Supplemental Table 1: Results of voting on the original consensus statements from 2020. At the beginning of the process to update the consensus, all authors participated in an anonymous voting session. For each of the original statements, authors were asked to vote on whether the statement should remain unchanged, be adapted, or be deleted.

Statement #	Wording of original consensus statement from 2020	Voting results		
		unchanged	adapt	delete
1	Traditional SMA types (e.g. type 0, 1, 2,3, 4) alone are not sufficient to define patient populations who might benefit most from gene therapy. In symptomatic patients age at onset, disease duration and motor function status at the start of treatment are the most important factors that predict response to treatment.	14	4	1
2	In presymptomatic patients *SMN2* copy number is the most important predictor of clinical severity and age of onset. As long as no better biomarkers or predictors are available, treatment decisions for presymptomatic patients should primarily be based on *SMN2* copy number. Determination of *SMN2* copy number needs to be performed in an expert laboratory with adequate measures of quality control.	12	7	0
3	Approval of gene therapy for SMA with Zolgensma® is based on clinical trials with patients with SMA less than 6 months of age. Additional data of patients up to 2 years and weighing up to 13.5 kg are made public through congress presentations. These data mainly come from non-systematic data collection in the US, where Zolgensma® is approved up to the age of 2 years. When administered after the age of 6 months and/or in advanced stages of the disease, parents or patients should clearly be made aware that there are so far no published data on efficacy and safety. In this patient population it is particularly important for physicians to discuss the benefit/risk ratio and to carefully manage parents' or patients' expectations.	3	15	1
4	In patients presenting symptoms at birth, treated after a long disease duration, or with already severe evolution, parents should be clearly made aware that despite the use of gene therapy there is a high risk of living with a very severe disability. Palliative care should be discussed as an alternative treatment option in these circumstances.	17	2	0
5	Since the risk of gene therapy increases with the dose administered and since the dose is directly proportional with the weight, patients above 13.5 kg should only betreated in specific circumstances. For these patients, treatment with other disease modifying therapies or future intrathecal administration of Zolgensma® should be considered as an alternative.	11	8	0
6	Until now there is no published evidence that combination of two disease modifying therapies (e.g. gene therapy and nusinersen) is superior to any single treatment alone.	12	7	0
7	Centres performing gene therapy for SMA should have broad expertise in the assessment and treatment of SMA according to international standards. They should also have the ability and resources to deal with potential side effects of gene therapy. Personnel should be trained and have experience in the use of standardized and validated outcome measure for SMA to document treatment effects. Recognition as European Reference Centre (www.ern-euro-nmd.eu) or national accreditation as neuromuscular centre of expertise might serve as additional selection criteria.	17	2	0
8	There is convincing evidence that early initiation of treatment e ideally in the presymptomatic stage of the disease e is associated with markedly better outcome as compared to later start of treatment. Spinal	13	6	0

	Muscular Atrophy is therefore a good candidate for inclusion in newborn screening programs. In newly diagnosed patients any delay of treatment should be avoided. Ideally, the time frame between diagnosis and initiation of a disease modifying treatment should be no longer than 14 days. This is particularly important in infants due to the progressive course of the disease.			
9	Data concerning effectiveness and safety should be collected systematically for all patients treated. Treatment centres should be provided with adequate resources to perform long-term monitoring of treated patients with standardized outcome measures. Where available disease specific registries should be used for data collection to allow comparison between different treatments. Data analysis should be performed primarily by academic institutions and networks.	16	3	0
10	On the basis of the currently available data and in light of existing effective treatment alternatives, intravenous gene replacement therapy with Zolgensma® for patients with a body weight >13.5 kg should only be performed under a more rigorous protocol with continuous monitoring of safety and efficacy. This data collection might be best achieved in a clinical trial setting.	9	10	0
11	As the use of Zolgensma® will generate additional evidence during the coming years, pharmaceutical industry, regulators, patient representatives, and academic networks should collaborate to ensure that any new data on effectiveness and safety are publicly available in an unbiased and timely manner. This growing body of evidence is indispensable for an improved risk-benefit assessment for future patients and should not be hampered by particular commercial or academic interests	19	0	0

Supplemental Table 2 Wording and rationale as per 2020 publication[1] for statements that remained unchanged.

Statement #	Wording from original consensus statement from 2020
1	Traditional SMA types (e.g. type 0, 1, 2,3, 4) alone are not sufficient to define patient populations who might benefit most from gene therapy. In symptomatic patients age at onset, disease duration and motor function status at the start of treatment are the most important factors that predict response to treatment. Rationale: SMA represents a continuous spectrum of disease severity. The traditional classification is based on disease onset and the maximal motor milestone acquired. However, there is significant overlap between the different types. As SMA is a progressive disease, the clinical status of an individual patient does not only depend on the type of SMA but also on the stage of the disease. For example, the clinical condition of a patient with severe SMA type 2 in advanced stages of disease can be significantly more severe compared with a patient in early stages of SMA type 1. In addition, since the introduction of disease-modifying treatments, several patients originally belonging to type 1 or type 2 have acquired sitting position or ambulation, respectively, and thus cross the boundaries of the traditional classification. In fact, disease stage and duration might be more important predictors of outcome than the subtype of SMA. Therefore, traditional SMA types alone are not sufficient to characterize individual patients and one should consider additional factors to define populations that might benefit most from gene replacement and other disease-modifying treatments.

2	In presymptomatic patients *SMN2* copy number is the most important predictor of clinical severity and age of onset. As long as no better biomarkers or predictors are available, treatment decisions for presymptomatic patients should primarily be based on *SMN2* copy number. Determination of *SMN2* copy number needs to be performed in an expert laboratory with adequate measures of quality control. Rationale: The growing evidence that initiation of disease modifying treatments in the presymptomatic stages of SMA is associated with significantly better outcome leads to an increasing number of newborn screening programs and patients who are diagnosed before they develop any symptoms. As the traditional classification of SMA is based on clinical symptoms, it is not applicable in the presymptomatic stages of SMA. Currently, *SMN2* copy number is the best available predictor of disease severity, even if limitations of the predictive value remain. Work is underway to identify additional biomarkers, such a phosphorylated neurofilaments, but none has so far reached either the sufficient robustness, either the current clinical practice. Determination of *SMN2* copy numbers is not trivial, and discordant results have been reported between different methods and laboratories. Therefore, appropriate quality control measures are indispensable, especially when *SMN2* copy numbers are used for treatment decisions in presymptomatic patients with SMA.
4	In patients presenting symptoms at birth, treated after a long disease duration, or with already severe evolution, parents should be clearly made aware that despite the use of gene therapy there is a high risk of living with a very severe disability. Palliative care should be discussed as an alternative treatment option in these circumstances. Rationale: All disease modifying therapies for SMA have demonstrated a better efficacy when administered early. Patients treated with Zolgensma® who present with the most impressive evolution are patients treated before symptom onset or with a very short disease duration. This is exemplified by circulating videos of individual patients with SMA type 1 achieving the ability to walk and climb stairs at a young age. This improvement is exceptional in symptomatic children with SMA type 1 and may be misleading both for some parents of much more affected children, and for clinicians who are not deeply involved in this field of research. For treatment with Nusinersen Aragon-Gawinska et al. have shown that higher baseline motor function is associated with higher probability of acquisition of motor milestones. At the other end of the spectrum, more severely affected patients, who do already depend on respiratory support and tube feeding at initiation of treatment, do in most cases only demonstrate very modest improvement if at all. In these severe cases, gene replacement therapy and other disease modifying treatments might stabilize the disease but not necessarily reduce disability or improve quality of life.
7	Centres performing gene therapy for SMA should have broad expertise in the assessment and treatment of SMA according to international standards. They should also have the ability and resources to deal with potential side effects of gene therapy. Personnel should be trained and have experience in the use of standardized and validated outcome measure for SMA to document treatment effects. Recognition as European Reference Centre (www.ern-euro-nmd.eu) or national accreditation as neuromuscular centre of expertise might serve as additional selection criteria. Rationale: Zolgensma® is the first approved gene therapy for neuromuscular diseases. As outlined above selection of appropriate patients is challenging and requires comprehensive knowledge of the clinical presentation of SMA, available treatment options and potential risks associated with the use of gene therapy. To ensure appropriate monitoring and to generate more robust evidence, treatment centres should use established and standardized outcome measures. As most patients will remain with significant disease burden even after application of gene therapy, treatment centres should also be capable to provide appropriate multidisciplinary care according to international consensus recommendations. National health systems need to ensure that treatment centres are appropriately qualified and provided with sufficient resources to implement, monitor and evaluate the use of gene therapy for SMA in the best possible manner.
9	Data concerning effectiveness and safety should be collected systematically for all patients treated. Treatment centres should be provided with adequate resources to perform long-term monitoring of treated patients with standardized outcome measures. Where available disease specific registries should be used for data collection to allow comparison between different treatments. Data analysis should be performed primarily by academic institutions and networks.

	Rationale: As often inevitable with orphan diseases, approval of Zolgensma® for the treatment of SMA is based on limited data. Available clinical trials cover only a subgroup of patients mostly in the early stages of the disease and with a short observation period. Although real-world data collections can never reach the internal validity of controlled clinical trials, they can significantly contribute to evaluate the long-term effectiveness and safety of gene therapy for SMA. Considering the existing evidence gaps and the financial burden associated with gene replacement therapy, long-term follow up data should be collected for all patients treated with Zolgensma®. As this follow-up is often not part of an interventional clinical trial but routine care, adequate and sustainable funding needs to be allocated through the health system. Ideally, data collection should be performed in disease specific registries with shared datasets, that will also allow comparison of different disease modifying treatments. Data ownership, analysis and publication by academic institutions and networks should help to reduce any potential commercial bias.
11	As the use of Zolgensma® will generate additional evidence during the coming years, pharmaceutical industry, regulators, patient representatives, and academic networks should collaborate to ensure that any new data on effectiveness and safety are publicly available in an unbiased and timely manner. This growing body of evidence is indispensable for an improved risk-benefit assessment for future patients and should not be hampered by particular commercial or academic interests. Rationale: Currently the number of subjects exposed to gene therapy with Zolgensma® is still limited. Ongoing clinical trials and real-word experience will generate additional evidence including long-term effects. However, the fact that the data on safety and effectiveness are collected by different institutions such as pharmaceutical company, regulatory authorities and academic networks might impede to generate an integrated body of evidence in a timely manner. All contributing parties should make these data available in an unbiased manner. Identification of new safety signals is specifically important for orphan drugs where the experience is still limited at the time of approval. Therefore, any new safety signal should not only be communicated with clinical trial sites but with all treatment centres.

1. Kirschner J, Butoianu N, Goemans N, et al. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. *Eur J Paediatr Neurol* 2020; **28**: 38-43.