included five pediatric neuropsychologists with expertise in MPS disorders, two pediatric neuropsychologists with expertise in other neurological conditions, one neurodevelopmental pediatrician and five clinical geneticists with expertise in MPS disorders, a statistician and a healthcare attorney/MPS caregiver. All participating clinicians and psychologists have authored peer-reviewed publications on the MPS disorders and have been engaged in clinical trials for MPS disorders, except for two pediatric neuropsychologists who have published extensively on neurocognitive testing in their respective fields.

The expert panel convened for a 1-day face-to-face consensus meeting in Orlando, FL, USA, on 9 February 2020. The meeting was facilitated by an independent clinical epidemiologist with experience in conducting Delphi-style consensus panels and who had led the first International MPS Consensus Conference [30]. The focus of the meeting was to reassess previous recommendations for evaluating cognitive function and adaptive behavior in patients with MPS, I, II and III, as well as approaches for assessing behavior and social-emotional state, caregiver burden and quality of life.

In addition to revisiting previous recommendations, nine new topics were identified for discussion based on pre-meeting survey responses. In preparation for the consensus meeting, panel members were provided with currently available data relating to each topic. A PowerPoint presentation summarizing the available literature on each topic was prepared by each member of the panel with expertise in the specific area of concern. A copy of the presentations can be found in the online supplementary materials. The slides were distributed to panel members prior to the meeting and were used as a starting point for discussion. Subsequently, a draft statement for each topic was proposed by the moderator or by one of the panel members and discussed by all panel members. The formulation of each statement was adapted during the discussion until there was consensus.

Following the consensus meeting, a full draft of all new consensus statements, plus those from the 2016 consensus process, was sent electronically to the panel members for comment. In instances where consensus was not reached, suggested amendments were circulated among panel members, discussed and agreed via a shared electronic document site, and revised draft statements were sent to all panel members for voting point by point.

3. Results

Ten members of the 2016 expert panel and 15 additional expert clinicians responded to the pre-meeting survey, in which they were asked to select the five most important topics from a list of 10 topics, as well as any other topics they felt it would be important to consider. The results are shown in Table 1.

Eleven representatives of pharmaceutical companies responded to a

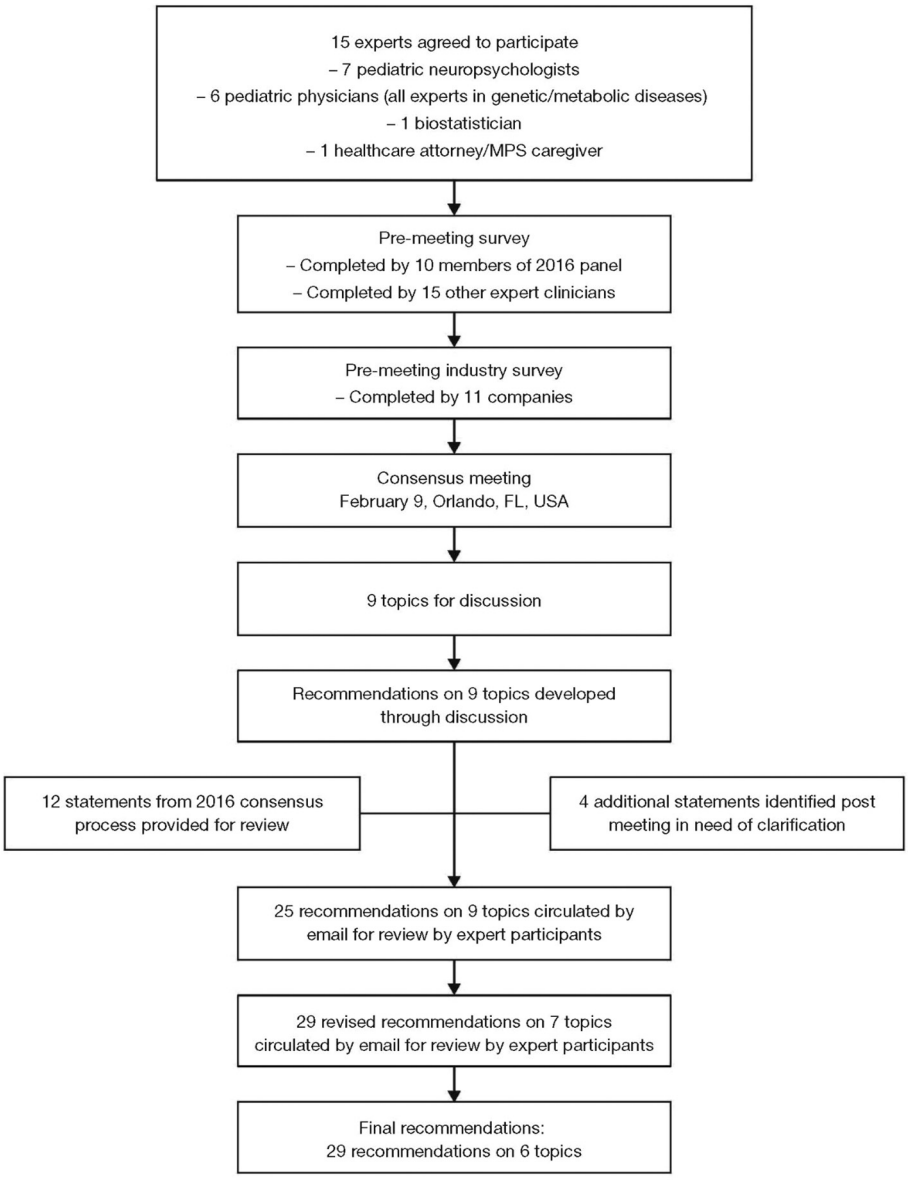

Fig. 1. Flow chart of the consensus process.

pre-meeting survey relating to challenges in clinical trial design and conduct in patients with MPS disorders. Responders were asked to identify the most significant challenges from a list of seven, as well as any other topics they felt would be important to consider. The results are shown in Table 2. In addition to the seven challenges listed in the survey, one responder identified 'acceptance by regulatory agency of age equivalent scores' as a significant challenge. Feedback on the previous consensus recommendations (van der Lee *et al.* [30]) indicated that 10 of 11 pharmaceutical companies followed the guidance when designing their clinical trials, and six representatives stated that the consensus recommendations informed other efforts of their company. By contrast, two companies used assessments that were not recommended in van der Lee *et al.* [30]; one stated that the consensus recommendations did not apply to their study "because of the language"; one stated that the recommendations did not apply to their study because of other factors.

Based on the responses to the pre-meeting surveys, the agenda for the Delphi consensus meeting was compiled from the results with nine topics for discussion:

- Natural history studies; genotype and biomarkers for monitoring disease
- Design issues: recommendations for metrics for endpoints by age and disease severity; design and statistical recommendations
- Management of new versions of tests, including electronic adaptations of scales
- International trials: need for validated and translated measures
- Challenges in testing patients with MPS disorders
- Cognitive function in patients with attenuated phenotypes: recommendations for measuring other functions
- Measurement of behavior and social-emotional state
- Measurement of caregiver burden
- Measurement of QoL

At the conclusion of the consensus meeting, a series of nine new consensus recommendations was presented to the group. These were sent, along with the original recommendations from the 2016 consensus process, to the panel members for comment. In addition, four further statements relating to items identified post-meeting as needing clarification were sent to panel members by email for comment. After two

Table 1
Assessment of the importance of topics for consideration in the Delphi process (sum of times ranked in the top five most important topics).

Topic	2016 expert panel (N = 10)	Other expert clinicians (N = 15)
Problems with international trials	7	2
Measurement of other neuropsychological functions	6	3
Metrics for endpoints	5	10
Management of new versions of tests	5	5
Measurement of patient burden	5	5
Behavior/social-emotional measures	5	5
Testing older patients	4	5
MRI/biomarkers in lieu of neuropsychological tests	4	4
QoL measures	2	7
Natural history from chart review	2	4

MRI, magnetic resonance imaging; QoL, quality of life.
Survey respondents were asked to select the five most important topics from a list of 10. The table lists the number of times each item was ranked in the top five for the total number of raters. For example, 'problems with international trials' was ranked in the top five by 7 of the 10 raters from the 2016 expert panel; 'metrics for endpoints' was ranked in the top five by 10 of 15 other expert clinicians; etc.

Table 2
Challenges to clinical trial design and delivery in patients with MPS disorders, frequency of endorsement by pharmaceutical industry representatives (N = 11)

Challenge	Number of endorsements
Availability of validated and translated scales for use in international trials	8
Lack of available natural history data	8
Consistency of implementation across sites	6
Training of raters	6
Time it takes to administer assessments	6
Difficulty in analysis of data from cognitive measures	4
Applicability of collected data to disease in question	3
Acceptance by regulatory agency of age equivalent scores	1

rounds of review, discussion and revision of the statements via email, a consolidated list of 29 recommendations was agreed across six topics. 100% consensus was reached for statements for five of the six topics (Table 3), indicated by expression of agreement by all expert panel members. For statements for the remaining topic, agreement was provided by 13 of 15 panel members (87%), with two panel members abstaining. All recommendations are listed in Table 3 and additions or updates to the 2017 recommendations described below.

3.1. Natural history of MPS disorders

3.1.1. High quality natural history studies, albeit limited in size, are published for MPS IIIA and B, and are in review for MPS II. These studies may be used as historical controls for prospective trials evaluating experimental treatments. For MPS I, trials of new treatments for the Hurler phenotype should use patients who have received hematopoietic stem cell transplantation (HSCT) as a comparator

3.1.1.1. Rationale. When evaluating natural history, it is important to identify variables that correlate with disease progression, taking into account the phenotypic spectrum of the disease and associated morbidities. When robust longitudinal natural history data are available, they may be appropriate historical controls depending on the similarity of patient populations and measurement of the primary clinical endpoint. However, it is worth noting that natural history studies are rarely designed for regulatory use.

Robust longitudinal natural history data are available for MPS IIIA and B. Prospective natural history studies of these conditions suggest that for the majority of patients the progressive course is rapid and relatively predictable [36–39]. There are well defined inflection points in the development curves for cognition in patients with severe disease, with a slowing of development in the first 18–24 months of age, plateauing until 36–42 months of age and a loss of skills thereafter. These studies use age-equivalent scores and have the full range for MPS IIIA [36,37], although less is known about early development of MPS IIIB [37,38]. These natural history studies and published data from clinical interventional trials in MPS IIIA and B suggest that to see an improvement of cognitive skills, interventions will need to occur before 24 months of age [36–41]. However, maintaining a plateau or slowing the loss of skills are alternative treatment goals.

In MPS II, the clinical course has a spectrum of severity, although patients are traditionally characterized as having neuronopathic or non-neuronopathic disease [1]. For patients with neuronopathic disease, natural history studies point to a slowing of cognitive development in the first 2 years of life, followed by a long plateau phase [6,42,43]. The timing and rate of cognitive decline is variable. Due to the long plateau phase noted for cognitive function, alternative methods to demonstrate clinical efficacy will be necessary; for example, using age equivalents to demonstrate that cognitive development can be restarted. Overall, detailed longitudinal data on cognitive function in MPS II are limited in patients prior to onset of developmental decline.

The clinical course for patients with MPS I is a spectrum, as illustrated by the historical designation of patients into three disease severity categories: Hurler, Hurler–Scheie and Scheie [1], which has since been updated to two categories of severe (Hurler) and attenuated phenotypes [44]. Studies have reported disease progression for untreated patients or for those given enzyme replacement therapy alone [45–47], and hematopoietic stem cell transplantation (HSCT) has been associated with improved cognitive ability [17,21], particularly when administered at an early age [20,48]. Due to the recent implementation of newborn screening for MPS I, many severely affected children are diagnosed and receive HSCT very early in life [49]. Consequently, novel therapies for severe MPS I should be assessed against historical data from early identified 'HSCT-treated' patients, as this is current standard of care.

It should be noted that heterogeneity in clinical course and severity is an important consideration in clinical trials. This has necessitated study designs that employ within-child changes over time. Such an approach, using changes in age-equivalent scores (or other types of scores), allows comparison across tests [50]. In addition, studies can incorporate appropriate statistical methods to adjust for age and other factors contributing to patient heterogeneity.

Natural history studies of adaptive functions have generally found similar trajectories as cognitive testing [51]. The Vineland Adaptive Behavior Scales, Second edition [52,53], has been used in most studies and was reviewed extensively in Janzen *et al.* [54], which accompanied the recommendations from the first consensus conference. More recent studies continue to indicate sensitivity to change and similar findings in MPS IIIB and MPS II [38,55]. Ahmed and colleagues found below average but relatively stable adaptive functions in attenuated MPS I [56]. Examination of specific domains has indicated initial preservation of motor function with declines in communication, daily living skills and socialization in MPS IIIA [57–59].

Overall, studies of the natural history of behavioral and social-emotional functioning in MPS disorders are few. One study found that in patients with MPS III a generic measure did not detect change [37]. Because generic measures have not been sensitive to the specific symptoms in MPS II and MPS III, disease-specific measures have been developed [60,61], although their sensitivity to change has yet to be determined. A review of generic measures used in MPS disorders can be found in the supplemental material. An example of the use of generic measures can be found in cross-sectional studies in MPS IV [12,62], indicating social-emotional difficulties.

Table 3
Consensus voting on final recommendations

Topic and recommendation	Change to 2017 recommendations (section)	Agree	Disagree	Abstain
Natural history of MPS disorders		15 (100%)	-	-
• High quality natural history studies, albeit in limited in size are published for MPS IIIA and B and are in review for MPS II. These studies may be used as historical controls for prospective trials evaluating experimental treatments. For MPS I, trials of new treatments for the Hurler phenotype should use patients who have received hematopoietic stem cell transplantation as a comparator	New (3.1.1)			
• We strongly recommend building and sustaining an infrastructure to collect and share well-curated natural history data for all MPS disorders	Updated: guidance on data quality provided (3.1.2)			
• We recommend the establishment of a committee to implement data sharing	New (3.1.3)			
• Families should not be subjected to the unnecessary collection of natural history data that remain within a single study	New (3.1.4)			
Cognitive, behavioral and related tests, including management of new versions of tests and electronic adaptations of scales		13 (87%)	-	2 (13%)
• As new versions of tests are released, trials need to consider ease of use, sensitivity to change, availability of translations, and consistency and comparability to past data collected	New (3.2.1)			
• For trials evaluating the effect of treatment in patients with MPS I, II or III aged up to 3 years (age equivalent), the recommended instrument to measure cognitive outcomes is the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)	None (3.2.2)			
• For (multinational) trials evaluating the effect of treatment in patients with MPS disorders with less severe cognitive impairment (higher functioning MPS I, II and VII, MPS IV and MPS VI), the recommended instruments to measure cognitive outcomes are the Wechsler tests (Wechler Preschool and Primary Scales of Intelligence Fourth Edition [WPPSI-IV; in patients with functional age 2.6–7.7 years] and the Wechsler Intelligence Scale for Children, Fifth Edition [WISC-V; in patients with functional age 6.0–16.11 years]).	New (3.2.3)			
• For (multinational) trials evaluating the effect of treatment on cognitive outcomes in patients with MPS disorders who (a) are over 3 years of age, (b) have age-equivalent scores exceeding 2.5 years, and (c) find the Wechsler scales too difficult because of neuronopathic disease, a non-verbal scale such as the Kaufman Assessment Battery for Children, Second Edition Non-Verbal Index (KABC-II NVI) is appropriate to ensure consistent application between trial sites across multiple countries in which tests have not been translated	Updated: expanded to all MPS disorders; recommendation for KABC-II NVI over DAS-II (3.2.4)			
• For trials evaluating the effect of treatment in patients with MPS disorders of all ages, the recommended instrument to measure adaptive skills is the Vineland Adaptive Behavior Scales, Second Edition (Vineland-2) or Third Edition (Vineland-3), using the standard interview format	Updated: expanded to all MPS disorders; interview format changed (3.2.5)			
• We acknowledge the usefulness and value of historical data that elucidate the natural history of MPS I, II and III, including standardized cognitive and development outcomes measures other than those recommended in these consensus statements	None (3.2.6)			
• If motor functions, both gross and fine motor, are one of the trial outcomes, acceptable measures include the Peabody Development Motor Scales II (PDMS-II), the Bayley-III motor domain and the Bruininks-Oseretsky test of motor proficiency, second edition (BOT-II)	New (3.2.7)			
• We acknowledge that many patients with attenuated and/or treated MPS have documented cognitive and behavioral manifestations that are under studied and merit new therapies directed at the CNS. Domains of assessment should be relevant to the patients and informed by the patients, and may include: executive function/attention, memory, motor function, and behavioral/social-emotional function (internalizing problems such as social isolation, depression and anxiety, and externalizing problems such as hyperactivity)	New (3.2.8)			
• Disease-specific measures for behavior and social-emotional state should be used when available and, if not available, should be a priority for future development for young and very impaired children with neuronopathic disease	New (3.2.9)			
• We recommend against the social/emotional/behavioral subtests of the Bayley and the Vineland (any editions) as they are not sensitive to the challenges of MPS disorders	New (3.2.10)			
• Because caregiver and family burden is high in MPS disorders and includes physical, social-emotional, financial, relational, psychological, social and other impacts, consideration should be given to measure and gauge these impacts in clinical trials	New (3.2.11)			
• Quality of life (QoL) is an important outcome. In patients functioning at or near age-appropriate intellectual abilities, generic QoL measures may be appropriate if the concepts of interest are sufficiently captured by the generic measure	New (3.2.12)			
• When using generic caregiver-proxy QoL scales for patients with significant cognitive impairment, the test used should be appropriate for the patient's functional level rather than those recommended for their chronological age	New (3.2.13)			
Metrics for endpoints by age and disease severity		15 (100%)	-	-
• Trial designs should consider analysis plans that incorporate multiple endpoints to evaluate different functions, as well as patient-specific disease progression modeling to evaluate the efficacy of an intervention	New* (3.3.1)			
• For patients with progressive neurodegenerative diseases, age equivalents or raw scores are recommended to track developmental trajectories	New* (3.3.2)			

(*continued on next page*)

Table 3 (*continued*)

Topic and recommendation	Change to 2017 recommendations (section)	Agree	Disagree	Abstain
• For patients who are higher functioning or with attenuated diseases, either standard scores or raw scores could be utilized. Because age-equivalent scores are available and useful only to 6 years of functional age, we do not recommend tracking higher-functioning patients over time with either age-equivalent scores or developmental quotients	New* (3.3.3)			
• For patients who are less cognitively impaired, standard scores provide an accurate assessment of cognitive ability compared with normative data	New* (3.3.4)			
• When transitioning from one test to another because of developmental or chronological age, we recommend administering the two tests concurrently at least once during the same visit (on separate days) to compare and calibrate test results	None			
Consistency of protocols		15 (100%)	-	-
• In a multisite trial, we recommend using the same protocol for all trial sites worldwide; including, if possible, the same test version	None			
Challenges in assessments of patients with MPS disorders		15 (100%)	-	-
• Testing patients in MPS trials requires explicit understanding and consideration of disease-specific characteristics that have the potential to limit performance and interpretation of testing	New (3.5.1)			
• We recommend the input of families and the study principal investigator to inform trial logistics and to improve the precision of outcome measurement	New (3.5.2)			
• If neurocognitive assessments are included as endpoints, the cost should be included in the trial budget and paid for by the study sponsor and not by the patients or their families	New (3.5.3)			
International trials		15 (100%)	-	-
• We recommend the use of a standard written translation of the measurement instrument, including the administration instructions, produced by a professional translator with experience in standardized tests. Such a professional translation should always be accompanied by a back-translation. We also recommend cross-cultural adaptation. Lastly, we recommend that a local psychologist/psychometrician should review the fidelity of the translation and of the cross-cultural adaptation	Updated: guidance provided on offsetting socioeconomic variations in multinational trials (3.6.1)			
• We acknowledge that in multinational trials it may be necessary and appropriate to use one set of psychometrically sound normative data; however, this is only recommended for a non-verbal outcome measure. If a specified verbal tool has not been validated in a country, we recommend the parallel use of a country-specific instrument to establish concurrent validity with a translated version	None (3.6.2)			
• For international trials, in-person onsite training is preferred so that trainers can (a) directly experience and understand the local context of test administration, and (b) evaluate the assessor for experience in test- and disease-relevant domains, with the goal of understanding the assessor's need for additional training	New* (3.6.3)			

* Supersedes guidance provided in 2017 recommendations

3.1.2. We strongly recommend building and sustaining an infrastructure to collect and share well-curated natural history data for all MPS disorders

3.1.2.1. Rationale. Further to previous guidance [30], the panel strongly recommends that investigators should assess critically all existing data to identify important gaps; existing natural history study data and related biorepositories (including genotype and biomarkers data) must be cataloged, consolidated and examined for quality. These data are critical for the informed design of clinical trials and could serve as historical comparator data.

A global database with common data elements is recommended. Data should be FAIR: 'Findable', 'Accessible', 'Interoperable' and 'Reusable' [63]. Such a database should include standardized cognitive and developmental measures that are gathered in a prospective, carefully scrutinized and unbiased manner. Precedents for shared natural history can be found in other conditions such as international registries for cystic fibrosis and Duchenne muscular dystrophy [64,65].

3.1.3. We recommend the establishment of a committee to implement data sharing

3.1.3.1. Rationale. Given the urgency to treat patients with MPS disorders as early as possible to prevent irreversible neurological and somatic deterioration, collaboration and data sharing between academic centers and industry is an ethical imperative, even when two parties are working on competing products. The panel strongly recommended the establishment of a committee to implement long-term sustainable data sharing among research stakeholders. This may include data collected as part of post-marketing studies required by regulatory bodies. The committee must identify roadblocks and solutions to natural history data collection and sharing. The panel suggests that this be spearheaded by patient organizations and openly attended by all stakeholder groups, including industry, regulatory authorities and academic institutions. To ensure continued access to data for research purposes, data ownership should rest with the patients.

3.1.4. Families should not be subjected to the unnecessary collection of natural history data that remain within a single study

3.1.4.1. Rationale. For all neuronopathic MPS disorders, very early treatment is necessary to avert irreversible cognitive decline; thus, caregivers naturally want their child to have access to experimental treatments as early as possible. A delay in treatment initiation due to the need to generate duplicative natural history data for a single study or clinical trial is unethical and should likely be unnecessary if natural history data are available as a shared resource.

The panel recommends that data ownership should remain with the patients and caregivers participating in clinical studies collecting natural history data, rather than with the trial sponsor or clinical site. Patient consent agreements should include a clause requiring that any data collected as part of such natural history data are made available to other parties working to develop therapies for their condition. Before enrolling in natural history studies, it is important for patients and caregivers and ethics committees to consider the intended use of the data; for example, to help inform clinical trial design or as a control arm to an interventional study. For some conditions, there are sufficiently robust historical data available, so it is not reasonable to ask patients to provide further untreated data when access to a potential disease-altering treatment is possible.

3.2. Cognitive, behavioral and related tests, including the management of new versions of tests and electronic adaptation of scales

3.2.1. As new versions of tests are released, trials need to consider ease of use, sensitivity to change, availability of translations, and consistency and comparability to past data collected

3.2.1.1. Rationale. There are many psychometric measures that can be used to evaluate cognitive, adaptive and other functions in patients with MPS disorders [54]. Many of these tests undergo periodic revision to improve their psychometric properties, normative data, relevance of stimuli, and ease of administration. In addition to test revision, there is ongoing development of new tests to evaluate these constructs. However, there is limited guidance available concerning the factors that should be considered when making decisions about new tests and whether or when to make the transition to a revised or new test.

Considerations when deciding on whether to incorporate a new version of a test into a trial should include the languages available, ease of use, sensitivity to change, consistency and comparability with past data collected and the available metrics (age equivalents, standard scores, raw scores). Although newer tests and versions may include updates that more accurately reflect abilities of the current population, this does not render data from prior versions obsolete. Until a revised or new test has published evidence of improved ability to help clinicians assess change over time, the choice to delay adoption of revised or new tests may be reasonable and appropriate. Summary guidance for adoption of new versions of tests can be found in Bush SS *et al.* [66].

The development and use of electronic versions of neuropsychological assessments can add complexity [67]. Some tests have been created specifically for electronic administration, whereas others were originally administered on paper and were adapted in later versions to electronic administration. In the latter instance, it is advisable that any trial using electronic versions of any tests also maintain paper versions of the same version, in the event of malfunction. Raters who administer electronic tests must be trained in the paper versions as well as the electronic versions. The potential for differences in performance on paper versus electronic versions, such as scales of processing speed, should also be accounted for when analyzing data [68].

3.2.2. For trials evaluating the effect of treatment in patients with MPS I, II or III aged up to 3 years (age equivalent), the recommended instrument to measure cognitive outcomes is the Bayley-III

3.2.2.1. Rationale. Consistent with previous guidance [30], the Bayley-III is recommended for use in patients with MPS I, II or III aged up to 3 years (age equivalent) with one disagreement, supporting the Mullen Scales of Early Development as an alternative. The consensus from panel members indicated that none had used the recently published Bayley-4 [69]. This test has not yet been utilized in any natural history studies, it has not been translated into languages other than English and Spanish, and it has not been used in any clinical trials. A cross-validation study of Bayley-III and Bayley-4 in patients with MPS disorders is also needed, particularly as the truncated nature of the Bayley-4 compared with the Bayley-III may reduce sensitivity in cognitively impaired patients. Until such information is available, it cannot be recommended.

3.2.3. For (multinational) trials evaluating the effect of treatment in patients with MPS disorders with less severe cognitive impairment (higher functioning MPS I, II and VII, MPS IV and MPS VI), the recommended instruments to measure cognitive outcome are the Wechsler tests

3.2.3.1. Rationale. The Wechsler Preschool and Primary Scales of Intelligence Fourth Edition (WPPSI-IV) and the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V) can be useful when monitoring children who have been treated successfully and continue to increase their cognitive skills. The WPPSI-IV is available and validated in most languages and earlier versions of this measure have been used successfully to assess the longitudinal effects of bone marrow transplantation in children with MPS I [7,18]. These tests should be used in clinical trials in which the patient's functional age is estimated to be above the floor of the chronological-age-appropriate Wechsler test; that is 2.6 years for the WPPSI-IV and 6.0 years for the WISC-V [70,71]. Similarities in design and overlapping age ranges for use mean that transition from the WPPSI-IV (age, 2.6–7.7 years) to the WISC-V (age, 6.00–16.11 years) is likely to be straightforward.

If other measures of cognitive ability are considered for children

with less severe cognitive impairment, there needs to be a very strong rationale for doing so. One example of such a rationale is that previous trials have successfully employed another measure that demonstrated sensitivity to change.

It is noted that the Differential Ability Scales, Second Edition (DAS-II) has been used successfully to assess the longitudinal effects of HSCT in children with MPS I and in a recent preliminary report of a natural history study of patients with MPS II [20,55,72]. This instrument is only available in English and Spanish, which limits its utility in multi-national clinical trials. The DAS-II also has limitations due to the floor of 2 years 7 months (or higher for some subtests) for age-equivalent scores and the lack of continuity of raw scores between the early years and school age version of the test.

Similarly, the Kaufman Assessment Battery for Children, Second Edition (KABC-II) Non-Verbal Index (NVI) can be useful due to its wide age range of use (3–18 years), good reliability and validity [73]. It is considered by the panel to be less sensitive to change compared with the Wechsler tests in patients capable of performing the tasks required in the WPPSI-IV and WISC-V.

3.2.4. For (multinational) trials evaluating the effect of treatment on cognitive outcomes in patients with MPS disorders who (a) are over 3 years of age, (b) have age-equivalent scores exceeding 2.5 years, and (c) find the Wechsler scales too difficult because of neuronopathic disease, a non-verbal scale such as the KABC-II NVI is appropriate to ensure consistent application between trial sites across multiple countries in which tests have not been translated

3.2.4.1. Rationale. Some patients with low functional ages may struggle with the WPPSI-IV and WISC-V due to task demands related to fine motor skills and sustained attention span, as well as the greater emphasis on speed of performance compared with other cognitive tests. Factors to consider in the selection of a measure for these impaired populations are: the need for verbal interaction in the language of the patient; availability of consistent raw scores/age-equivalent scores across time; the time required to administer the test; fine motor requirements; and availability of normative data and comparative historical data.

The KABC-II has been found to be sensitive to change in patients with MPS III [36,51,74,75]. Its non-verbal components (KABC-II NVI) take approximately 30 min to complete and can be done in pantomime; enabling the administrator to demonstrate to the patient how each task should be completed. In patients with low functional ages, use of the KABC-II NVI is appropriate to ensure consistent application between trial sites in multinational studies.

If measures other than the KABC-II NVI are considered, such as the DAS-II or the Leiter International Performance Scale, there should be a rationale for doing so. One example of such a rationale is that previous trials have successfully employed another measure that demonstrated sensitivity to change.

3.2.5. For trials evaluating the effect of treatment in patients with MPS disorders of all ages, the recommended instrument to measure adaptive skills is the Vineland-2 or Vineland-3, using the standard interview format

3.2.5.1. Rationale. Measures of adaptive behavior help put scores of cognitive function into context. Consistent with previous recommendations [30], the Vineland Adaptive Behavior Scales – Second Edition (Vineland-2) continues to be recommended for the measurement of adaptive behavior in patients of all ages, although the Vineland-3 [52] may also be considered depending on the need for and availability of translations and its appropriateness for the functional age of the patient. Although experience with the Vineland-3 is minimal, it benefits from updated normative data (2014–2015) and similar to the Vineland-2, can be used to determine which battery of cognitive tests is suitable based on functional age [51]. The Vineland-3 also has the advantage of electronic administration and has been adopted in some new clinical trials.

It is noted that there is an age-equivalent floor of 3 years of age for some subscales of the Vineland-3. Thus, more specific information on the functional age below 3 years cannot be determined. In such instances, raw scores should be used, particularly to track change. Similarly, it is noted that motor scales cannot currently be calculated for the electronic versions of Vineland-3 for patients older than 10 years. If a clinical trial will include patients older than 10 years, it is recommended that the paper version be employed for that trial, not the electronic version. Use of the Expanded Interview Format of the Vineland (any edition) is no longer recommended due to the burden that the length of the interview imposes on the caregiver for little incremental benefit for this population.

The adaptive scales on the Bayley-III are not recommended for use in future trials as they are derived from the Adaptive Behavior Assessment System, which has been found to be unsuited to the MPS III population because the floor is too high [37]. The Vineland-2 or -3 is a better choice for measuring adaptive skills.

3.2.6. We acknowledge the usefulness and value of historical data that elucidate the natural history of MPS I, II and III, including standardized cognitive and development outcome measures other than those recommended in these consensus statements

3.2.6.1. Rationale. Consistent with previous guidance [30].

3.2.7. If motor functions, both gross and fine motor, are one of the trial outcomes, acceptable measures include the Peabody Developmental Motor Scales II (PDMS-II), the Bayley-III motor domain and the Bruininks–Oseretsky test of motor proficiency, second edition (BOT-II)

3.2.7.1. Rationale. Motor function is frequently the most affected area in many MPS disorders. Problems include decreased range of motion, difficulty balancing, joint contractures, abnormal gait and carpal tunnel syndrome, which affects fine motor control [1,58,59]. As patients live longer due to improved standards of care, deficiencies in motor function are becoming an increasing problem, particularly as they can indirectly impact other areas of development such as learning and independent living skills.

There are several standardized tools for the measurement of gross motor function in children, but only a handful have good reliability and validity in MPS disorders [76]. In patients less than 2 years of age, the panel considers the Bayley-III motor domain to be an appropriate tool for evaluating gross and fine motor control, especially in patients with cognitive impairment. The PDMS-II is a norm-referenced and standardized clinical assessment tool frequently used by physical and occupational therapists to evaluate motor abilities in children with disabilities compared with typically developing children [77]. It can be used in patients from birth to 71 months and enables assessment of reflexes (< 1 year of age), balance, gait and object manipulation (> 1 year of age). It is most appropriate for use in non-cognitively impaired patients under 4 years of age. The BOT-II provides a comprehensive assessment of fine and gross motor skills in children and young adults within the school age range (4–21 years) [78]. Subtests include fine motor precision, fine motor integration, manual dexterity, bilateral coordination, balance, running speed and agility, upper-limb coordination and strength. The BOT-II correlates well with the PDMS-II, and both tests have been used successfully in patients with MPS disorders [58,79,80].

3.2.8. We acknowledge that many patients with attenuated and/or treated MPS have documented cognitive and behavioral manifestations that are under studied and merit new therapies directed at the CNS. Domains of assessment should be relevant to the patients and informed by the patients, and may include: executive function/attention, memory, motor function, and behavioral/social-emotional function (internalizing problems such as social isolation, depression and anxiety, and externalizing problems such as hyperactivity)

3.2.8.1. Rationale. Quantitative data on the cognitive and behavioral

challenges faced by patients with attenuated and/or treated forms of MPS disorders are limited, meaning that the level of medical need in these individuals is not well understood. Although intellectual function is not affected as dramatically as in more severe phenotypes of these conditions, patients with attenuated MPS I and MPS II still appear to suffer from attention deficits, processing difficulties and behavioral challenges [7,10,11,81,82]; yet further study is needed. Similarly, patients receiving treatment for severe forms of neuronopathic MPS disorders may develop a more attenuated phenotype, and it is important to understand the challenges they may continue to face. Even in conditions such as MPS IV and MPS VI, which are traditionally associated with normal intelligence, patients experience behavioral challenges and evidence of cognitive impairment [12,83–85].

Natural history studies and clinical trials for new therapies directed at the CNS manifestations of patients with attenuated disease are clearly warranted. The design and implementation of studies in this population should be done in consultation with patients and caregivers to ensure that the domains of assessment are relevant. They may include social isolation, depression, anxiety, executive function, attention and motor function.

There are many tests that can be considered for patients with mild-to-moderate cognitive and behavioral impairment [86]. An exhaustive list is not provided here, but suggestions have been made based on the experience of several panel members and previous use in published studies in MPS disorders (Table 4). Regardless of the test used, fatigue and motivational issues need to be considered to maintain the validity of the data captured.

3.2.9. Disease-specific measures for behavior and social-emotional state should be used when available and, if not available, should be a priority for future development for young and very impaired children with neuronopathic disease

3.2.9.1. Rationale. Current FDA guidance for industry suggests that clinical trials should include aspects of the disease that are meaningful to the patient and that could be assessed to evaluate a drug's effectiveness [15]. Numerous studies of the perspectives of patients with MPS disorders and their families have shown that neurobehavioral manifestations of their disease are particularly meaningful to them [6,43,44,61,87–91]. It is often difficult to capture changes in behavior with available standard tools as they were developed for children with normal intelligence and assume a level of functioning and behavioral repertoire that many patients with MPS disorders don't have. As a result, the use of generic measures risks misrepresenting disease severity for severely impaired and very young children. In one study, a commonly used generic measure was found to be insensitive to the types of problems found in patients with severe forms of MPS III [37]. With this in mind, disease-specific measures are recommended for assessment of behavior and social-emotional state, when they are available. Examples of disease-specific behavioral measures include the Sanfilippo Behavior Rating Scale (SBRS) and the Hunter Behavior Rating Scale [60,61]. For patients with few behavioral difficulties, such as those with MPS I, IV, VI and VII and attenuated forms of MPS II, the Child Behavior Checklist (CBCL), Behavior Assessment for Children (BASC) and the Behavior Rating Inventory of Executive Function (BRIEF) are appropriate [92–95].

3.2.10. We recommend against the Social-Emotional Scale of the Bayley and the Maladaptive Behavior domain of the Vineland (any editions) as they are not sensitive to the challenges in MPS disorders

3.2.10.1. Rationale. We do not recommend the Maladaptive Behavior Scale portion of the Vineland. It lacks sensitivity to the disease-specific symptoms that are part of some MPS disorders. The Bayley Social-Emotional Scale also lacks sensitivity to the specific problems of children with MPS disorders. For example, items such as 'exploration', which may be hampered by physical problems, and 'ease of engagement' or 'sensory sensitivity', may be confounded by sensory and language abnormalities. See the previous two sections for recommended measures.

Table 4
Domains of assessment and suggested tests for higher-functioning patients with MPS disorders.

Domain	Suggested tests	Comments	Use in MPS disorders
Verbal and non-verbal IQ	• Wechsler tests (short forms) [70,71,140,141]	Minimizes fatigue	[8,81]
Attention	• Tests of Variables of Attention (TOVA) [142] • Connors Continuous Performance Test [143]	TOVA can be used in international trials as there are no letters or numbers used	[10,11,83,144]
Memory	• Hopkins Verbal Learning Test [145] • Rey Auditory Verbal Learning Test [146]	Alternative forms to minimize practice effects	[144,147]
Visual Motor Integration	• Beery Buktenica Development Test of Visual Motor Integration [148] • Rey-Osterrieth Complex Figure [149]	Selection depends on age and function	[11,150]
Motor function	Fine motor: • Purdue Pegboard [151] • 9-hole pegboard [152] Gross motor: • Peabody Motor Development Scale [77] • Bruininks–Oseretsky Test of Motor Proficiency [78]	Selection depends on age and function	[58,124,153–155]
Behavior/social-emotional function	• Behavior Assessment System for Children (BASC) [94,95] • Child Behavior Checklist (CBCL, brief) [92] • Behavior Rating Inventory of Executive Function (BRIEF) [93]	Both self-report and proxy-report forms are available	[12,56,81,83,156–160]
Computerized batteries containing tests that measure impulse control, problem solving, working memory, processing speed, motor speed, and multiple other possible domains	• Cambridge Neuropsychological Test Automated Battery (CANTAB) [161] • NIH Toolbox [162]	Ease of administration; normative data available	[11,82,163]

3.2.11. Because caregiver and family burden is high in MPS disorders and includes physical, social-emotional, financial, relational, psychological, social and other impacts, consideration should be given to measure and gauge these impacts in clinical trials

3.2.11.1. Rationale. Caregiver and family burden (CFB) is not well defined for MPS disorders. It includes physical, social-emotional, financial, psychological, relational and social components, such that caring for and living with an individual with a neuronopathic degenerative condition can have a substantial impact on health-related QoL and activities of daily living and can impose emotional and financial stress on the family unit [61,91,96,97]. Despite its importance, there are currently no disease-specific measures to assess CFB for MPS disorders, although a Caregiver Burden Questionnaire is in development for MPS II, MPS III and metachromatic leukodystrophy [98].

Recent clinical trials in MPS III have begun to include CFB as a secondary outcome measure, employing a mix of semi-structured interviews and validated generic tools [99–101]. Measures used in previous and ongoing MPS clinical trials include broad QoL instruments with a CFB component, such as the Child Health Questionnaire Parent Form 50 (CHQ-PF50) and the Infant Toddler Quality of Life (IT-QoL) score [102–105], as well as CFB-specific measures like the PedsQL Family Impact Module (PedsQL-FIM), Parenting Stress Index™, 4th Edition (PSI-4) and the Zarit Burden Interview (ZBI) [100,101,106–112]. Attention to the mental health of caregivers should be considered in light of recent studies [113–115].

In the absence of a tool specific to MPS disorders, approaches to measurement of CFB with generic measures need to be undertaken in collaboration and consultation with caregivers to ensure that the domains of assessment are relevant and appropriate.

3.2.12. QoL is an important outcome. In patients functioning at or near age-appropriate intellectual abilities, generic QoL measures may be appropriate if the concepts of interest are sufficiently captured by the generic measure

3.2.12.1. Rationale. Quality of life is known to be affected in both patients with MPS disorders and caregivers/family members, and the ability to demonstrate treatment-related improvements in QoL is likely to be an important driver for reimbursement of novel therapies. A range of QoL measures has been employed in clinical trials involving patients with MPS disorders, and they have proved useful for attenuated forms of MPS I and II, MPS IV and VI, as well as MPS IH (Hurler syndrome) following HSCT [62,81,116–120]. In patients functioning at or near age-appropriate intellectual abilities, generic QoL measures may be appropriate if the concepts of interest are sufficiently captured by the generic measure. The Child Health Questionnaire (CHQ), Pediatric Quality of Life Inventory (PedsQL), 36-Item Short Form Survey (SF36) and EQ5D have shown decreases in physical QoL with age, and improvement with treatment [62,81,116–125].

The ability of generic QoL measures to ask meaningful questions about disease-specific QoL issues is limited in patients with neuronopathic phenotypes. Items on generic measures are often not applicable to very low functioning children; parents comment that items are not appropriate for the cognitive level of the patient. For example, one study of MPS IIIA and IIIB eliminated a generic measure part-way through after preliminary analyses found it 'unsuitable' because most patients scored at the severe end of impairments in QoL and multiple items were not applicable because they assumed higher levels of functioning [37]. Whether proxy-QoL measures can be sensitive to change using generic tools is still to be determined. Modification of existing tools is another possibility that has not been clarified. Several studies have used the form of the generic test appropriate to the functional level of the patient (eg using the Infant Toddler Quality of Life Questionnaire [ITQoL] instead of the CHQ) [38].

Disease-specific measures of QoL are not currently available for application across the spectrum of MPS disorders. Available tools that are specific to a particular MPS disorder or type of outcome have their own limitations. The MPS Health Assessment Questionnaire (MPS HAQ), a measure of disability, is only suitable for use in patients over 12 years of age and lacks validity for younger patients due to a lack of normative data [126]. The HS-FOCUS for MPS II, a similar type of measure, faces the same limitations [127,128].

Pain is especially difficult to measure for nonverbal patients with neuronopathic disease. Patients with MPS II and III are generally unable to reliably report and/or localize pain due to cognitive impairment, and caregivers report significant distress over uncertainty regarding the child's pain experience [61,97,129]. Patients with MPS III often have hip dysplasia and other musculoskeletal manifestations [130,131], which leads to pain and the need for surgery in some individuals. Although parents could identify pain in these children, a substantial proportion of parents reported pain in children without manifestations [132].

In light of the complicated behavioral overlay during decline in some of the neuronopathic phenotypes, the presence of pain is not always easy to determine for caregivers and families, who may agonize over whether behavioral exacerbations are the result of pain [61,96,97,129]; thus, raising concerns that generic caregiver proxy measures or observational rating scales of pain may not be appropriate in these unique diseases. Observational methods to assess pain in cognitively impaired or very young children may provide a more objective alternative [133,134].

What constitutes good QoL is likely to vary during the disease process [135]. In young patients, adaptive and disability measures may be relevant to assess QoL, so it is important to consider how these may be incorporated.

3.2.13. When using generic caregiver-proxy QoL scales for patients with significant cognitive impairment, the test used should be appropriate for the patient's functional level rather than those recommended for their chronological age

3.2.13.1. Rationale. For example, questions about QoL-related academic/school adjustment are not a focus for patients functioning at a preschool level.

3.3. Metrics for endpoints by age and disease severity

3.3.1. Trial designs should consider analysis plans that incorporate multiple endpoints to evaluate different functions, as well as patient-specific disease progression modeling to evaluate the efficacy of an intervention

3.3.1.1. Rationale. To capture disease progression and treatment outcomes, multiple metrics may be considered, including raw scores, age equivalents (where appropriate, considering the instrument and the impairment of the child) and standard scores. Each of these metrics has strengths and limitations, and their suitability for use depends on the characteristics and chronological and developmental ages of patients to be included in a clinical study. For example, evidence is emerging that age equivalent scores can be highly variable in very young patients (ie < 1 year of age) (Eisengart JB, unpublished data) and age-equivalent scores are not available for the Wechsler tests. Raw scores are preferred for longitudinal tracking in patients under 1 year of age until age-equivalent scores become more stable.

We also note that age equivalents can be imprecise when the test produces them in ranges, such as ' < 3 years', which obscures whether there is any developmental movement below this age equivalence. However, in such an instance, a loss or gain of several raw score points would be more informative.

Clinical studies should be able to assess the stability, improvement or decline of cognition or other functions relative to a patient's chronological age or disease progression over the course of the disease. Therefore, the choice of metric to enable within-patient comparison is critical. While standard scores and developmental quotients provide a cross-sectional measure of a patient's functional level, they do not provide information about whether a child is developmentally

progressing, stagnating or declining [30]. Relevant metrics may vary between patients, depending on age, severity and stage of disease progression. With these limitations in mind, multiple metrics should be used to evaluate cognitive function, rather than any single metric. Multivariate modeling (eg Bayesian disease progression models) can be used to leverage the strengths of multiple endpoints and efficiently characterize disease progression [136].

Endpoint selection for early phase trials should keep in mind the needs of subsequent trials. Patients enrolled in a phase 1/2 study may also take part in subsequent phase 3 trials, so it is important that the endpoints and metric employed are suitable for patient cohorts across studies.

For trial eligibility, norm-referenced scores should be used whenever truly calculable (ie when the patient is the intended age for the test and does not bottom-out or hit the floor). However, consideration should be given to relative importance of functional age (and therefore ability to perform a test) versus chronological age when determining which patients to include in the trial. If a norm-referenced score above the floor is available, it is preferable to use this instead of age-equivalent scores used for developmental quotient calculation.

3.3.2. For patients with progressive neurodegenerative diseases, age equivalents or raw scores are recommended to track developmental trajectories

3.3.2.1. Rationale. Age equivalents allow understanding of the rate of development, particularly slowing and halting of development, often followed by loss of skills. Raw scores may also be used for this purpose, providing the test structure has continuous point accumulation across ages (ie modular test formats prohibit time-span tracking and should not be used) [50].

3.3.3. For patients who are higher functioning or with attenuated diseases, either standard scores or raw scores could be utilized. Because age-equivalent scores are available and useful only to 6 years of functional age, we do not recommend tracking higher-functioning patients over time with either age-equivalent scores or developmental quotients

3.3.3.1. Rationale. Age equivalent scores are generally not available for patients functioning above an age-equivalent of 6 years. Developmental quotients (age equivalent divided by chronological age, multiplied by 100) are not recommended to determine trial eligibility. Like age-equivalent scores from which they are derived, intervals between developmental quotient units are unequal and do not consider the range of normality. Standard scores when calculable above the floor of the test provide reliable classification of impairment level, but multiple metrics may be considered.

3.3.4. For patients who are less cognitively impaired, standard scores provide an accurate assessment of cognitive ability compared with normative data

3.3.4.1. Rationale. Use of standard scores is different than tracking by raw scores or age equivalents. For standard scores, maintaining the same score over time is a positive goal, and lower standard scores do not necessarily mean skill loss.

For patients being monitored using standard scores, practice/learning effects are likely – especially in older patients – so intervals between tests often need to be up to 1 year. By contrast, younger patients – especially those under 3 years of age – can be tested more frequently than annually, as items change at each test administration due to the rapidity of cognitive growth at this age. The lower the chronological age, the more frequently patients may be tested without being impacted by practice/learning effects.

3.3.5. When transitioning from one test to another because of developmental or chronological age, we recommend administering the two tests concurrently at least once during the same visit (on separate days) to compare and calibrate test results

3.3.5.1. Rationale. Consistent with previous guidance [30].

3.4. Consistency of protocols

3.4.1. In a multisite trial, we recommend using the same protocol for all trial sites worldwide; including, if possible, the same test version

3.4.1.1. Rationale. Consistent with previous guidance [30].

3.5. Challenges in assessments of patients with MPS disorders

3.5.1. Testing patients in MPS trials requires explicit understanding and consideration of disease-specific characteristics that have the potential to limit performance and interpretation of testing

3.5.1.1. Rationale. Children with MPS conditions have a range of challenges that make cognitive assessment demanding. These include hearing loss, visual difficulties, musculoskeletal abnormalities, limited attention span, fatigue and sleep disturbances [50]. Children and young people with attenuated forms of MPS disorders may still display significant cognitive impairment [137].

Given that intelligence tests do not routinely include children with neurodegenerative disorders in their population samples, it is important that steps are taken to account for the challenges that patients face. Table 5 lists specific factors that should be considered and recommendations for how they should be managed to minimize disruption and errors in interpretation.

3.5.2. We recommend the input of families and the study principal investigator to inform trial logistics and to improve the precision of outcome measurement

3.5.2.1. Rationale. The level of experience of the examiner, as well as conditions the patient experiences, will directly affect the quality of the data gathered. For instance, pain episodes, fatigue and emotional stress due to closely scheduled appointments, or effects of concomitant medication can affect how a patient performs in cognitive and behavioral assessments. The testing environment (eg size of room, background noise, light levels) may also have an impact.

To avoid unnecessary disruption, the testing environment and schedules need to be flexible to patient needs. Caregivers should be consulted to determine the most appropriate time for assessment, as this will vary by patient. The caregiver can also provide valuable information about how their child is that day; are they behaving as normal, or are they being affected by any internal or external factors? Taking such factors into account can help to optimize the precision of data from assessments.

To avoid causing undue stress to the patient, and to optimize consistency of measurement, the test should be administered and scored by the same person/people consistently throughout a trial, where possible.

3.5.3. If neurocognitive assessments are included as endpoints, the cost should be included in the trial budget and paid for by the study sponsor and not by patients or their families

3.5.3.1. Rationale. Participation in clinical studies often requires patients and their families to attend clinics outside of their standard care schedule. Any costs associated with this, including travel, accommodation, subsistence, and others, should be paid for, and ideally arranged by the study sponsor to minimize the burden on patients and their families. In the United States, differences in health coverage can create disparity and significant financial burden for families, even when neurocognitive tests are considered standard of care. Therefore, when cognitive endpoints are included in a study design, their measurement should be supported financially by the sponsor.

Table 5
Considerations and recommendations for testing in patients with MPS disorders. Adapted from Delaney *et al.* [51].

Challenge	Consideration/recommendation
Hyperactivity	• Correct and flexible seating, non-stimulating environment • Management support from caregivers • Accommodated seating and permission to stand during testing
Motor deficits	• Allow additional time • Choose lower start points to encourage success • Don't allow too much time for frustration to become a concern
Corneal clouding	• Are glasses being worn? • Is lighting optimal in the room?
Hearing impairments	• Are hearing aids fitted? • Is the environment quiet?
Cognitive impairment	• Is the floor of the test low enough? • Does it cover the age equivalent of the patient?
Uneven levels of impairment across diverse domains	• Interpretation error may occur when performance on multiple subtests of diverse skills is calculated into a single score. To avoid interpretation error, such as over- or underestimation of abilities, it is best to use domain-level index scores, not summary scores
Inattention	• Test breaks, rewards, caregiver-informed scheduling (ie time of day) of assessments • Be flexible in presentation
Slow processing	• Speak slowly • Allow extra time for responses • Allow delayed responses (ie responding to an earlier item during presentation of a later item)
Chewing/orality	• Use chew aids/pacifiers to distract
Difficult behavior	• Make sure psychologists/psychometricians are experienced in working with children with neurodegenerative conditions and understand that classic behavioral techniques may not work, that a flexible approach is needed, and that there are wider impacts of the condition affecting behavior (eg pain, hearing loss, appointment fatigue)
General comments	• To test in optimal conditions, consider timing, travel fatigue, appointment fatigue, medical trauma, time zone differences, etc. • Trial design should consider these circumstances and have flexibility to meet the needs of the patient

3.5.4. We recommend the use of a standard written translation of the measurement instrument, including the administration instructions, produced by a professional translator with experience in standardized tests. Such a professional translation should always be accompanied by a back-translation. We also recommend cross-cultural adaptation. Lastly, we recommend that a local psychologist/ psychometrician should review the fidelity of the translation and of the cross-cultural adaptation

3.5.4.1. Rationale. Further to previous guidance [30], the examiner should be fluent in the language of the patient and qualified in test administration. Interpreters may be used only to indirectly assist in test administration or in giving instruction to caregivers and must have received appropriate training so as not to inadvertently interfere with standardized test administration.

To offset socioeconomic variations that can affect the homogeneity of outcome data from multinational trials, assessors should be able to adapt their approach to local context and factors that can affect the general education and care of patients.

3.5.5. We acknowledge that in multinational trials it may be necessary and appropriate to use one set of psychometrically sound normative data; however, this is only recommended for a non-verbal outcome measure. If a specified verbal tool has not been validated in a country, we recommend the parallel use of a country-specific instrument to establish concurrent validity with a translated version

3.5.5.1. Rationale. Consistent with previous guidance [30].

3.5.6. For international trials, in-person onsite training is preferred so that trainers can (a) directly experience and understand the local context of test administration, and (b) evaluate the assessor for experience in test- and disease-relevant domains, with the goal of understanding the assessor's need for additional training

3.5.6.1. Rationale. Assessors must be qualified in and credentialed to administer neurodevelopmental measurement instruments and have experience in their use, preferably with the disease being evaluated. In-person training should be provided on how to perform the specific measurements in the protocol and should be subject to periodic retraining and quality control and auditing of scoring.

Assessors with significant experience in the assessment of children with MPS disorders who regularly use the recommended instruments do not need repetition of training with every trial. Repetition of training can cause 'training fatigue'. Trial administrators should be aware of this and take it into account during trial design. However, even experienced assessors may still need periodic feedback to ensure accurate assessment of all clinical trial participants.

4. Discussion

The early success of enzyme replacement and other strategies for alleviating symptoms in lysosomal storage diseases has resulted in unprecedented levels of research and development into therapies for MPS disorders. There is an emphasis on treating the CNS in addition to improving somatic manifestations, ranging from enzyme replacement therapies to a plethora of approaches to gene therapy [138,139]. For these strategies to be successful, it is essential that clinical trials are designed and implemented in a way that enables the generation of consistent and reliable data that demonstrate meaningful clinical benefit to patients. This consensus document has been developed to provide updated guidance regarding approaches to evaluating cognitive function in patients with MPS disorders, and to include potential approaches for assessing behavioral and social-emotional state, caregiver burden and QoL in individuals with these conditions. The recommendations made are based on all available evidence and decades of experience in designing and administering neuropsychological studies in patients with MPS disorders and related conditions.

The ever-increasing number of novel therapies for MPS disorders, coupled with increasing downward pressure on healthcare budgets, means that the bar for achieving reimbursement and patient access for these interventions will continue to rise. Increasingly, reimbursement bodies are looking beyond clinical and surrogate endpoints in favor of evidence of meaningful clinical benefit to patients and caregivers. The incorporation of cognitive, behavioral, social-emotional, burden and QoL endpoints in clinical trials is a positive step in providing a broad characterization of the benefits treatment provides for how the patient feels, functions or survives. The effective design and implementation of clinical studies including these endpoints requires an in-depth understanding of the available measurement tools and when it is appropriate

to use them. Consideration must also be given to statistical power and which scoring system should be used to ensure that improvements are detectable. Until the previous version of these recommendations was published, there was limited formal guidance available to study sponsors and clinicians working to develop treatments for MPS disorders. It is hoped that by updating and expanding this guidance to include neuropsychological measures of disease through a structured expert-led process, this document will provide much-needed clarity to an important area of study.

It has not been possible to address here every issue associated with the assessment of neuropsychological outcomes in patients with MPS disorders, as some aspects are beyond the scope of this consensus development process. For example, the absence of disease-specific measures for behavior, caregiver and family burden and QoL means that compromises have to be made in determining the most appropriate generic test for a study based on the specific disease and phenotype it is intended to measure or treat. The development and validation of disease-specific measures for these outcomes should be priority for further research. Similarly, the process and requirements for developing and maintaining an infrastructure for the sharing of natural history data among investigators warrants extensive discussion and a call to action.

It should be noted that the recommendations described herein reflect current understanding and experience with available instruments. As evidenced by the updated guidance contained in this document for cognitive and adaptive behavior, new tools and new editions and translations of available measures will inevitably become available in the future. Therefore, it is the intention of the panel to review and update these recommendations regularly to ensure that views of best practices remain current.

5. Conclusion

The recommendations described above provide an update and expansion on expert consensus recommendations published in 2017 [30]. Here, a modified Delphi process has been used to generate 29 expert consensus recommendations relating to the design and conduct of clinical studies for novel therapies for MPS disorders. By revisiting and expanding upon previous guidance to include recommendations on testing of patients with attenuated phenotypes, and the evaluation of behavioral and social-emotional state, caregiver burden and QoL, it is hoped that the guidance provided in this article will stimulate and contribute to the development of robust clinical programs that investigate the effects of novel therapies on the outcomes that matter most to patients and their families, regardless of their disease severity. In addition to the conduct of interventional studies, the collation, curation and sharing of high-quality natural history data remains an area in need of attention. Importantly, these consensus recommendations aim to provide clarity to clinicians, regulatory bodies and others to derive a clear unbiased understanding of what constitutes good study design so that the relative benefits of available treatments can be assessed objectively.

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Author contributions

Although Johanna H van der Lee is the first author, all members of the panel contributed to this manuscript to a substantial degree. Johanna H van der Lee chaired the consensus meeting, assisted in designing and analyzing the pre- and post-meeting surveys, and edited the manuscript.

Jonathan Morton attended and observed the consensus meeting and drafted the article in consultation with expert panel members.

Heather R Adams, Lorne Clarke, Julie Eisengart, Maria L Escolar, Roberto Giugliani, Paul Harmatz, Melissa Hogan, Shauna Kearney, Joseph Muenzer, Nicole Muschol, Stewart Rust, Benjamin R Saville and Margaret Semrud-Clikeman took part in the consensus meeting, conducted literature analyses to provide evidence for consensus development, and provided critical appraisal of the manuscript.

Raymond Wang took part in the consensus meeting and provided critical appraisal of the manuscript.

Elsa Shapiro designed the pre- and post-meeting surveys, attended the consensus meeting, conducted literature analyses to provide evidence for consensus development and edited the manuscript.

Declaration of Competing Interest

Johanna H van der Lee has no conflicts of interest.

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