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Minireview

Cognitive endpoints for therapy development for neuronopathic mucopolysaccharidoses: Results of a consensus procedure

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ABSTRACT

The design and conduct of clinical studies to evaluate the effects of novel therapies on central nervous system manifestations in children with neuronopathic mucopolysaccharidoses is challenging. Owing to the rarity of these disorders, multinational studies are often needed to recruit enough patients to provide meaningful data and statistical power. This can make the consistent collection of reliable data across study sites difficult. To address these challenges, an International MPS Consensus Conference for Cognitive Endpoints was convened to discuss approaches for evaluating cognitive and adaptive function in patients with mucopolysaccharidoses. The goal was to develop a consensus on best practice for the design and conduct of clinical studies investigating novel therapies for these conditions, with particular focus on the most appropriate outcome measures for cognitive function and adaptive behavior. The outcomes from the consensus panel discussion are reported here.

Contents

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1. Introduction

Mucopolysaccharidoses are inborn errors of metabolism characterized by the progressive accumulation of glycosaminoglycans in tissues throughout the body [1]. There are currently eleven known mucopolysaccharidoses, each caused by a different lysosomal enzyme deficiency.

Mucopolysaccharidoses vary in their prevalence and presentation, although most include extensive somatic involvement affecting the heart, lungs, airway, bones, joints, vision, hearing, and gastrointestinal system [1]. In the most severe forms of mucopolysaccharidosis (MPS) types I, II and III, this is accompanied by central nervous system (CNS) dysfunction or decline, becoming evident in the second or third year of life and ultimately resulting in the loss of attained skills. The CNS manifestations of these conditions are devastating to parents, relentless in their decline, and result in premature death. CNS manifestations are also observed in MPS VII; an ultra-rare disease that is not discussed in this article.

Treatments for MPS I and II have been available for several years in the form of hematopoietic cell transplantation (HCT) and enzyme replacement therapy (ERT). Although both have been found to have benefits in addressing and preventing progression of many of the somatic features of these disorders [2–16], only HCT has been found to have any effect on CNS decline owing to the inability of ERT to cross the blood–brain barrier [16–20].

Currently, there are several potential disease-modifying products in pre-clinical and clinical development to address the CNS manifestations of MPS I, II and III, with the ultimate aim of preventing or halting the neurologic decline characteristic of these disorders. The design and conduct of clinical studies to evaluate the effects of novel therapies on CNS manifestations in children with neurodegenerative diseases is challenging. The most appropriate measures of the effects of novel therapies on the CNS are changes in cognitive function and adaptive skills (i.e. the ability to engage in day-to-day activities). Until now there have been a great variety of approaches taken to evaluate cognition and adaptive behavior in patients with mucopolysaccharidoses, which is perhaps understandable given the plethora of psychometric measurement instruments available for these purposes. To enable clinicians, investigators, regulatory bodies and caregivers to fully understand the relative effectiveness of treatments for mucopolysaccharidoses, it is essential that standard protocols are applied consistently to ensure reliable measurement of cognitive outcomes and adaptive behavior in clinical trials. The importance of this was emphasized at a workshop convened by the Food and Drug Administration on cognitive assessment in inborn errors of metabolism and in guidelines developed by the National Institutes of Health (NIH; www.nlm.nih/gov/cde) [21,22]. Owing to the rarity of mucopolysaccharidoses, multinational studies are often needed to recruit enough patients to provide meaningful data and achieve statistical power. However, this brings with it diversity of testing languages and cultures. The availability of the most up-to-date versions of tests also varies between countries, meaning that older versions of a psychometric measurement instrument may be used by some countries within the same study.

To address these challenges, an International MPS Consensus Conference for Cognitive Endpoints took place on 2–3 December 2016, organized by the US and UK MPS Societies and supported by industry. During this meeting an international panel of experts was convened to discuss approaches for evaluating cognitive function in patients with mucopolysaccharidoses. The goal was to achieve consensus on best practice for the design and conduct of clinical studies investigating novel therapies for these conditions, with a focus on the most appropriate outcome measures for cognitive function and adaptive behavior. The outcomes from the consensus panel discussion are reported here.

2. Methods

A modified Delphi technique was used to reach consensus on best practice for evaluating cognitive and adaptive function in patients with mucopolysaccharidoses. This methodology, developed by the Rand Corporation/University of California, Los Angeles (UCLA), CA, USA [23], is based on the original Delphi process [24], which has been widely used to achieve consensus on a specific issue and is increasingly used for the developing of clinical guidelines when there is insufficient evidence [20,25,26]. An overview of the consensus process is shown in Fig. 1.

In consultation with the UK Society for Mucopolysaccharide Diseases and US National MPS Society, an 18-member steering committee was formed and chaired by Elsa Shapiro, PhD. A comprehensive literature review was performed by a member of the steering committee – a psychologist with expertise in another inborn error of metabolism (DJ) – to consolidate the best available published information on the methods used to assess cognitive function and adaptive behavior in patients with MPS diseases, including psychometric properties, usefulness in various settings, and use and sensitivity to change in MPS diseases. Full details and findings from the literature review can be found in Janzen et al. elsewhere in this issue of *Molecular Genetics and Metabolism* [27]. The steering committee discussed and determined the composition of an expert panel to participate in a Delphi consensus process. The final composition of the expert panel included four pediatric neuropsychologists with expertise in mucopolysaccharidoses, two pediatric neuropsychologists with expertise in other neurological conditions, one neurodevelopmental pediatrician with expertise in psychological assessment in mucopolysaccharidoses, six pediatric physicians with expertise in mucopolysaccharidoses, a statistician, and a healthcare attorney/MPS caregiver. All participating clinicians and psychologists have authored peer-reviewed publications on mucopolysaccharidoses, with the exception of 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 meeting in London, UK. The meeting was facilitated by an independent clinical epidemiologist with experience of conducting Delphi-style consensus panels. The focus of the meeting was approaches for evaluating cognitive function and adaptive behavior in patients with MPS I, II or III. Methods for assessing behavior were not included in the discussion.

Before the meeting the panel members were provided with information about 14 measurement instruments previously used to evaluate cognitive outcomes in patients with mucopolysaccharidoses; these tools are discussed in detail in Janzen et al. elsewhere in this issue of *Molecular Genetics and Metabolism* [27]. Having reviewed this information, panel members with asked to answer an e-mail survey about:

- Whether they would want to consider these instruments during the consensus meeting, and
- Their assessment of the importance of 14 measurement characteristics on an 11-point scale (0, not important; 10, very important). Measurement characteristics included the psychometric properties of the instruments (e.g. reliability, sensitivity, validity), feasibility, and cross-cultural relevance.

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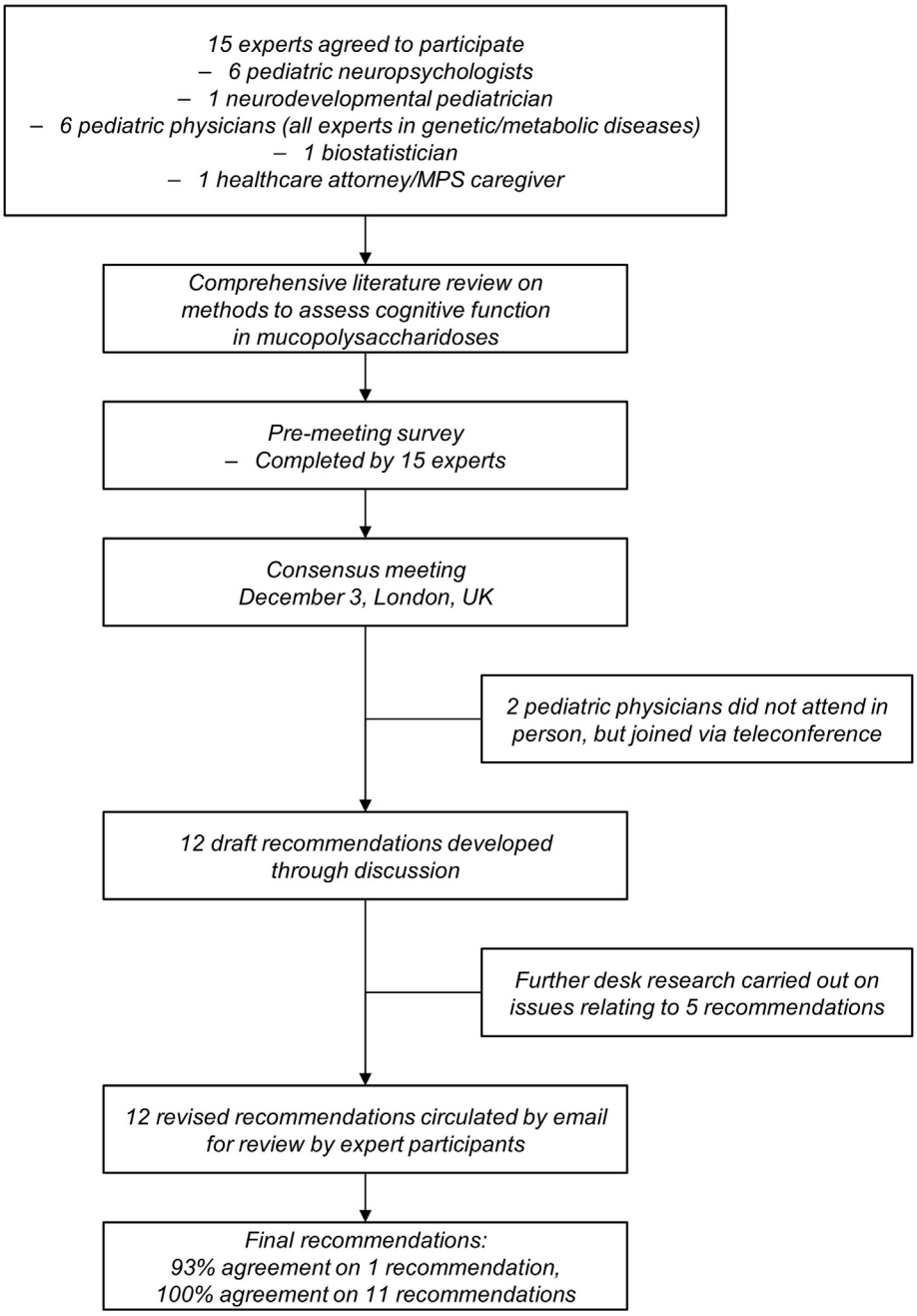

Fig. 1. Flow chart of the consensus process.

During the consensus meeting, all panel members participated in setting the agenda; deciding the topics for discussion and areas for recommendation. With regard to choice of which measurement instrument to use in each disease and age group, panel members were first asked to eliminate those that were not relevant or deemed not suitable for use, and then to rank those measurement instruments that remained. 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. When considered necessary, the literature review and survey results were consulted to provide evidentiary support and to remind panel members of their own priorities.

For some statements, it was decided during the meeting that additional information from the literature was needed, and several panel members agreed to provide that information after the meeting. This information was incorporated into the statements before they were presented to the panel members for final approval.

Following the consensus meeting and supplementary research, a full draft of all consensus statements was sent by email to the panel members for comment. In instances where the position of the panel was not clear, further surveys were sent to all panel members to further explore the topic in question and to formulate potential recommendations. Suggested amendments were discussed and agreed via email and incorporated into the final statements presented here.

3. Results

In the pre-meeting survey, six members (all experts in psychological testing) of the 15-person panel provided input into which of the 14

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Table 1
Proportion of respondents stating that a particular measurement instrument should be considered for discussion.

Category	Instrument	Proportion of positive respondents (n = 6)
Test for children <6 years of age	Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) [28]	100%
	Mullen Scales of Early Learning (MSEL) [29]	50%
	Griffiths Scales of Child Development, Third Edition (Griffiths-III) [30]	33%
	Differential Ability Scales, Second Edition (DAS-II) [31]	67%
	Wechsler Preschool and Primary Scales of Intelligence, Fourth Edition (WPPSI-IV) [32]	67%
	Stanford Binet Intelligence Scales, Fifth Edition (SB5) [33]	17%
	Kaufman Assessment Battery for Children, Second Edition (KABC-II) [34]	100%
	Leiter International Performance Scale, Third Edition (Leiter-3) [35]	83%
Observer-reported outcomes, adaptive Skills	Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) [36]	100%
	Scales of Independent Behavior, Revised (SIB-R) [37]	50%
	Adaptive Behavior Assessment System, Third Edition (ABAS-3) [38]	50%
>6 years of age	Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) [39]	67%
	Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V) [40]	67%
	Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) [41]	67%

Table 2
Assessment of the importance of measurement characteristics (scale, 1–10).

Characteristic	Importance score (n = 13)				
	Mean	SD	Median	Min.	Max.
Sensitivity to change	9.08	0.93	9	7	10
Feasibility for the specific disease	9.08	1.26	10	5	10
Applicability to a range of functional levels	8.92	1.56	9	7	10
Development characteristics of the test	8.46	1.94	8	7	10
Cross-cultural validity	8.23	1.74	8	4	10
Error of measurement	8.08	1.83	8	7	10
Availability of modern normative data	7.77	0.95	8	6	10
Concurrent validity	7.77	1.36	8	5	10
Content of face validity	7.54	1.44	8	5	10
Availability and familiarity	7.54	1.04	8	5	10
Construct validity	7.46	1.24	8	4	10
Interpretability – MCID[a]	7.23	1.98	8	5	9
Ease of administration	7.15	1.13	8	4	10
Additions by responders (n = 1 for each)					
Ability to reflect actual cognitive ability and not merely behavioral aspects of the child on that day	8.00	–	8	8	8
Acceptability to the participant	7.00	–	7	7	7

[a] MCID, minimal clinically important difference.

measurement instruments should be considered during the consensus meeting. The results are shown in Table 1. The instruments that all respondents indicated they would consider were the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III); the Kaufman Assessment Battery for Children, Second Edition (KABC-II); and the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3). The Stanford Binet Intelligence Scales, Fifth Edition (SB5) was the least considered; only one respondent wanted to include this instrument in discussions. Full descriptions of each of the instruments discussed in this article and an explanation of technical terms can be found in Janzen et al. elsewhere in this issue of *Molecular Genetics and Metabolism* [27].

Thirteen of the 15 panel members submitted their assessment of the importance of the 14 measurement characteristics of the tools to be discussed (Table 2). "Sensitivity to change" and "feasibility for the specific disease" were rated the most important characteristics for measurement tools. "Ease of administration" received the lowest score; although there was not much variability between the scores given each characteristic. Median scores ranged between 8 and 10. Two further characteristics were added, each by one respondent: "ability to reflect actual cognitive ability and not merely behavioral aspects of the child on that day", which received a score of 8, and "acceptability to the participant", which received a score of 7.

At the conclusion of the consensus meeting, a series of 12 initial consensus recommendations was presented to the group. Following the meeting, further background research and discussion and revision of the draft statements via email led to 93% consensus (14 of 15) on the first statement and full consensus, indicated by expression of agreement by all expert panel members, on the remaining 11 statements. All are described below.

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

Of the available tools for evaluating cognitive function in this age group, both the Bayley-III (and earlier versions of this measure) and Mullen Scales of Early Learning (MSEL) have been used extensively in clinical studies of mucopolysaccharidoses in the past [6–9,14,15,42–61], and both have been shown to be feasible and sensitive to change in patients with these conditions [8,12,42–45]. Although earlier versions of the Griffiths Scales of Child Development have also been used to study the characteristics, natural history and treatment outcomes in mucopolysaccharidoses, experience with the latest iteration is limited. Furthermore, the absence of validated translated versions of the Griffiths-III and the requirement for intensive training on the test indicate that it is not recommended for use in clinical trials currently, although this may change in the future.

The availability of validated translations of each measurement tool is particularly important given the multinational nature of most trials for mucopolysaccharidoses. The Bayley-III has been translated and validated in multiple languages, making it an attractive option for use in multicenter studies, whereas the MSEL has been translated in only a few countries. Another distinguishing factor between the Bayley-III and MSEL is the recency of the underlying normative data (Bayley-III, 2004; MSEL, 1980s) [62]. Generally, performance may be overestimated in tests that have normative data more than a decade old due to the Flynn effect of increasing IQ over time [63].

A show of hands from panel members indicated that the Bayley-III was used most often in patients under 3 years in this group, although it is not yet available in all countries. It was acknowledged that the relatively narrow development age range of the Bayley-III (1–42 months) compared with other instruments (MSEL, 0–68 months; Griffiths-III, birth–6 years) may necessitate transition to an alternative instrument in long-term studies.

With these factors in mind, there was 93% consensus among panel members that the Bayley-III may be the most suitable instrument for widespread use in clinical trials evaluating cognitive function in patients with MPS I, II or III, based on the widespread availability of validated translations of this instrument and the recency of its normative data. One panel member did not agree with this recommendation, preferring a statement recommending both the Bayley-

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III and the MSEL; the choice depending on the clinical trial design and the feasibility of use in the population being studied.

2. **For trials evaluating the effect of treatment in children with MPS I, II or III of all ages, the recommended instrument to measure adaptive behavior is the Vineland, using the extended interview format**.

Rationale

Measures of adaptive behavior help to put scores of cognitive function into context. A show of hands by panel members indicated that the majority used the Vineland-2 most often when evaluating children with MPS I, II or III. The Vineland-3 would also be appropriate, but has only recently been introduced. The Scales of Independent Behavior, Revised (SIB-R) was viewed as out of date and is rarely used by this group. The Adaptive Behavior Assessment System, Third Edition (ABAS-3) is never used by this group. These comments are consistent with the number of published studies that have used the Vineland-2 (27 studies), SIB-R (9 studies) and ABAS-3 or prior versions (0 studies) in patients with mucopolysaccharidoses [7,9,12,14,43–46,48,50,51,55,56,64–79].

The recently updated Vineland-3 benefits from modern normative data (2014–2015); especially compared with the SIB-R (1990s), which is viewed as out of date. The Vineland-3 is also well correlated to changes in cognitive function compared with the SIB-R and ABAS-3 [80], and it can be used to determine which battery of cognitive tests is suitable based on developmental age [68]. With these factors in mind, the Vineland-3 is recommended as an instrument for evaluating adaptive behavior in patients of all ages with mucopolysaccharidoses.

The panel noted, however, that to be fully informative, the extended interview format (approximately 45 min) of the Vineland-3 must be used. Wherever possible when using this format, the same caregiver should be the informant on every visit to ensure consistency across time points, and examiners must receive training on how to administer patient/caregiver interviews most effectively. A disadvantage of the Vineland is the limited availability of the latest version (3) in non-English languages. However, strong correlation between the second edition (Vineland-2) and the Vineland-3 means that the earlier version of this instrument, which is widely available in non-English languages, can still be used in clinical studies as an alternative. The newer version also has an improved parent rating form, which may provide a useful alternative assessment during follow-up visits or when trained interviewers are not available.

3. **For (multinational) trials evaluating the effect of treatment in children with MPS I aged 3 years and over (age equivalent), the recommended instruments to measure cognitive outcome are the Wechsler tests. We recognize the utility of the Kaufman Assessment Battery for Children, Second Edition (KABC-II) and the Differential Ability Scales, Second Edition (DAS-II) in particular populations because of their reduced fine motor demand and less emphasis on speed of performance compared with the Wechsler tests**.

Rationale

Of the instruments available for evaluating cognitive function in patients with a developmental age of 3 years and over, two were not recommended for use in patients with MPS I. The Leiter-3 was originally designed for use in deaf children and, although the nonverbal nature of the instrument may have some benefits in this population, its lower reliability and validity compared with other available instruments meant that this test was not deemed the strongest candidate for use in MPS I clinical studies. Similarly, the SB5 has a large verbal component that makes it suitable for use in older patients (e.g. 5–6 years), but not in children as young as 3 years with MPS I.

The DAS-II has been used successfully to assess the longitudinal effects of HCT in children with MPS I [12]. It was noted that the instrument can take a long time to administer (approximately 20–40 min) and includes a number of tests that rely on previous learning, which can be challenging for severely affected patients. The DAS-II is only available in English, although there is a Spanish-language supplement available in the early years version. Naturally, this will limit its utility in multinational clinical trials; however, the wide developmental age range suitable for the DAS-II (2.6–18.0 years) makes it an attractive option for longitudinal study within English- or Spanish-speaking populations.

The Wechsler Preschool and Primary Scales of Intelligence, Fourth Edition (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 [8,15]. Some patients with low developmental ages may struggle with the fine motor demand and greater emphasis on speed of performance of the WPPSI-IV compared with the DAS-II and KABC-II. On the other hand, the WPPSI-IV can be useful when monitoring children who have been treated successfully and continue to increase their cognitive skills. Importantly, minimally clinically important difference (MCID) values have been calculated for the WPPSI-IV. A potential limitation is the narrow age range of the WPPSI-IV (2.6–7.7 years), which would require patients to transition to another test once the ceiling has been reached. However, it is unlikely that many patients with MPS I will show an increase of >4 age-equivalent years during a clinical trial; plus, similarities in design mean that transition from the WPPSI-IV to the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V; age, 6.00–16.11 years) is likely to be straightforward.

The panel acknowledged the utility of the KABC-II non-verbal scale owing to its wide age range for use (3–18 years), good reliability and validity. It also benefits from ease of administration in children with hearing problems and in older patients with low levels of cognitive function. However, it was deemed to be less sensitive to change than the Wechsler tests in patients who are capable of performing the tasks required in the WPPSI-IV and WISC-V, and may be most useful in older low-function children with MPS I. Thus, the consensus among panel members was that age-appropriate Wechsler tests should be used in patients with MPS I whenever possible, unless the clinical trial design benefits from alternative measures.

4. **For (multinational) trials evaluating the effect of treatment in children with MPS II or III aged 3–18 years (age equivalent), the recommended instruments to measure cognitive outcome are either the DAS-II or the KABC-II. The use of only the non-verbal domain/index may be appropriate if this is necessary to ensure consistent application between trial sites across multiple countries. Other factors to consider in the selection of the measure and on whether to use the entire test or only the non-verbal domain are: the need for verbal interaction; the time required to administer the test; fine motor requirements; availability of normative data; availability of translations**.

Rationale

The SB5 and Leiter-3 were not considered appropriate for use in children with MPS II or III for the same reasons outlined above for MPS I.

As has been mentioned above, the WPPSI-IV and WISC-V can be challenging for patients with low development ages owing to task demands on fine motor skills and sustained attention span, and the emphasis placed on speed of performance. With this in mind, the panel felt that the Wechsler tests are not suitable for the assessment of cognitive function in children with MPS II or III, who often exhibit behavioral abnormalities and have low levels of cognitive function. If treatment is sufficiently effective to allow the child to increase the rate of skill development, as is observed in HCT in MPS I,

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and in all attenuated forms of mucopolysaccharidoses, then the Wechsler tests may be preferred.

The DAS-II has a large verbal component, which may pose a challenge to some patients with MPS II or III; although it is possible to calculate a cognitive function score based on the non-verbal subtests only. The DAS-II has been widely used in patients with MPS II and takes 20–40 min to complete, depending on the age and developmental capacity of the child [44,45,48,71,81].

The KABC-II has been found to be sensitive to change in patients with MPS III [43], and it is available and validated in multiple languages. Its non-verbal components 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. This is particularly useful in patients with low developmental ages. For such patients, use of the non-verbal components only may be acceptable in some clinical trial settings with sufficient justification, especially in multinational studies or when patients must cross borders to take part in such initiatives.

Considering the above, the consensus of the panel is that the DAS-II or the KABC-II should be used in patients with MPS II or III with a developmental age of 3 years or older.

5. **In a set of trials within the same program, we recommend using the same test protocol for all trial sites worldwide; including, if possible, the same test editions or, if not, the most recent**.

Rationale

Minimizing inter-rater variability is crucial to providing reliable data in multisite clinical trials [82], so it is important that the same test protocol – including the specific measurement instrument, choice of subtests and method of administration – is applied to consistently high standard across all trial sites in a single study, but also across an entire program of clinical trials for a given treatment or disease. Importantly, the study protocol should be feasible for use in multiple centers and across multiple languages and cultures, and the risk of loss of accuracy and reliability of data in multicenter studies should be offset through the use of precise and simple measurements obtained by experienced, highly trained examiners [68,83].

Wherever possible, the same version of the chosen measurement instrument should be used across all sites. Depending on the test being used, there can be great differences between versions, both in terms of the normative data underlying them and in their reliability and applicability in the specific patient population being studied, which can threaten trial data validity. In multinational studies this may present a challenge owing to the variable availability of translated and validated versions of some instruments in non-English-speaking countries.

In cases where the most recent version of a measurement instrument is not available in the local non-English language, it may be acceptable to make use of an earlier version of the same instrument across all sites when the two editions correlate well.

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 developmental outcome measures other than those recommended in these consensus statements**.

Rationale

Although these recommendations provide guidance on the most robust and widely available instruments to use to evaluate cognitive function in patients with mucopolysaccharidoses in future multinational clinical trials, this does not discount the value and use of natural history data for these disorders that were generated using other cognitive outcome measures.

For example, the MSEL have been used extensively in the study of cognitive function in patients with MPS I, II and III [9,12,14,44,45,48,50,57], and the Leiter-3 has played an important role in enhancing current understanding of the natural history of cognitive decline in patients with MPS III [50]. The panel strongly recommends that the value of these data be recognized and utilized as a basis for further study of the neurodegenerative changes in patients with mucopolysaccharidoses.

7. **We strongly recommend building and sustaining an infrastructure to share natural history data**.

Rationale

As with many rare conditions, natural history data relating to cognitive function in patients with mucopolysaccharidoses are scarce. The geographic spread of patients with these conditions makes it likely that data are available for small cohorts of patients at individual treatment centers, with a variety of measurement instruments being used. These data provide valuable insights into the natural history of mucopolysaccharidoses, and the cumulative value of these findings is likely to be greater than the sum of their parts.

The panel strongly recommends the development of an infrastructure by which investigators around the globe can easily share and review each other's natural history data in a collaborative fashion. This will of course rely on the willingness of both industry members and investigators to collaborate. Recommendations for the design and implementation of such an initiative are beyond the scope of this article, but warrant further in-depth discussion.

8. **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 tool has not been validated in a country, we recommend the parallel use of a country-specific instrument to establish concurrent validity**.

Rationale

Ideally, all instruments used in a multinational trial will have been translated and validated for use in each country and language that is taking part in the study, taking into account cultural variations. This includes validation of normative data to ensure its appropriateness for use in the host country. If a fully translated and validated measurement instrument is not available for use across all study sites, the choice of normative data against which to evaluate changes in cognitive function becomes an important factor in the potential success of the trial.

In the absence of a validated translation of the measurement instrument, an additional country-specific test should be used in parallel to the main assessment to establish the concurrent validity of the two tests in each country. This procedure will help to calibrate the findings of the primary measurement instrument in each country.

9. **We recommend the use of a standard written translation of the measurement instrument, including the administration instructions, produced by a professional translator with experience with 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**.

Rationale

Translation of cognitive measurement instruments to non-English languages and cultures is a precise task that must be carried out in advance of a trial by a skilled professional translator with knowledge of psychological tests [84]. The translation should be provided as a standardized written script for use by all assessors when administering the test. Back-translations should always be carried out by a third party who is a native speaker to ensure the appropriateness of the translation. Where possible, the translation should also be reviewed by a local psychologist/psychometrician to evaluate the wording and the cultural suitability of the translated test.

We do not recommend that the assessor translate the instructions as the test is administered. Similarly, we do not recommend that verbal instructions to patients are translated by an interpreter in

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the room. These approaches may de-standardize the instructions provided to study participants, therefore introducing unnecessary variability.

For non-native patients attending a study site in another country, it is acceptable to provide a translator for the testing session to give non-test-related instructions and assistance. However, the translator must have received appropriate training so as not to inadvertently interfere with standardized test administration.

10. **Assessors must be qualified in administering neurodevelopmental measurement instruments and have experience in their use, preferably with the disease being evaluated. Assessors need to be trained in person to perform the specific measurements in the protocol and should be subject to periodic quality control and auditing of scoring**.

Rationale

As has been mentioned already in this article, poor inter-rater reliability, along with poor interview quality and rater bias, can significantly impact the validity and statistical power of clinical studies [82,85]. The skilled administration of neurodevelopmental measurement instruments is therefore essential to the generation of reliable and robust data [68].

The behavioral challenges that manifest in some patients with mucopolysaccharidoses mean that familiarity with these conditions is extremely beneficial when administering cognitive assessments [83]. In particular, assessors should have enough clinical experience with patients who have the disorder being evaluated at all levels of development to recognize and judge the severity of each cognitive symptom rated in the scale, and to determine the level of difficulty of tasks that a child with that condition is likely to be able to perform within the protocol [68]. Furthermore, all assessors must be trained in the use of the test as per the study protocol, including what constitutes an appropriate environment for assessment and how to recognize when a test result is not valid and data cannot be used.

We acknowledge that there are challenges in maintaining reliable and valid cognitive assessment for mucopolysaccharidoses. There is no current, established, published standard for training, supervision and ongoing maintenance of the quality of cognitive assessment, scoring, and data management in clinical trials. However, it is imperative that even experienced assessors receive regular re-training and are subject to quality control and monitoring of test administration.

11. **We recommend analyzing and reporting age-equivalent scores in all trials, and standard scores where possible**.

Rationale

When considering endpoints for cognitive function in clinical trials there are three potential metrics that could be used: age-equivalent scores (i.e. the test score achieved by a healthy individual of that age), developmental quotient (i.e. ratio of age-equivalent scores to chronological age), and standard scores derived from test normative data.

Standard scores have traditionally been used as the primary measure of cognitive function in psychological tests; however, their use is problematic in patients with low levels of cognitive function [68]. The standard scores in most tests have a high floor that many patients with mucopolysaccharidoses will score below, making the scores insensitive to any change. Age-equivalent scores have been used in patients with mucopolysaccharidoses to examine treatment effects using both cognitive and adaptive behavior scales [7–9,86]. They are easily interpretable and, when used in a longitudinal context in neurodegenerative diseases, provide information about whether a child is developmentally progressing, stagnant or declining. Standard scores and developmental quotients do not provide this context, but do provide valuable information about the discrepancy between the patient's development and that of typically developing peers [68]. Thus, it is preferable to obtain both age-equivalent scores and standard scores or developmental quotients when possible.

12. **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 the test results**.

Rationale

There is no single test that provides precise measures of all developmental domains from infancy to adulthood, making it necessary to use different tests across age boundaries. By overlapping two psychometric tests it is possible to cross-validate the test findings, to see what the discrepancy is and adjust for that discrepancy in the trajectory [87]. The choice of initial and subsequent tests, the age-equivalent when the transition should occur, and the approach to transition between them, should be defined in the study protocol and/or statistical analysis plan.

4. Discussion

The promise of novel therapies that address the varied CNS manifestations of mucopolysaccharidoses is encouraging for both families affected by these devastating conditions and the clinicians who treat them. However, before these treatments can be made available to patients, it is essential that reliable and consistent data are obtained so that we can fully understand and feel confident of the effects they have on neurocognitive development. This consensus document has been developed to provide a clear set of considered recommendations based on all available evidence and decades of experience of designing and administering neuropsychological studies in patients with mucopolysaccharidoses and related conditions.

Avoiding missteps in the design and implementation of clinical studies to evaluate natural history and treatment effects on cognition and adaptive behavior requires an in-depth knowledge of the relative strengths and weaknesses of the available measurement tools and when it is appropriate to use them. Investigators must also consider which scoring system to use to ensure that improvement is detectable, and also have sufficient practical experience with the conditions being studied to predict and circumvent potential methodological challenges associated with the somatic and behavioral features of the disease. Until now, the formal guidance available to study sponsors and clinicians working the field of mucopolysaccharidoses has been limited and varied [46,68,88,89], with much of the advice provided by the authors of this article. By bringing together recognized experts in the field and facilitating consensus development through a structured Delphi-based process, we believe the recommendations listed here will provide much-needed clarity to a complex yet important area of study.

It was not possible to address here every issue associated with the study of neurocognition and adaptive behavior, as some aspects are beyond the scope of this consensus development process. For example, it is desirable to calculate MCID values for each of the cognitive tests discussed, but this is not currently possible without further research. Similarly, there needs to be extensive and dedicated discussion of how to develop and maintain an infrastructure for the sharing of natural history data among investigators. Both issues warrant investigation and action as a matter of priority.

This is the first example of such a consensus panel on pediatric cognitive and adaptive measures as endpoints in clinical trials in lysosomal or other neurodegenerative diseases. As new treatments are developed, such a disease-specific consensus may be a model for conditions other than mucopolysaccharidoses. It should be noted that the recommendations described here reflect current understanding and experience with the instruments available. New tools and new editions and translations of current tests will inevitably become available in the future. With this in mind, it will be important that this guidance is reviewed and updated regularly (e.g. every 3 years) by a panel of appropriate qualified experts.

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5. Conclusion

The modified Delphi process described here was successful in generating 12 expert consensus recommendations relating to best practice for the design and conduct of clinical studies for novel therapies for MPS I, II and III. It is hoped that the guidance provided in this article will contribute to the development of robust clinical programs and study protocols that will help accelerate the development of novel therapies to address the neurologic impact of these devastating conditions, and enable clinicians, regulatory bodies and patients/caregivers to derive a clear unbiased understanding of the relative benefits of the treatment options available to them.

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Author contributions

- 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, Margaret Semrud-Clikeman, and Maria Escolar took part in the consensus meeting, conducted literature analyses to provide supplementary evidence for consensus development, and provided critical appraisal of the manuscript.
- Lorne Clarke, Berendine Johanne Ebbink, Robert Giulgliani, Paul Harmatz, Melissa Hogan, Simon A Jones, Shauna Kearney, Joseph Muenzer, Stewart Rust, Frits A Wijburg, and Zi-Fan Yu took part in the consensus meeting and provided critical appraisal of the manuscript.
- Darren Janzen conducted an exhaustive literature review as source material for the consensus meeting and attended and observed the consensus meeting.
- Elsa Shapiro assisted in designing the pre- and post-meeting surveys, attended the consensus meeting, conducted literature analyses to provide supplementary evidence for consensus development, and edited the manuscript.

Conflicts of interests

- Johanna H van der Lee has no conflicts of interest.
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- Lorne Clarke has no conflicts of interest.
- Berendine J Ebbink has no conflicts of interest.
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- Joseph Muenzer has been a consultant to Shire, BioMarin Pharmaceutical, Sanofi Genzyme, PTC Therapeutics, Janssen Pharmaceuticals, Green Cross, and Eloxx. He serves on advisory boards for Genzyme, BioMarin, Shire, and Eloxx. He is currently the principal investigator for a Phase I/II and Phase II/III intrathecal enzyme replacement clinical trials for MPS II sponsored by Shire HGT.
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