Supplementary appendix

The modified real-time Delphi method for recommended clinical scales in VWM trials

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Introduction

The Delphi technique is a scientific method to reach expert-based consensus. A traditional Delphi study starts with an open questionnaire and uses multiple rounds of questionnaires to reach consensus among experts.[1] A modified Delphi study starts with a selected number of discussion topics, based on a literature review, to reduce the number of rounds needed for reaching consensus.[2] The real-time (rt-) Delphi study uses an online software tool to increase the efficiency of the process.[3] This method does not use successive rounds of questionnaires. Instead, participants can give their opinion on the online platform during a period of time. Participants are encouraged to give arguments for their choices. Participants can revise their answers as many times as they want based on the answers and arguments of other respondents. The process is stopped after a predefined stop criterion.

Methods

General

The EDELPHI 2021[4] was used, an open source software tool that provides all requirements needed for an rt-Delphi study. Participants were asked to indicate on a 5-point Likert-scale whether or not they agree to include a scale or questionnaire.[3] As predefined criteria, inclusion of a scale was defined by ≥75% of the participants agreeing on inclusion; exclusion was defined as ≤25% of the participants agreeing on inclusion; the end of the procedure was defined as consensus reached on all scales.

The expert panel consisted of the nine VWM consortium members. The procedure was executed between April 20, 2021 – May 20, 2021. An additional consensus meeting took place on December 3, 2021 on the subject of neuropsychological scales.

Input

Input for the topics to be discussed in this rt-Delphi procedure was provided by a systematic literature review, results of a recent Delphi procedure on metachromatic leukodystrophy (MLD) and the experts' opinion of the panelists (**figure 1**).

A systematic review of the literature published between 2000 and March 2021 was performed. The VU Libsearch machine was used to identify relevant publications on VWM in, amongst others, the Pubmed, Cochrane, Medline, and Embase databases (see **box 1** for complete search string). English, peer-reviewed studies in human subjects with five or more VWM patients were included for full-text analysis focusing on the use of scales and questionnaires. In total 2158 hits were screened on title and abstract by one physician reviewer (DHS). This led to the full text screening of 166 papers, during which all clinical scales and questionnaires of which the use was described in VWM patients were added to the list of discussion points. Very few scales and questionnaires have been used in VWM. From literature, only 4 scales were extracted.

Panelists were encouraged to suggest other scales that might be useful according to their experience; they suggested 15 questionnaires and scales, also based on the use of these scales in ongoing trials in various leukodystrophies. Recently, a Delphi procedure among experts on MLD resulted in a consented list of scales and questionnaires (unpublished data). Because MLD and VWM are comparable leukodystrophies, those scales were added to our rt-Delphi procedure. In total, 24 instruments were reviewed by the expert panel.

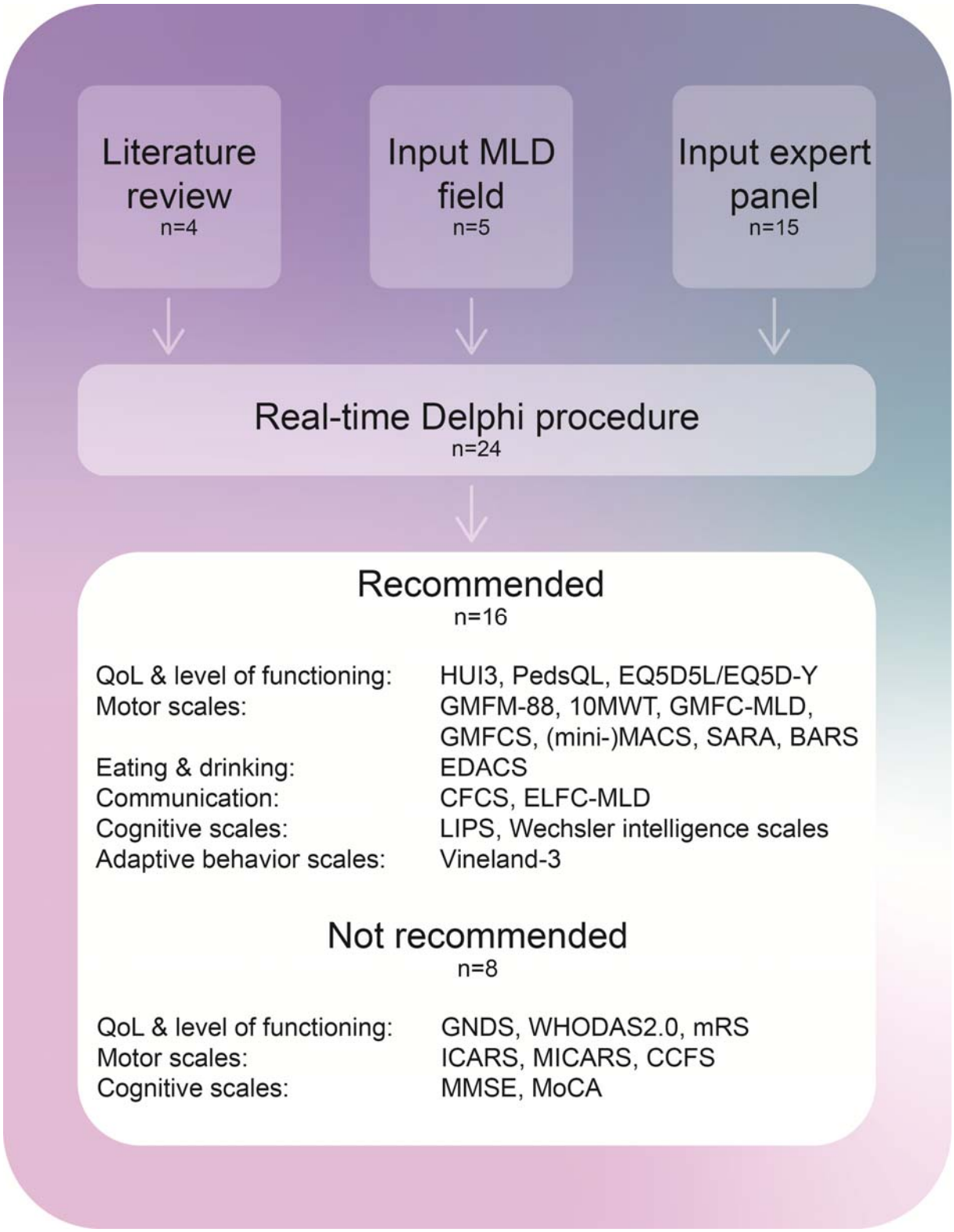

Figure 1. Flowchart of rt-Delphi procedure on scales and questionnaires. Number of instruments is indicated by 'n=...'

BARS, Brief Ataxia Rating Scale; CFCS, Communication Function Classification System; CCFS, Composite Cerebellar Functional Severity Score; EDACS, Eating and Drinking Ability Classification System; EQ5D/5L, EuroQol 5D/5L; EQ5D-Y,

EuroQoL5D-Young; ELFC-MLD, Expressive Language Function Classification - Metachromatic Leukodystrophy; GMFC-MLD, Gross Motor Function Classification - Metachromatic Leukodystrophy; GMFCS, Gross Motor Function Classification System; GMFM, Gross Motor Function Measure; GNDS, Guy's Neurological Disability Scale; HUI, Health Utility Index; ICARS, International Cooperative Ataxia Rating Scale; LIPS, Leiter International Performance Scale; MACS, Manual Ability Classification System; MMSE, Minimal Mental State Examination; MICARS, Modified International Cooperative Ataxia Rating Scale; mRS, Modified Rankin Scale; MoCA, Montreal Cognitive Assessment; PedsQL, Pediatric Quality of Life Inventory; QoL / QL, Quality of Life; SARA, Scale for Assessment and Rating of Ataxia; 10MWT, 10-meter Walk Test; Vineland-3, Vineland Adaptive Behavior Scales 3rd edition; WHODAS2.0, WHO Disability Assessment Schedule 2.0

Box 1. Search string and databases used for the literature review.

Search string

kw:(Vanishing white matter) OR ti:(Vanishing White Matter) OR ti:(VWM) OR kw:(Childhood ataxia with central hypomyelination) OR kw:(CACH) OR kw:(Childhood ataxia with central nervous system hypomyelination) OR hm:(Vanishing White Matter Leukodystrophy with Ovarian Failure) OR kw:(Vanishing White Matter Leukodystrophy with Ovarian Failure) OR kw:(Eukaryotic initiation factor 2B related dis*) OR kw:(Eukaryotic initiation factor 2B-related dis*) OR kw:(eIF2B-related dis*) OR kw:(eIF2B related dis*) OR kw:(eIF2B related leukodystroph*) OR kw:(eIF2B-related leukodystroph*) NOT kw:(animals) NOT en:(animals) NOT ti:(mimic)

Databases

BioOne, BioMed Central, SciELO Journals, Annual Reviews, Future Medicine, New England Journal of Medicine, MEDLINE, SpringerLink, Oxford Journals, BMJ Journals, World Scientific Journals, African Journals, NARCIS, ACP Journals, Bentham Science Journals, Public Library of Science, Karger Journals, PubMed Central, Institute of Physics eJournals and Archive, Cochrane Library, AMS Journals, PsycARTICLES, Hindawi eJournals, ScienceDirect, SAGE Journals, ACM Digital Library

Results and discussion

General

In total, 16 scales were recommended by the expert panel. The remaining 8 scales were not advised to be used in clinical trials in VWM (**figure 1**).

Scales

Patient- and proxy-reported outcome measures (PROMs) are questionnaires that evaluate patient's quality of life (QoL) and their level of functioning. The patient's perspective is central. The last decade, the use of PROMs has increased. Nowadays, they are considered essential in evaluation of therapy effects.[5]

The VWM natural history study used two similar PROMs: the Health Utilities Index Mark 3 (HUI3) and Guys Neurological Disability Scale (GNDS).[6]

The HUI3 assesses health-related QoL and has been applied extensively as outcome measure for different neurological disorders.[6, 7] It has one scale to measure vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. HUI scores can be assessed from the age of 1 year onwards. There are possibilities for proxy-assessment, self-assessment and interviewer-assessment, depending on the age and degree of disability.

The GNDS is used to assess neurological disability in the previous month.[8] It is a comprehensive scale that evaluates 12 categories of ability. This scale does not use different versions for different subgroups. This results in a score between 0 - 60, in which a higher score means a higher level of disability. The GNDS is validated in multiple sclerosis (MS) patients from 18 years of age. In VWM it has been used in patients from eight years of age on.[6]

The availability of previous data for the HUI3 and GNDS in VWM made these scales advisable in VWM. Since the scales are very similar and the scores correlate

closely[6], collecting both was not considered useful. The HUI3 was preferred over the GNDS because of its wider applicability regarding age.

The Pediatric Quality of Life Inventory (PedsQL) assesses physical, emotional, psychosocial, social, and school functioning. It has different versions for age groups 2-4, 5-7, 8-12, and 13-18 years.[9, 10] The PedsQL is validated in non-specific pediatric populations. The PedsQL has been widely applied in pediatric populations, among which in MLD.[11] Thus, it was preferred by the consortium.

The EuroQol 5D/5L (EQ5D5L) assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[12] It has different scales for age groups 4-7, 8-15, and >15 years. The EQ5D/5L is the updated version of the EQ5D/3L. For children the EQ-5D-Youth was developed.[13] A self-complete version can be used for children aged 8-15 years. For children aged 4-7 years, a proxy version should be used. It is validated in non-specific populations. Reference values for different subgroups of patients and geographical regions are increasingly available.[14] It is widely used and preferred by regulatory authorities, such as the European Medicine's Agency. Therefore, the consortium advised to collect this scale.

WHO Disability Assessment Schedule 2.0 (WHODAS2.0) evaluates six domains of functioning, including cognition, mobility, self-care, getting along, life activities, and participation. The scale was developed for and validated in adults, but the use is described in children of 12 years and older.[15] The WHODAS-Child was developed for children. This version can be completed by children of age 11 and older or completed by parents/guardians for children of age 10 and younger.[16] The WHODAS2.0 is not recommended by the consortium. The consortium argued that it has never been used in VWM or other leukodystrophies and has limited additional value compared to the HUI and EQ5D-5L.

The Modified Rankin Scale (mRS) is a robust and fast scale to classify the degree of disability in daily life. It was developed for patients with a stroke, but it is also used in other neurological conditions.[17] It was not recommended by the consortium. Main arguments for this decision were that the scale is not suitable to measure change in the context of clinical trials because it has a very low sensitivity and does not take cognitive function into account.

Motor function

The gross motor function measure (GMFM-88) is designed to measure changes in gross motor function over time in handicapped children. The GMFM-88 is the original 88-item measure. Items span the spectrum of gross motor activities in 5 dimensions: 1) lying and rolling, 2) sitting, 3) crawling and kneeling, 4) standing, and 5) walking, running, and jumping. The GMFM-66 uses a 66-item subset of the original 88 items. The 10 steps walk test (10SWT) is a measure from the GMFM-88 that can be applied separately to assesses gait quality. The tool has been validated for children, aged between 5 months and 19 years, with brain injury.[18] It has been applied in leukodystrophy trials,[19] is currently applied in several ongoing leukodystrophy trials (unpublished data) and therefore preferred by the consortium, although some comment that the clinical meaningfulness of a percentage of change is unclear.

The 10 meter walk test (10MWT) assesses walking speed over a short distance.[20, 21] Different normative values apply per age group. It is validated in individuals ≥ 2 years.[22] It is easily applicable, but not in non-ambulant patients. It was preferred by the consortium because of its easy applicability and quantifiability.

The Gross Motor Function Classification System (GMFCS) and Manual Ability Classification System (MACS) have been developed to score the level of motor functioning in patients with cerebral palsy. Those classification systems are easy-to-

use and not time consuming to obtain. The use of these scales outside cerebral palsy is debated[23], but they have proven useful in numerous different conditions.

The GMFCS is a 5-level clinical classification system validated in children with cerebral palsy aged <18 years.[24] Age-appropriate levels are available for children below 2 years, from 2 to 4 years, 4 to 6 years, 6 to 12 years, and 12 to 18 years. The scale is not validated in VWM patients, but its use is described in a few VWM studies.[25-27] The consortium argues that it is a simple and useful scale and recommend it in VWM patients, although, its insensitivity for change was considered a limitation.

The Gross Motor Function Classification for MLD (GMFC-MLD) is a modified version of the GMFCS and has been developed for children and adolescents with MLD with ages between 1.5 and 18 years.[28] It has clinically meaningful scores, has been used in clinical trials and can easily be assessed from medical records, which makes it a valuable tool regarding historical controls.[28] For these reasons, the consortium recommended the GMFC-MLD.

The MACS describes how children use their hands to handle objects in daily activities.[29] The MACS is validated in children with cerebral palsy aging from 4 to 18 years. The Mini-MACS is developed for children between 1 and 4 years of age. The scores range from 1, which means normal, to 5, which means severely impaired. The MACS is not validated in leukodystrophies. The system is, however, used in MLD too (unpublished data). The consortium stated that collection might be useful to quantify fine motor function. Some members mentioned that it is not sensitive to change and scoring might be subjective.

The Scale for Assessment and Rating of Ataxia (SARA)[30] and Brief Ataxia Rating Scale (BARS)[31] assess cerebellar ataxia in a semi-quantitative way. There are no different versions for different subgroups for the SARA and the BARS, although

age-dependent interpretation is advised for all ataxia rating scales in children below the age of 13.[32] Although ataxia is typically a dominating clinical feature in VWM, some patients are predominantly spastic, hampering interpretation of ataxia scales. However, both can be used to measure degree of motor disability, change over time and are widely used. The SARA and the BARS were the ataxia scales preferred by the consortium.

The SARA scale is validated in a wide range of populations, including MS and spinocerebellar ataxia (SCA). It is validated in persons aged eight and older.[33] The SARA was recommended because it is widely used and also collected in the MLD research field (unpublished data).

The International Cooperative Ataxia Rating Scale (ICARS) was developed to quantify the level of impairment as a result of ataxia in hereditary ataxias (non-specific patient population, but mainly used in SCA and Friedreich ataxia).[34-36] Posture and gait disturbance, kinetic function, speech disorder, and oculomotor disorders are rated. The ICARS is validated in individuals ≥ 4 years. This scale does not use different versions for different subgroups. The Modified International Cooperative Ataxia Rating Scale (MICARS) was developed by adding seven additional tests to the ICARS in kinetic function: decomposition of leg movement, decomposition of leg tapping, the rebound of the arms and overshoot of the arms, speech disorders, and oculomotor function.[31] Further instrument characteristics correspond to the ICARS. None of the experts preferred the ICARS and MICARS.

The BARS is an abbreviated version of the MICARS.[31] The BARS is validated in patients ≥ 4 years from heterogeneous populations (healthy children, SCA, and brain tumors) and it highly correlates with the ICARS, MICARS and the SARA. The scale has been used in other diseases including Niemann-Pick and MS.[37]Advantages of the BARS include that it is very brief and it is validated in populations ≥ 4 years.

Therefore, the consortium members preferred the BARS over the ICARS and the MICARS.

The Composite Cerebellar Functional Severity Score (CCFS) is a clinical score to rate ataxia.[38] It uses different functional tests, namely the nine-hole pegboard test and the click test. The test is validated for persons ≥7 years of age.[39] As far as we know, only age-dependent normative values are available ≥20 years.[38, 40] None of the experts preferred the CCFS.

For motor tests that have been validated up to 18 years, the consortium assumed that their use can be extended to adults.

Eating and drinking

The Eating and Drinking Ability Classification System (EDACS) describes feeding and swallowing in everyday life in a five-level classification system.[41] Level 1 implicates normal eating and drinking abilities and level 5 means that the patient is unable to eat or drink safely. The EDACS is validated in children with cerebral palsy from 2 to 18 years.[41] This classification system does not use different versions for different subgroups. The consortium advised to collect this scale because it is easy to use and it is collected within the field of MLD (unpublished data). Some consortium members, however, experienced that the EDACS is not sensitive and might be subjective.

Communication

The Expressive Language Function Classification – MLD (ELFC-MLD), has been specifically developed in MLD. The ELFC-MLD has been validated in children with MLD aged 1.5 years and older.[42] The consortium agreed that collection is useful in VWM because it is simple, fast and robust.

The Communication Function Classification System (CFCS) describes everyday communication performance by using five levels to classify the effectiveness of communication.[43] The CFCS is validated in children with cerebral palsy from 2 to 18 years.[43] This classification system does not use different versions for different subgroups. Because of its easy use, it was preferred by the consortium. However, the consortium also emphasizes that, like the ELFC-MLD, it is not very sensitive to change.

Cognition

The Leiter International Performance Scale (LIPS) is designed for nonverbal assessment of cognitive functions in children, adolescents, and adults.[44] The test has been validated for an age range of 2 to 20 years, but its use can be extended to older ages. It measures nonverbal intelligence in reasoning, visualization, visuospatial memory, and attention and can be administered completely without the use of oral language, including instructions, and requires no verbal response from the patient. The engaging, nonverbal format makes it ideal for use in individuals with speech/language disorders, as well as those who do not speak English. It provides individual subtest scores and numerous composite scores that measure intelligence and discrete ability areas. These scores identify strengths and weaknesses in individual skills and skillsets. This scale was preferred by the consortium.

The Montreal Cognitive Assessment (MOCA) is a widely used one-page measure with 30 items, specifically useful in subcortical dementia and therefore applicable in leukodystrophies, but can only be used in adults.[45, 46] The consortium recognized its value as cognitive screening tool in adults with VWM, but felt it was too crude for use in clinical trials.

Minimal mental state examination (MMSE) is an easy-to-use cognitive test.[47] This scale does not use different versions for different subgroups but can only be used in adults. It is widely used as cognitive screening tool. The MMSE is not validated in VWM, but a few VWM studies described the use adult patients.[48, 49] The consortium did not recommend the MMSE in VWM.

The consortium agreed on the use of extensive neuropsychological tests to assess cognitive function, in particular the Wechsler intelligence scales for different ages.[50-52] The consortium members argued that in the context of trials extensive testing is appropriate. VWM and other leukodystrophies are associated with subcortical dementia, which is mostly characterized by loss of processing speed, problems with executive functioning, lack of initiative and flat affect, while verbal IQ is relatively preserved. The Wechsler scales comprise subtests that specifically assess these domains.[53]

The Vineland Adaptive Behavior Scales – third edition (Vineland-3) assesses communication, daily living skills, and socialization.[54, 55] There are different versions: interview form (all ages), parent/caregiver form (all ages), and teacher form (ages 3-21 years). It is used in the diagnosis and classification of behavioral, psychiatric, and intellectual problems. It has not been validated in VWM or other leukodystrophies. The Vineland scales are preferred as outcome measure by the FDA and were preferred by the consortium to assess behavior.

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