ИНФОРМАЦИЯ ЗА:
Наименование на заболяването
Спинална мускулна атрофия (СМА) тип 1
Определение на заболяването
Спиналните мускулни атрофии (СМА) са група наследствени заболявания, обусловени от дегенерация на двигателните алфа-мотоневрони на гръбначния мозък и мозъчния ствол. Класифицират се базата на разпределението на мускулната слабост (проксимална, дистална и булбарна), както и на начина на унаследяване (АД, АР, Х-свързан). Най-честата форма, отговорна за над 95% от случаите със СМА, е с АР тип на унаследяване и се дължи на хомозиготни делеции на SMN1 (survival motor neuron) гена на хромозома 5q13. Останалите форми, несвързани с мутации в SMN1, известни като не-5q СМА, са много редки, генетични и клинични хетерогенни синдроми (таблица 1). Дисталните СМА (дСМА) се характеризират с преобладаваща дистална мускулна слабост, като се припокриват с наследствените моторни невропатии (виж. наследствени моторни невропатии).
Четирицифрен код на заболяването по МКБ-10 (ако такъв е наличен)
G12.0
Код на заболяването по Orpha code
ORPHA83330

Епидемиологични данни за заболяването в Република България
Най-честата форма на СМА, обусловена от мутации в SMN1 гена, е със заболеваемост 1/6000-10 000 живородени деца, като честотата на носителство в популацията е 1/40-1/60 човека. В България 68 пациента със СМА бяха регистрирани в глобалния TREAT-NMD регистър.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
1. Йорданова А. Спинална мускулна атрофия. Молекулни характеристики и профилактика на болестта в България. Дисертация за присъждане на образователна и научна степен "Доктор ", София, 1998. 2. Кастрева К, Чамова Т, Търнев И. Български пациентски регистър за спинална мускулна атрофия като част от международния СМА регистър- анализ на клинични данни. Българска неврология. 2018;19 (1):15-19. 3. Jordanova A, Kargaci V, Kremenski I, Litvinenko I, Uzunova M, Turnev I, Ishpekova B, Kalaydjieva L. Spinal Muscular Atrophy among the Roma (Gypsies) in Bulgaria and Hungary. Neuromuscular Disorders 2002; 12: 378-385. 4. Bladen CL, Thompson R, Jackson JM, Garland C, Wegel C, Ambrosini A, Pisano P, Walter MC, Schreiber O, Lusakowska A, Jedrzejowska M, Kostera-Pruszczyk A, van der Pol L, Wadman RI, Gredal O, Karaduman A, Topaloglu H, Yilmaz O, Matyushenko V, Rasic VM, Kosac A, Karcagi V, Garami M, Herczegfalvi A, Monges S, Moresco A, Chertkoff L, Chamova T, Guergueltcheva V, Butoianu N, Craiu D, Korngut L, Campbell C, Haberlova J, Strenkova J, Alejandro M, Jimenez A, Ortiz GG, Enriquez GV, Rodrigues M, Roxburgh R, Dawkins H, Youngs L, Lahdetie J, Angelkova N, Saugier-Veber P, Cuisset JM, Bloetzer C, Jeannet PY, Klein A, Nascimento A, Tizzano E, Salgado D, Mercuri E, Sejersen T, Kirschner J, Rafferty K, Straub V, Bushby K, Verschuuren J, Beroud C, Lochmüller H. Mapping the differences in care for 5,000 Spinal Muscular Atrophy patients, a survey of 24 national registries in North America, Australasia and Europe.J Neurol. 2014;261(1):152-63. doi: 10.1007/s00415-013-7154-1; 5. Peeters K, Chamova T, Jordanova A. Clinical and genetic diversity of SMN1-negative proximal spinal muscular atrophies. Brain Brain. 2014;137(Pt 11):2879-96. doi: 10.1093/brain/awu169;
Епидемиологични данни за заболяването в Европейския съюз
Най-честата форма на СМА, обусловена от мутации в SMN1 гена, е със заболеваемост 1/6000-10 000 живородени деца, като честотата на носителство в популацията е 1/40-1/60 човека.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
1. Йорданова А. Спинална мускулна атрофия. Молекулни характеристики и профилактика на болестта в България. Дисертация за присъждане на образователна и научна степен "Доктор ", София, 1998. 2. Brzustowicz LM, Lehner T, Castilla LH, Penchaszadeh GK, Wilhelmsen KC, Daniels R, Davies KE, Leppert M, Ziter F, Wood D, Dubowitz V, Zerres K, Hausmanowa-Petrusewicz I, Ott J, Munsat TL, Gilliam TC: Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q11.2-13.3. Nature 1990, 344:540-41. 3. D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. Orphanet J Rare Dis. 2011;6:71. 4. Harding AE, Thomas PK, Baraitser M, Bradbury PG, Morgan-Hughes JA, Ponsford JR. X-linked recessive bulbospinal neuronopathy: a report of ten cases. J Neurol Neurosurg Psychiatry. 1982;45:1012–9. 5. Jordanova A, Kargaci V, Kremenski I, Litvinenko I, Uzunova M, Turnev I, Ishpekova

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8. Lunn MR, Wang CH. Spinal muscular atrophy. Lancet 2008; 371: 2120–33.
9. Mariotti C, Castellotti B, Pareyson D, Testa D, Eoli M, Antozzi C, Silani V, Marconi R, Tezzon F, Siciliano G, Marchini C, Gellera C, Donato SD. Phenotypic manifestations associated with CAG-repeat expansion in the androgen receptor gene in male patients and heterozygous females: a clinical and molecular study of 30 families. Neuromuscul Disord. 2000;10:391–7.
10. Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversiesand challenges. Lancet Neurol 2012; 11: 443–52.

Оценка на съответствието на заболяването с дефиницията за рядко заболяване съгласно § 1, т. 42 от допълнителните разпоредби на Закона за здравето

Заболяването отговаря на критериите за рядко заболяване.

Критерии за диагностициране на заболяването

Диагностични критерии:

1. Началото на заболяването е

А/ от раждането до 6 месец при СМА тип I

Б/ преди 18 месец при СМА тип II

В/ след 18 месец при СМА тип III

Г/ начало 2-3 декада при СМА тип IV

2. Ход на заболяването

Децата със СМА тип I не могат да седят без подкрепа, не задържат главата си, налице са тежка хипотония, вяла парализа и слаб плач; понякога се установява хипотрофия на езика и фасцикулации;

Децата със СМА тип II не прохождат, но могат да седят самостоятелно. Налице е и фин тремор в горните крайници. Установяват се затруднено откашляне и преглъщане. Развива са прогресираща сколиоза, налагаща хирургични интервенции.

Пациентите със СМА тип III и тип IV развиват способността за ходене, впоследствие в различна възраст се появява слабост в проксималните мускули на крайниците. Много често се развива сколиоза слад загубата на самостоятелна походка.

При СМА тип I смъртта настъпва преди 2 г., вск. на булбарната и дихателна слабост

При СМА тип II - над 2 г.; При СМА тип III и IV - в зряла възраст.

3. Симетрична мускулна слабост в трупа и крайниците (проксималните мускули са по-засегнати от дисталните; долните крайници са по-засегнати от горните). Липсват сетивни нарушения.
4. КФК е повишена до 10 пъти над нормата.
5. ЕМГ данни за абнормна спонтанна активност - фибрилации, позитивни остри вълни, фасцикулации; повишена средна продължителност и амплитуда на акционните потенциали
6. Хистологичното изследване показва групи от атрофични влакна от двата типа и хипертрофични влакна от тип I
7. Молекулярно-генетичният анализ установява мутации на SMN1 гена върху 5q12.2-q13, най често делеция на екзон 7. Копията на SMN2 гена могат да определят тежестта на заболяването.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Brzustowicz LM, Lehner T, Castilla LH, Penchaszadeh GK, Wilhelmsen KC, Daniels R, Davies KE, Leppert M, Ziter F, Wood D, Dubowitz V, Zerres K, Hausmanowa-Petrusewicz I, Ott J, Munsat TL, Gilliam TC: Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q11.2-13.3. Nature 1990, 344:540-41.
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6. Lefebvre S, Burglen L, Reboullet S, Clermont O, Burlet P, Viollet L, Benichou B, Cruaud C, Millasseau P, Zeviani M, Le Paslier D, Frézal J, Cohen D, Weissenbach J, Munnich A, Melki J: Identification and characterization of a spinal muscular atrophy-determining gene. Cell 1995, 80:155-65.
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9. Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol 2012; 11: 443–52.

Алгоритми за диагностициране на заболяването

Диагнозата се поставя въз основа на клиничните особености, СРК, ЕМГ изследване, мускулна биопсия и генетично изследване. Предвид напредъка на молекулярно-генетичните изследвания, мускулната биопсия има все по-малко значение. При ЕМГ изследване предимно в проксималните мускули на крайниците се установява тежка частична денервация, като проксималните мускули на ръцете са по-леко засегнати. Отвеждат се фасцикулации. Броят на двигателните единици е редуциран. При волево съкращение потенциалите са с удължена продължителност и по-високи амплитуди. ЕМГ изследването доказва преднорогова увреда. СРК в серума е нормална или повишена до 5 пъти над нормата. От хистологичното изследване на мускул се открива денервационна атрофия с малки групирани, ангулирани еозинофилни мускулни влакна. Молекулярно-генетичното изследване включва Multiplex ligation-dependent probe amplification (MLPA) и PCR, а в случаите, при които се установява делеция само в единия SMN1 ген се налага и директно секвениране на кодиращата част на гена. При 95%-98% от болните със СМА се установява делеция на екзон 7 от SMN1 гена в хомозиготно състояние, а при останалите 2-5% са двойни хетерозиготи за делеция в SMN1 гена и точкови мутации, малки делеции или инсерции, водещи до конверсия на SMN1 в SMN2.

Диференциална диагноза. В диференциално диагностичен план за СМА тип I и II се обсъждат други заболявания, проявяващи се със синдром на „вялото бебе" като вродени миопатии и вродени мускулни дистрофии, конгенитална форма на миотонична дистрофия тип 1, конгенителни миастенни синдроми, метаболитни миопитии (болест

на Pompe), наследствени сетивно-моторни полиневропатии, като конгенитална хипомиелинизация, други не 5q СМА, синдром на Prader- Willi, хипотонична форма на детска церебрална парализа. СМА тип III и IV следва да се диференцират от ПМД тип Дюшен и Бекер, вродени миопатии, метаболитни миопатии, други не 5q СМА с късно начало, дефицит на хексозаминидаза А (GM2 ганглиозидоза), латерална амиотрофично склероза.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

1. Brzustowicz LM, Lehner T, Castilla LH, Penchaszadeh GK, Wilhelmsen KC, Daniels R, Davies KE, Leppert M, Ziter F, Wood D, Dubowitz V, Zerres K, Hausmanowa-Petrusewicz I, Ott J, Munsat TL, Gilliam TC: Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q11.2-13.3. Nature 1990, 344:540-41.
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4. Jordanova A, Kargaci V, Kremenski I, Litvinenko I, Uzunova M, Turnev I, Ishpekova B, Kalaydjieva L. Spinal Muscular Atrophy among the Roma (Gypsies) in Bulgaria and Hungary. Neuromuscular Disorders 2002; 12: 378-385.
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8. Mariotti C, Castellotti B, Pareyson D, Testa D, Eoli M, Antozzi C, Silani V, Marconi R, Tezzon F, Siciliano G, Marchini C, Gellera C, Donato SD. Phenotypic manifestations associated with CAG-repeat expansion in the androgen receptor gene in male patients and heterozygous females: a clinical and molecular study of 30 families. Neuromuscul Disord. 2000;10:391–7.
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10. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Qian Y, Sejersen T; SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018;28(2):103-115. doi: 10.1016/j.nmd.2017.11.005.
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Алгоритми за лечение на заболяването

Nusinersen (SPINRAZA) е модифициран антисенс олигонуклеотид, който се свързва с интрона, следващ екзон 7 в пре-информационната РНК на SMN2. По този начин модулира сплайсинга на иРНК, за да включи екзон 7 и за да се синтезира по-голямо количество пълноверижен SMN протеин. Това е единственият медикамент, одобрен за лечение на всички форми на 5q СМА (през декември 2016 от FDA- Food and drug agency и през май 2017 ог EMA- European medicines agency). Препоръчителната доза на медикамента е 12 мг. (всеки флакон е 5 мл/12 мг), приложени интратекално. Терапията започва с четири натоварващи дози- три през 14 дни и четвъртата 30 дни след третата. След това подържащите дози се прилагат през четири месеца. При пресимптоматично започнато лечение при болни със СМА тип се наблюдава двигателно развитие, близко до това на здрави деца. При другите клинични проучвания децата на терапия постигат статистически значимо подобрение на двигателните функции спрямо sham групата. Наблюдава се статистически значимо повишена преживяемост на пациентите със СМА тип 1.

Най-честите нежелани лекарствени реакции са инфекции на горните и долните дихателни пътица, констипация, белодробни ателектази, протеинурия.

Критерии за започване на терапия с Nusinersen

- Пациенти с генетично доказа 5q СМА, вкл. мутации в SMN1- гена
- Пациенти, при които се прилагат стандартите за грижи при СМА

В КХП е посочено, че медикаментът е одобрен за всички форми на заболяването.

Изключващи критерии за започване на терапия с Nusinersen

- Анамнеза за за заболяване на централната или периферната нервна система, което би затруднило интратекалното приложение
- Тежка сколиоза, която би затруднила интратекалното приложение на медикамент
- Анамнеза за имплантиран шънт
- Участие в кринично проучване за СМА
- Нарушение в кръвосъсирването, което би направило приложението на медикамента опасно за болния

Проследяването на ефекта от лечението следва да се прави на всеки 6 мес.

При пациентите със СМА тип 1 оценката на двигателните функции следва да се извършва по следните скали:

- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
- Hammersmith Infant Neurological Examination (HINE)

При пациентите със СМА тип 2 и 3 оценката на двигателните функции се извършва чрез:

- Hammersmith Functional Motor Scale Expanded (HFMSE) score
- Revised Upper Limb (RULM)

За изпълнението на тези тестове е необходимо предварително обучение.

Оценка на вентилаторните показатели при късните форми чрез функционално изследване на дишането

Подържане на дихателните функции. Препоръчва се проследяване на всеки 3-6 мес. на дихателните функции чрез провеждане на полисомнография, пулс-оксиметрия, измерване на кръвните газове и оценяване на способността за откашляне при пациенти с СМА тип I. Полисомнографията дава възможнаст да се оценят дихателните нарушения по време на сън, дори при липса на симптоми на хиповентилация. Към допълнителните скринингови изследвания се отнасят рентгенографията на бял дроб.

При пациентите със СМА тип II важат същите препоръки, като допълнително се провеждат спирометрия и оценяване на прогресията на сколиозата чрез провеждане на рентгенографии на гръбначен стълб. Пациентите със СМА тип III и IV по-рядко развиват дихателна недостатъчност, но и при тях рутинно се провежда спирометрия. .
Важни мероприятия, профилактиращи дихателните нарушения и подобряващи качеството на живот на пациентите със СМА са:

- Механично и ръчно подпомагане на откашлянето
- Неинвазивна вентилация чрез BiPAP при пациенти с нощна и/или дневна хиповентилация
- Приложение на ваксини „противогрипни и пневмококови)

Приложението на инвазивна вентилация при пациенти със СМА тип I поставя редица етични въпроси.
Оценка на гълтателните нарушения при пациенти със СМА тип I и поставяне на назогастрална или назойеюнална сонда
Физиотерапия Основите й цели са да забави намалението на мускулната сила и маса, да профилактира развитието на ставните контрактури и да подобри качеството на живот на болните. Физиотерапия следва да се започне непосредствено след поставянето на диагнозата. Използват се ортезни средства за превенция на ставните контрактури.
Ортопедична хирургия на сколиозата при запазени дихателни обеми забавя прогресията на дихателната слабост.

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Алгоритми за проследяване на заболяването

Основно значение за болните със СМА имат правилните грижи и проследяване от мултидисциплинарен екип от специалисти, в зависимост от формата на заболяването и скоростта на прогресията. Дихателните и гълтателните нарушения, типични за СМА I и

II налагат проследяване на дихателните капацитети, възможността за откашляне, провеждане на пулсоксиметрия и капнография за оценка на епизодите на нощна хиповентилация и при необходимост приложение на неинвазивна и инвазивна вентилация. При гълтателни нарушения се обсъжда хранене чрез гастростома. Прилагат се ортезни средства за подпомагане на походката, а ортопедичната хирургия на сколиозата следва да се съобразява с виталния капацитет и тежестта на гръбначното изкривяване. Рехабилитацията е от съществено значение.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
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Алгоритми за рехабилитация на заболяването

Цел на рехабилитационните мероприятия- да се максимализира функционалният капацитет, да се удължи или поддържа независимо функциониране и подвижност, да се предотврати или подтисне развитието на деформитети и сърдечно-белодробни нарушения и да се осигури достъп за пълно интегриране в обществото с добро качество на живот. Лечението е най-добре да се извършва от екип от лекари, физиотерапевти, работни терапевти, логопеди, социални работници, психолози и други. Лечението е целенасочено и многостранно.

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Необходими дейности за профилактика на заболяването (ако такива са приложими)

Генетичното консултиране и пренаталната диагностика във фамилно обременените семейства е от изключителна важност за профилактика на нови случаи.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

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Предложения за организация на медицинското обслужване на пациентите и за финансиране на съответните дейности, съобразени с действащата в страната нормативна уредба

На този етап диагностиката, проследяването и рехабилитацията при тези пациенти се поемат по клинични пътеки.

Описание на опита с конкретни пациенти със съответното рядко заболяване (ако има такъв)

Национални регистри за невромускулни заболявания

Създаден беше български/TREAT-NMD регистър за следните три групи невромускулни заболявания: Прогресивни мускулни дистрофии тип Дюшен и Бекер, Спинална мускулна атрофия и миотонични дистрофии, с който България участва в европейската TREAT-NMD мрежа. Неврологична клиника към УМБАЛ „Александровска" се регистрира като клиничен център в България в Координационния център за клинични проучвания на TREAT-NMD към Медицинския университет във Фрайбург, Германия. Попълват се два формуляра – Информация за пациента и информирано съгласие и регистрационен формуляр В регистрационния формуляр се попълват задължителни критерии и препоръчителни (незадължителни) критерии за включване в регистъра. В препоръчителните критерии фигурират данни от различни изследвания (функционално изследване на дишането при СМА).

След получаване на подробна информация от нашия екип за целите на регистъра и попълване на съответните формуляри 68 пациента със СМА бяха регистрирани и получиха съответен уникален идентификационен номер, с който да бъдат включени в глобалния TREAT-NMD регистър. Участието в глобалния TREAT-NMD регистър по анонимен начин позволява идентифицирането на пациенти в България от екипа отговорен за регистрите и съобразено с типа заболяване и генетичен дефект. Това се очаква да създаде условия за провеждане на патогенетично терапия, както и включване на български пациенти в клинични проучвания за различни други видове генна терапия. Участието в клинични проучвания по тези редки и трудно лечими заболявания отговаря на очакванията на пациентите и техните роднини, но така също би приобщило българската неврология и генетика към постиженията в това ново и обещаващо направление в световен мащаб.

Всички регистрирани пациенти се информират за новостите по отношение на терапията и проследяването на тяхното заболяване. Периодично в зависимост от състоянието им болните със СМА се хоспитализират за проследяване на състоянието и терапия в Неврологична клиника, УМБАЛ „Александровска", Детска неврологична клиника СБАЛНПБ „Св. Наум" и СБАЛДБ „Проф. д-р Ив. Митев".

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Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care

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Abstract

Spinal muscular atrophy (SMA) is a severe neuromuscular disorder due to a defect in the survival motor neuron 1 (*SMN1*) gene. Its incidence is approximately 1 in 11,000 live births. In 2007, an International Conference on the Standard of Care for SMA published a consensus statement on SMA standard of care that has been widely used throughout the world. Here we report a two-part update of the topics covered in the previous recommendations. In part 1 we present the methods used to achieve these recommendations, and an update on diagnosis, rehabilitation, orthopedic and spinal management; and nutritional, swallowing and gastrointestinal management. Pulmonary management, acute care, other organ involvement, ethical issues, medications, and the impact of new treatments for SMA are discussed in part 2.

Keywords: Spinal muscular atrophy; Care; Diagnosis; Orthopedic; Phisotherapy; Nutrition

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1. Introduction

Spinal muscular atrophies (SMA) include a group of neuromuscular disorders characterized by degeneration of alpha motor neurons in the spinal cord with progressive muscle atrophy, weakness and paralysis [1]. The most common form of SMA is due to a defect in the survival motor neuron 1 (*SMN1*) gene localized to 5q11.2-q13.3 [2]. It includes a wide range of phenotypes that are classified into clinical groups on the basis of age of onset and maximum motor function achieved: very weak infants unable to sit unsupported (type 1), non-ambulant patients able to sit independently (type 2), up to ambulant patients with childhood (type 3) and adult onset SMA (type 4).

In 2004 an International Conference established a committee of experts in SMA to create a consensus statement on SMA standard of care [3]. Different working groups were established, addressing different aspects of diagnosis and management, focusing on rehabilitation and orthopedic, pulmonary, nutritional and palliative care. Each group had two leaders, facilitating the work of other experts who were invited to participate. The Delphi technique [4] was used to explore consensus expert opinion and to identify topics where no consensus could be reached for which further study was needed.

A report of the SMA SOC consensus statement was published in 2007 [3]. The guidelines have been widely adopted by clinicians all over the world and were translated and promoted by patient advocacy groups and international neuromuscular networks such as TREAT-NMD. More recently, with the advent of clinical trials in SMA [5–8], the guidelines have also been used in protocols as a benchmark for care for recruitment and during participation in a clinical trial.

Over the last decade there has been increasing evidence of improvements in the natural history of all the SMA types [9–11]. Even in type 1, the most severe form of SMA, there has been an increase of survival as a result of a more proactive approach, following the introduction of non-invasive ventilation and enteral feedings, suggested in the original SOC recommendations [12,13]. These improvements are likely to be the result of the recommendations provided in the consensus statement and of new advances in care that are not always reflected in the existing literature.

In this paper we report an update of the consensus statement, following the need to include more recently published data and more generally advances in the topics addressed in the original version. New aspects, such as those related to acute and emergency care, medications or the involvement of other organs have also been added.

The need for an update has also been driven by the advent of clinical trials [14]. The approval of the first drug for SMA in December 2016 and promising early results from other clinical trials have changed the perspective of physicians and families who are now more willing to be proactive in the management of this disorder, especially in type 1.

2. Method

Nine topics were included in this update:1. Diagnosis and genetics; 2. Physical therapy and rehabilitation; 3. Orthopaedic care, growth and bone health care; 4. Nutrition; 5. Pulmonary care; 6. Acute care in the hospital setting; 7. Other organ system involvement; 8. Medication; 9. Ethics and palliative care.

For each topic, two leaders, in most cases one from Europe and one from the United States, were identified to head a working group inviting other clinicians with expertise in the topic and, when appropriate, at least one SMA patient or parent/caregiver. The choice of the participants in each subgroup was based on strict criteria, inviting the experts from all continents who had published on the specific topic, or had a large experience in the field and were part of national or international working groups.

A literature search identified all the relevant articles that were classified according to their consistency with the previous recommendations [3], or whether they included novel or contrasting findings.

Each working group (WG) had 2 preliminary conference calls, and at least 2 web-based Delphi rounds of inquiry. The first round of Delphi used open-ended questions to generate specific topics. The second round focused on the topics ranked the highest on the first round.

The review of the literature and the results of the first two rounds were analyzed and discussed in an in-person workshop where the leaders of all the working groups convened. The American Academy of Pediatrics guidelines for classifying recommendations for clinical practice [15] were used to analyze the results.

Within each working group, each topic was summarized as to where a) Consensus was reached with uniform opinion; b) Consensus was reached with a majority opinion, and with minority opinions mentioned; c) No consensus is reached and more work has to be performed.

Following the workshop, more rounds of Delphi were performed to further define some aspects requiring further definition, highlighted during the workshop. Details of the methodology used have been recently published in the workshop report [16].

The results were subdivided using the functional classification from the original consensus statement document. Considering that type 3 patients who lost ambulation share many aspects with type 2 patients, the two groups are collectively indicated as "sitters", while the type 3 patients who are still ambulant are indicated as "walkers". Type 1 patients are indicated as non-sitters.

2.1. SMA diagnosis

The diagnostic process for SMA has not changed since the original consensus statement paper [3] but more accurate information on the genetic background has become available.

Unless there are previous familial cases, the diagnostic process is generally prompted by the clinical signs. Clinically, these infants present with hypotonia, progressive symmetric

and proximal weakness affecting the legs more than the arms, sparing of the facial muscles but often with bulbar muscle weakness. There is also weakness of the intercostal muscles with relative sparing of the diaphragm, which results in the typical "bell-shaped" chest and paradoxical breathing pattern. Childhood onset is similarly characterized by hypotonia and proximal weakness, but with less prominent bulbar and respiratory findings.

In approximately 96% of patients, SMA is caused by homozygous absence of exons 7 and 8 of the *SMN1* gene, or, in some cases, only of exon 7 [2,17–20]. The majority of patients inherit the *SMN1* deletion from their parents; in 2% de-novo deletions in one of the 2 alleles have been described [21]. In 3–4%, other mutations in *SMN1* can be found, typically with an *SMN1* deletion on the other allele [22].

Population studies have indicated variations in the carrier frequency of *SMN1* deletions, with the Asians having the highest carrier frequency (2.4%) [23]. The SMN locus is part of a genomic inverted duplication region on human chromosome 5, which contains a paralogue gene, *SMN2*. *SMN2* is intact in all SMA patients. The *SMN2* copy numbers however can vary between 0 and 4 per chromosome 5 in the general population. SMA patients always carry at least 1 *SMN2* copy.

The diagnosis of SMA is based on molecular genetic testing. Genetic testing of *SMN1/SMN2* is highly reliable and it is first line investigation when the condition is suspected in a typical case (Fig. 1). In a typical presentation there is no need for a muscle biopsy.

EMG is also usually not needed in type 1 and 2 children; this investigation can help in more chronic forms in which the phenotype might be less striking. CK serum levels are usually normal or only mildly elevated in SMA; however few exception with markedly (10×) elevated levels are on record hence this test does not necessarily exclude the diagnosis [24].

The gold standard of SMA genetic testing is a quantitative analysis of both *SMN1* and *SMN2* using multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing (NGS) [23,25–27]. Homozygous *SMN1* deletions can be identified also by PCR followed by restriction digest. This method is faster and is less expensive, and often readily available in any lab but does not allow quantification of *SMN1* or *SMN2* copy number. However, knowledge on *SMN1* copies is relevant for identification of heterozygous deletions whereas *SMN2* copies are important for prognosis and therapeutic approaches.

The absence of both full *SMN1* copies will provide diagnosis of SMA. If only 1 full copy is present and clinical phenotype is compatible with SMA, the remaining *SMN1* gene should be sequenced looking for other subtle mutations. If both full *SMN1* copies are present, a diagnosis of SMA is highly unlikely but the *SMN1* gene should be sequenced if there is a striking typical phenotype or consanguinity. If sequencing indicates an intact *SMN1* gene in the presence of a phenotype suggestive of SMA including also neurogenic EMG, other motor neuron diseases should be considered.

There was consensus that even if the number of *SMN2* copies is not essential to reach the diagnosis of SMA, this should be routinely assessed as it is an important factor influencing the severity of the SMA phenotype [26,28–30] (Supplementary Table S1).

The majority of type 1 SMA patients carry two *SMN2* copies, type 2 SMA and type 3a SMA patients (onset before the age of 3 years) three *SMN2* copies, type 3b SMA patients (age of onset after 3 years) four *SMN2* copies, and type 4 four to six copies [26,30]. Although there is a strong correlation between *SMN2* copies and severity of the disease, there are exceptions and in individual cases the number of *SMN2* copies may not predict the severity of the phenotype. This limitation should be

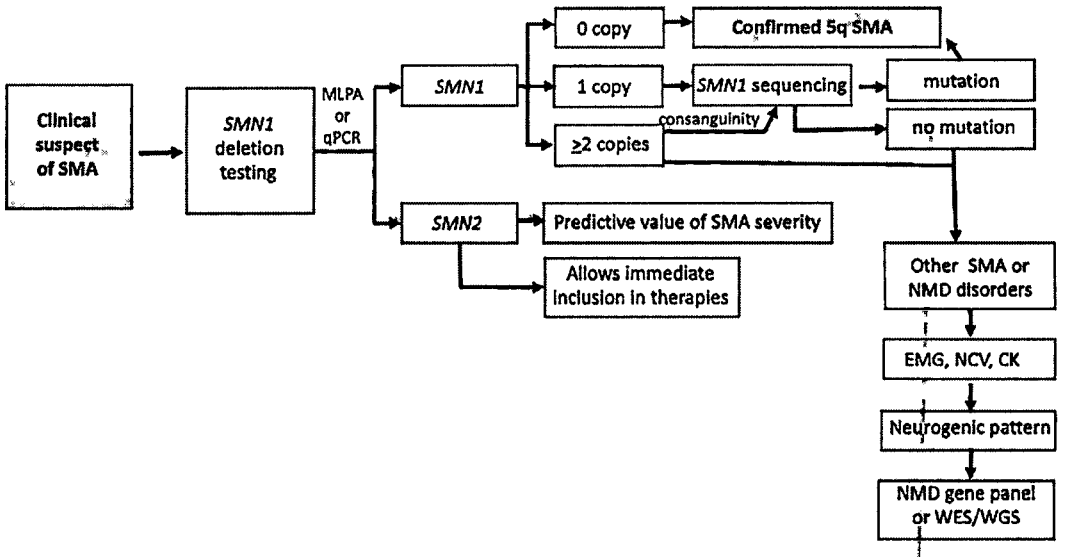

Fig. 1. Diagnostic algorithm for spinal muscular atrophy (SMA: spinal muscular atrophy; SMN1: survival motor neuronon 1; SMN2: survival motor neuron 2; NMD: neuromuscular disorders; EMG: electromyography; NCV: nerve conduction velocity; CK: creatine kinase levels; WES: whole exom sequencing; WGS: whole genome sequencing).

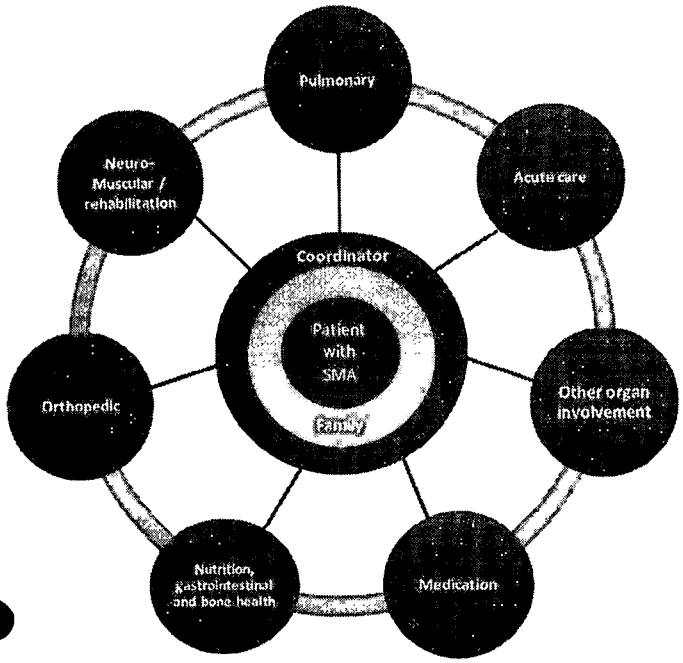

Fig. 2. Multidisciplinary approach.

mentioned when reporting the number of copies or counseling patients or their families.

Another reason for determining the number of *SMN2* copies is that this is currently used as a criterion for enrolment of patients into clinical trials [7,8].

Presence of *SMN1* but homozygous absence of *SMN2*, a genotype found in about 3–5% of control individuals, has no apparent phenotypic consequences [2,20]. The presence of at least one fully functional *SMN1* gene, as typically found in SMA carriers, is indeed sufficient to protect from SMA.

Genetic counseling is obviously important at the time of diagnosis, as is psychological support to the families, especially when a diagnosis of type 1 SMA is communicated.

2.2. Management: a multidisciplinary approach

A multidisciplinary approach is the key element in the management of SMA patients [1,3]. SMA is a complex disorder involving different aspects of care and professionals, and each of the aspects should not be dealt in isolation but as part of a multidisciplinary approach (Fig. 2). In the past families had to coordinate all the assessments and visits but it is now recommended that this should be coordinated by one of the physicians, generally the neurologist or pediatric neurologist, who is aware of the disease course and potential issues. This will allow to monitor the various aspects that are known to be part of the disease progression and, when possible, to provide anticipatory care.

2.3. Neuromuscular and musculoskeletal evaluation

Clinical assessment in SMA includes performing a physical examination, with a focus on the musculoskeletal system and related functional impairments. The choice of the assessments used will reflect the aspects that are more relevant for each level of severity (Supplementary Table S2).

These should include different means of assessments of strength and range of joint motion, relevant motor functional scales [31–35] and timed tests to monitor those aspects of function that reflect activities of daily living (Table 1).

These assessments should be performed routinely by trained examiners every 6 months, unless there are special circumstances requiring different follow up.

Regular monitoring of these aspects will allow to monitor possible changes over time, to identify aspects requiring intervention and response to intervention. The use of these assessments also allows to compare individual results to the trajectories of progression reported in recent studies [36,37].

2.4. Rehabilitation

Since the original consensus statement paper there has been increasing evidence that a proactive approach, including regular sessions of physical therapy (PT) may influence trajectories of progression. In a recent study on sitters and walkers, functional changes over 12 months were minimal in the whole cohort and the few outliers showing a more substantial loss of functional activities were often those with increase in their joint contractures, sudden scoliosis deterioration or excessive weight gain [36]. Other papers have reported the benefits of braces, orthoses and exercise [38–45] (Supplementary Table S3).

2.4.1. Non-sitters

The primary rehabilitation goals for non-sitters include: optimization of function, minimization of impairment, and optimizing tolerance to various positions (Table 1).

2.4.1.1. Stretching. This includes the use of orthoses and splints, active-assistive and passive techniques, supported supine/standing/standing frames and serial casting. Thoracic bracing is recommended for postural stabilization and to promote function. Cervical bracing is often used for head support particularly, as head control is often absent or not fully developed, to minimize risk of asphyxiation while upright.

Upper and lower limb orthoses are used to promote function and range of motion.

2.4.1.2. Positioning. Seating systems and postural supports should include supine positioning with rolls, beanbags, molded pillows or wedges. Custom and molded wheelchair seating systems as well as custom sleeping systems are recommended.

To promote mobility and transfers the use of strollers and power wheelchairs with recline/tilt options and adapted seating systems are recommended.

2.4.1.3. Mobility and exercise. To promote function, assistive technology and adaptive equipment are recommended. The use of eye tracking devices is also recommended to improve communication. Some non-sitters can participate safely in aquatic therapy with proper head and neck support and constant supervision.

2.4.1.4. Chest physiotherapy. Chest physiotherapy is an important part of the assessment and management. It is

Table 1
Rehabilitation assessment and intervention.

	Assessment	Intervention	Care considerations
Non-sitters	Postural control Scoliosis Hip dislocation Sitting tolerance Chest deformities	*Positioning and Bracing* Daily use of seating systems, postural and positioning supports, thoracic bracing and cervical bracing for head support. Static thoracic bracing should have incorporated modifications for respiratory support including abdominal cutouts.	To be effective, orthoses should be applied for more than 60 minutes to overnight. Session duration for effective stretching and range of motion depends on specific patient needs, joints, and rehabilitation aims.
	Contractures (ROM, goniometry)	*Stretching* Daily use of orthoses for upper lower limb orthoses for stretching and to promote function and range of motion. Static orthoses Knee immobilizers and hand splints are recommended for positioning and stretching. AFOs and KAFOs can be used for stretching and positioning. TLSOs are used for positioning. Supported standing	The minimal frequency for stretching and range of motion is 3–5 times per week The minimal frequency for bracing to be effective is 5 times per week.
	Muscle weakness (Antigravity movements) Functional scales (CHOP INTEND) Motor development (HINE)	*Promote function and mobility* Use of seating and mobility systems Mobile arm supports to assist upper extremity function.	Recommend toys with switches, light weight rattles, Bath equipment, adapted beds, upper extremity assistive devices, as well as hoists (lifts), Environmental controls, and eye tracking devices for computers and communication, Strollers with recline and the ability to lay flat, power wheelchairs should have recline/tilt, adapted seating systems
Sitters	Postural control Foot and chest deformities Scoliosis and pelvic obliquity Hip dislocation	*Positioning and Bracing* Thoracic bracing is recommended for posture and to promote function. Cervical bracing is often used for head support for safety and transportation.	Orthoses should be worn for more than 60 minutes to overnight. The minimal frequency for bracing: 5 times/week.
	Contractures (ROM, goniometry)	*Stretching* Orthoses are used for the upper and lower limbs to promote function and ROM Regular stretching for segments known to be at risk for contractures: hip, knee and ankle, wrist and hand Knee immobilizers, KAFOs, and AFOs are recommended for positioning and standing. RGOs and KAFOs can be used for supported ambulation. TLSOs and hand splints are used for positioning.	Minimal frequency for stretching and ROM: 5–7 times/week When stretching or performing joint mobilization ensure joint segments are aligned throughout the treatment. Supported standing should be up to 60 minutes and minimal frequency is 3–5 times/week, optimal 5–7 times/week.
	Functional scales (HFMSE, RULM, MFM) Muscle weakness (Strength tests)	*Promote function and mobility* Use of seating and mobility systems. Use of gait training devices and mobility devices to promote supported ambulation Mobile arm supports to assist upper extremity function.	Exercise can have an effect on function, strength, ROM, endurance, ADLs, participation, and balance Recommend swimming, hippotherapy, and wheelchair sports. All sitters should have electric/power wheelchairs with custom postural support and seating systems The option to tilt and/or recline and a seat elevator is sometimes necessary in weaker patients. Lightweight manual wheelchairs or power assist wheels are ideal to promote self-propulsion in stronger patients.
Ambulant	Mobility Timed tests Measure of endurance (6MWT) Falls Functional scales (HFMSE, RULM) Muscle weakness (Strength tests)	*Promote function and mobility*	Recommend aerobic and general conditioning exercise for SMA walkers. Options include: Swimming, walking, cycling, yoga, hippotherapy, rowing, elliptical/cross-trainers. Exercise program should be designed and monitored by a physical or occupational therapist, familiar with SMA. Optimal duration for aerobic exercise: at least 30 minutes
	Contractures (ROM, goniometry)	*Stretching*	Minimal frequency: 2–3 times/week, optimal: 3–5 Maintain flexibility through active assisted stretching and include the use of orthoses according to specific needs.
	Postural control Scoliosis Hip dislocation	*Positioning and Bracing*	Recommend some form of balance exercise. Lower limb orthoses are used for posture and function at the ankle and knee, Thoracic bracing may be used to promote posture in sitting

ROM, range of motion; CHOP INTEND, Children Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Examination; AFOs, ankle foot orthosis; KAFOs, knee ankle foot orthosis; TLSOs, thoraco lumbo sacral orthosis; HFMSE, Hammersmith Function Motor Scale Expanded; RULM, Revised Upper Limb Module; MFM, Motor Function measure; 6MWT, 6 minute walk test; ADL, activities of daily living; SMA, spinal muscular atrophy.

particularly important to implement during illness or perioperative periods and as prophylaxis pulmonary management to promote airway clearance and improve ventilation. Manual techniques include percussion, vibration and positioning to promote postural drainage.

2.4.2. Sitters

The main objectives for rehabilitation in sitters are to prevent contractures and scoliosis, and maintain, restore or promote function and mobility.

2.4.2.1. Stretching. Modalities for stretching include techniques that can be achieved manually and through the use of orthoses, splints, active-assistive stretching, supported standing/standing frames and positioning techniques such as serial casting. Stretching modalities should be performed and/or supervised by physical or occupational therapists. Parents and caregivers should also be instructed in daily stretching activities.

Session duration for effective stretching depends on specific patient needs, joints, and rehabilitation aims.

2.4.2.2. Positioning. Thoraco-lumbar sacral orthoses are recommended for posture and to promote function. Cervical bracing is often used for safety and transportation. Static, dynamic and functional orthoses are used for positioning and standing and, when possible, for supported ambulation.

Supported standing is important to facilitate lower extremity stretching but also to promote bodily functions and bone health, enable upright participation, and promote spine and trunk posture.

2.4.2.3. Mobility and exercise. All sitters should have electric/power wheelchairs with custom postural support and seating systems. Assessments for power wheelchair mobility can begin before 2 years of age [46]. Lightweight manual wheelchairs or power assist wheels are ideal to promote self-propulsion in stronger patients. Exercise programs and activities that encourage muscle activation should be encouraged since it can have an effect on maintaining and improving function, strength, range of motion, endurance, balance, activities of daily living, and participation in school, social activities and occupation. Recommended exercise for sitters include aquatic therapy, concentric and eccentric exercise and aerobic and general conditioning exercise with and without resistance.

2.4.2.4. Chest physiotherapy. Similar to non-sitters, chest physiotherapy is an important part of the assessment and management to implement, especially I the weak type 2, both as prophylaxis and during illness or perioperative periods. Manual techniques are similar to those reported for non-sitters.

2.4.3. Walkers

The main objectives for rehabilitation in walkers are to maintain, restore or promote function, mobility, and adequate joint range, and improve balance and endurance.

2.4.3.1. Exercise/activity programs. The exercise programs will include many of the suggestions used for sitters. In addition, some form of balance exercise, both, dynamic and static forms, should also be part of an exercise program.

2.4.3.2. Stretching and range of motion. Modalities of stretching and range of motion include: passive stretching and active-assistive techniques. Lower limb orthoses are mainly used for maintaining flexibility, posture and function at the ankle and knee. Thoracic bracing is not typically used during walking as it may adversely affect ambulation ability and limit effective compensatory strategies but, when needed, may be used to promote posture in sitting.

2.4.3.3. Mobility. To ensure functional independence, lightweight manual wheelchairs or power assist wheels are recommended when endurance is limited. Similarly, electric/power wheelchairs or powered scooters may also be considered to facilitate independent mobility over longer distances.

2.5. Orthopedic management

2.5.1. Spine deformity management

2.5.1.1. Non-sitters. Until now, because of their limited survival, spinal management was rarely discussed as a possible option in non-sitters, unless they had stable respiratory and nutritional function [3,47]. Specific rigid braces allowing stable sitting position may be used, provided they do not compromise pulmonary function (Fig. 3). Supine Cobb angle or that obtained in the sitting position using a trunk brace may be used in their follow up [47]. The advent of new therapies leading to increased survival and overall functional improvements [7,8], is rapidly changing the scenario of spinal management in these patients.

2.5.1.2. Sitters.

2.5.1.2.1. Assessment. Scoliosis is still highly prevalent in children with SMA 1 and 2, with incidence of 60–90% and initial presentation in early childhood [1,48]. The hypotonic spinal curves continuously progress through childhood. Thoracic kyphosis also develops in most patients to a variable degree.

Inspection of the spine should be conducted as part of the routine clinical examination. When kyphoscoliosis is suspected on forward bend test in sitting or standing posture, anterior-posterior and lateral projection spine radiographs should be performed in the most upright position independently attainable by the patient (i.e. sitting in children who can sit independently, standing in SMA 3) to define and quantify the extent of spinal deformity in both coronal and sagittal planes. For SMA 1 and 2 patients, scoliosis >20° should be monitored every 6 months until skeletal maturity and yearly after skeletal maturity. Management with spinal orthoses is often advocated to support the hypotonic trunk and treat scoliosis >20°, especially in a child with significant growth remaining [42,49]. There was no consensus on the type of brace to be used, as both rigid and soft spinal thoracolumbar orthoses were recommended.

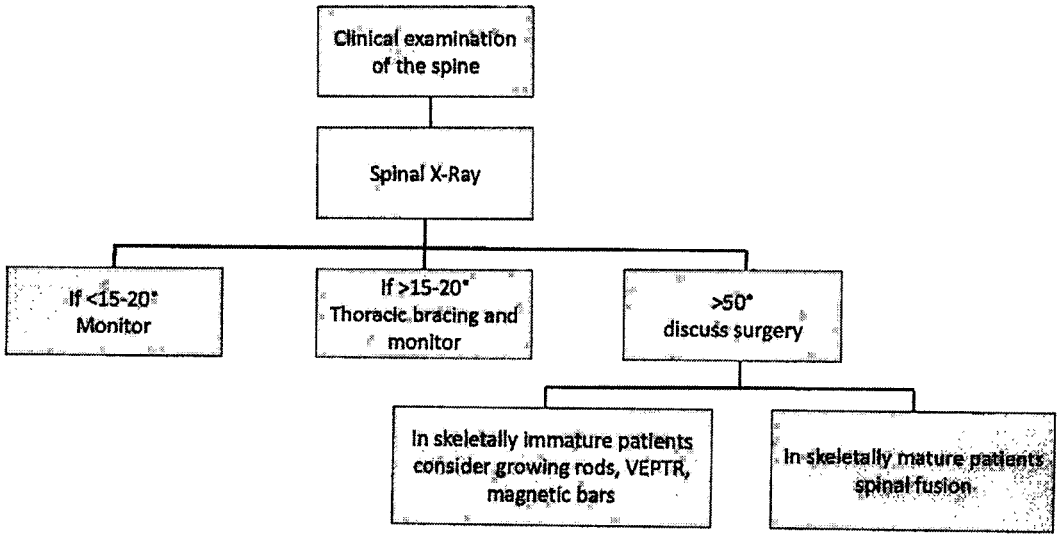

Fig. 3. Spine deformity management (VEPTR: Vertical Expandable Prosthetic Titanium Rib).

2.5.1.2.2. Surgical intervention. Bracing is palliative and unable to halt progression of spinal deformity [49,50]. As a result, spinal instrumentation is frequently indicated to preserve trunk balance in sitting, re-align the distorted thorax to facilitate respiratory function and improve overall quality of life [50–55]. The decision to surgically instrument the spine is predicated mainly on curve magnitude (i.e. major curve Cobb angle ≥50°) and rate of progression (≥10° per year). Other factors, such as decreasing respiratory function, parasol rib deformity, hyperkyphosis and adverse effects on functional mobility, pelvic obliquity, and trunk imbalance should also be considered. Pulmonary function tests should be considered as part of the pre-operative evaluation to determine surgical risk and post-operative respiratory management.

There was consensus that surgical treatment of spine deformity should be delayed until after the age of 4 years (Supplementary Table S4).

In skeletally *immature* patients younger than 8 to 10 years, "growth-friendly" instrumentation, that stabilizes and improves spinal deformity, but allows for continued spine growth should be considered [3,50,52,56–60]. To decrease the need for repeated surgery, magnetically controlled growing rods have recently been advocated [61] as an alternative to traditional growing rods that require sequential surgical lengthenings [62–65]. For children between the ages 8 to 12 years, there was variability in practice among members of the expert panel; the surgical approach depended on clinical variables, especially skeletal maturity and spine growth remaining. In nearly skeletally mature patients 12 years of age or older, definitive posterior spine fusion using dual rod, multi-segmental constructs should be implemented with or without extension to the pelvis, depending on whether the pelvis is part of the scoliotic curve [66]. While there were no published studies on how to accommodate for intrathecal access in patients undergoing spinal instrumentation, there was consensus that one or two mid-lumbar levels should be left unexposed in the midline to accommodate intrathecal access, necessary for the administration of recently approved drugs such as nusinersen, and antisense oligonucleotide which does not cross the blood brain barrier. Conversion of growth-friendly instrumentation to definitive posterior spine fusion should be decided on a case-by-case basis.

2.5.1.2.3. Chest deformity, thoracic insufficiency and pulmonary health. As a consequence of poor trunk and thoracic muscular support, children with SMA have an increased incidence of thoracic insufficiency, the result of scoliosis and distortion of the rib cage [50,67]. Collapse of the ribs (similar to closing an umbrella) contributes to "parasol rib" deformity [53,54,67–69]. Retrospective study of children with hypotonic scoliosis treated with either rib- or spine-based growth-friendly instrumentation systems have shown poor efficacy in ameliorating parasol rib deformity or increasing thoracic volume, and therefore are not recommended [67].

2.5.1.2.4. Hip instability. Hip instability is common in patients with SMA [3,50,55,70]. Several older studies recommended against surgical repair, noting that surgically treated hips tended to re-subluxate or dislocate, and that hip pathology rarely caused pain [3,50,55,70]. However, these studies failed to reflect modern surgical techniques and did not evaluate young adult and middle-aged patients. Unilateral and bilateral hip instability should be surgically managed only in patients with significant pain.

2.5.1.2.5. Contractures. Contractures are common in patients with SMA as a result of decreased range of motion, prolonged static positioning, and agonist-antagonist muscle imbalance [50,71,72]. Functionally and symptomatically, contractures can lead to pain and inhibit function in patients

with SMA [24,42–46,71–75]. Conservative management of joint contractures has been discussed in the rehabilitation section [24,42–46]. Surgical management of contractures of the upper or lower extremities should be considered when they cause pain or impair function.

2.5.1.2.6. Management of fractures. Owing to disuse, osteoporosis and low vitamin D levels, fragility fractures are common in children with SMA 1 and 2. Closed treatment with cast immobilization is generally recommended for non-ambulatory patients, but prolonged cast immobilization (>4 weeks) that aggravates muscle wasting and disuse osteoporosis should be avoided. Ambulatory patients with long bone fractures of the lower extremities and non-ambulatory patients with hip fractures generally benefit from surgical stabilization using intramedullary rods or bridging fracture plates to restore immediate bone stability to allow early range of motion of the extremity and to promote accelerated fracture healing.

2.6. Nutritional management, swallowing and gastrointestinal dysfunction

The main topics covered include swallowing dysfunction and dysphagia, weight control and gastrointestinal dysfunction (Table 2).

Table 2
Nutritional assessment and intervention.

	Assessment	Intervention	Care considerations
Non-sitters	Video Fluoroscopic Swallow Study shortly after diagnosis and when suggested by clinical signs suggestive of dysphagia (weak suck, fatigue, humid voice, pneumonias) Difficulties with feeding (pocketing, jaw contractures, increased mealtimes) Nutritional analysis of food records/feeding regimen Longitudinal anthropometrics Acute care monitoring 25 Hydroxy-vitamin D labs and Body Composition and Bone density Constipation	If swallow study is passed, consider referral to specialist for feeding therapy/modification For failure of a swallow study or for growth failure, for proactive care, place nasojejunal tube until a Gastric-tube can be placed with Nissen fundoplication. A dietitian should adjust caloric, fluid, macronutrient, micronutrient intake and timing of feeds. Nutrition labs may be indicated. Minimize fasting during acute care to less than 6 hours. Provide adequate fluid intake during illness. Monitor electrolyte levels and correct as needed. Monitor glucose levels to correct hypo/hyperglycemia. Provide adequate calcium, vitamin D intakes for bonehealth. Adequate hydration. Use of bowel regulation medications.	Determine appropriate calorie needs based on growth. Standardized growth charts are a good tool to track growth trends, but optimally, should be used with other body composition measurement tools to assess appropriate growth. For optimal care, recommend evaluation by a dietitian every 3–6 months for younger children and annually for older children/adults. Evaluation is especially important for those on specialized diets.
Sitters	Assessment of symptoms of dysphagia/aspiration/Difficulties with feeding Video Fluoroscopic Swallow Study if suggested by clinical signs suggestive of dysphagia. Nutritional analysis of food records/feeding regimen Longitudinal anthropometrics (height, weight, OFC) Nutrition labs may be indicated. Acute care monitoring Glucose metabolism labs 25 Hydroxy-vitamin D labs and Body Composition and Bone density (DXA) Constipation	If safe to swallow, refer to specialist for feeding therapy/modification. If failed swallow or interventions are not sufficient place nasofeeding tube as indicated prior to placement of a long term Gastric feeding tube. For growth failure, provide supplemental nutrition products. Referral to dietitian for increasing calories with nutrient dense foods. Adjust caloric, fluid, macronutrient, and micronutrient intake based on growth and intake. Limit calorie intake in overweight individuals and maximize nutrient intake. Minimize fasting during acute care. Appropriate fasting time depends on prior nutritional status and nature of acute event. Provide adequate fluid intake during illness. Monitor electrolyte levels and correct as needed. Monitor glucose levels to correct hypo/hyperglycemia. Indicated for individuals with increased body fat or other prediabetic symptoms. Adequate calcium, vitamin D intake. Diets rich in fiber are recommended to promote gastric motility and reduce constipation. Adequate fluid is needed with increased fiber intakes. Bowel regulation medication may be indicated.	At minimum, recommend evaluation by a dietitian shortly after diagnosis and for concerns of under/over nutrition. For optimal care, recommend evaluation by a dietitian every 3–6 months for younger children and annually for older children/adults. Evaluation is especially important for those on specialized diets.
Ambulant	See dietitian for concerns of over/under nutrition Nutritional analysis/monitoring if underweight or overweight Longitudinal anthropometrics (height, weight, OFC). Glucose metabolism labs 25 Hydroxy-vitamin D labs	Provide macro/micronutrient intakes based on guidelines for a healthy sedentary individual. Limit calories as indicated to prevent obesity. Minimize fasting during acute care Indicated for individuals with increased body fat or other prediabetic symptoms Provide adequate calcium, vitamin D intakes for bonehealth if needed	

For all SMA types regular assessments of growth are important and an expert nutritionist should be involved to promote an appropriate diet, monitoring not only weight but also fluid, macronutrient, and micronutrient intake, especially calcium and vitamin D intake for bone health [76–78]. SMA-specific growth charts are not yet available. Secondary to altered body composition in SMA [79–81], experts are divided in the use of standardized growth charts alone to monitor appropriate growth, but they may be helpful to monitor trends.

In all types it is important to ask and document details regarding GI symptoms such as presence of gastroesophageal reflux, constipation, use of bowel regulatory agents, delayed gastric emptying, and vomiting.

Over the last few years there has also been increasing evidence of possible metabolic abnormalities in SMA patients such as metabolic acidosis, abnormal fatty acid metabolism, hyperlipidemia, hyperglycemia, hypoglycemia, and muscle mitochondria defects [82–84]. Perturbations of glucose metabolism and pancreatic development have been reported in SMA mice [85–89]. Glucose metabolism abnormalities were later confirmed in some obese SMA patients [90,91] and pancreatic differences confirmed in deceased SMA 185.

2.6.1. Non sitters

2.6.1.1. Assessment. Safe swallowing is one of the most important aspects to consider for a non-sitter (Supplementary Table S5). Bulbar dysfunction can result in aspiration and pulmonary infections. A full modified barium swallow fluoroscopic study is recommended shortly after diagnosis and, if the initial test is normal, closely monitored to detect possible early signs of feeding difficulties. Contracture of the masseter muscles often develops in patients by one year of age and limits the opportunity for oral feeding. This may be a limiting factor for patients treated with nusinersen who demonstrate improvement in bulbar muscle strength.

Optimal nutritional management includes longitudinal evaluation of weight and length and dietary analysis. In type 1 patients, masticatory muscle weakness, dysphagia and respiratory problems are responsible for reduced calorie intake and risk of undernutrition. Additionally, increased work of breathing may increase energy expenditure and caloric requirements, further increasing the risk of undernutrition.

2.6.1.2. Intervention. For proactive care following a failed swallow study or growth failure, placement of a short-term nasogastric or nasojejunal tube is recommended until long term gastrostomy tube can be placed. There was no unanimous consensus but many experts prefer that Nissen fundoplication be performed in conjunction with gastrostomy tube placement secondary to decreased gastrointestinal motility, reflux, and increased pressure related to respiratory treatments [92] (Supplementary Table S6).

There is less consensus on the effect of the type of diet [12]. Consensus is divided on the use of the Amino Acid diet, a diet based on elemental formula [83,93]. Experts agreed that diet type and administration should be based on individual tolerance. Adequate hydration as well as bowel regulating agents, probiotics, and motility medications are recommended to ease symptoms of constipation and gastrointestinal dysmotility.

Regarding nutritional aspects during acute care in non-sitters, it has been strongly suggested that fasting should be avoided to prevent including metabolic acidosis, fatty acid metabolism abnormalities, and hyper/hypoglycemia [82,83,93–95]. Divided expert opinion suggests that nutrition including a protein source should be provided within 6 hours during acute episodes. Adequate hydration and electrolyte balance is imperative during illness.

2.6.2. Sitters

2.6.2.1. Assessment. For optimal care, nutrition evaluations are recommended after diagnosis and periodically, every 3–6 months for younger children and annual evaluations afterwards.

Chewing difficulties and fatigue with eating, are frequent in sitters [96,97]. Safe swallowing and risk of aspiration are also a concern. A history of choking or coughing episodes with feeds should be investigated and monitored with swallow studies.

Feeding evaluations are also recommended for possible feeding modifications/occupational therapy in order to swallow safely and eat effectively.

Longitudinal measures of weight and length in conjunction with body composition measures are recommended to promote appropriate growth.

Evaluation for obesity as well as glucose metabolism abnormalities may be recommended for overweight sitters. Some experts suggest that sitters with SMA should be evaluated for possibility of obesity/overfat at BMI greater than the 25th percentile [91].

Evaluation of fluid and fiber intake is recommended for frequent constipation.

2.6.2.2. Intervention. In a case series study 37% of sitters have growth failure and require intervention [96]. Feeding tubes are commonly used in this population for supplementary nutrition rather than total nutrition and suggestions for feeding tubes and GI surgical recommendations depend on the individual situation.

Sitters may be at risk for being overweight/obese as they grow older secondary to the reduction in physical activity due to weakness and altered body composition [80,91]. Concerns for overweight include reduced mobility and risks for related comorbidities including risk of metabolic syndrome [86,93].

Diet is variable in sitters. Calories, protein, fat and carbohydrate, are initially estimated using common standardized equations [98] and should be adjusted as appropriate growth and labs indicate. There is lack of consensus on the use of the amino acid diet and no data to support the use of synthetic amino acid as opposed to intact protein in patients with SMA.

Based on experience and case studies [93–95] experts recommend that fasting times should be limited during acute circumstances and electrolyte and fluids should be monitored and repleted as indicated.

Depending on severity of constipation, fiber intake, probiotics, and bowel regulating agents may be used to improve symptoms.

2.6.3. Walkers

In this population, swallowing dysfunction and feeding difficulties are rare. A dietitian/nutrition evaluation is recommended if there are nutritional issues. The largest nutritional concerns for walkers with SMA is the risk of obesity and overweight as this can reduce mobility and may increase risk of obesity-related comorbidities such as metabolic syndrome, high blood pressure, and diabetes.

2.6.3.1. Bone health. It has been recognized that SMN has a specific role in the metabolism of the bone interacting with osteoclast stimulatory factor osteoclast stimulatory factor [99]. Therefore, the high incidence of osteopenia and fractures in SMA patients may not be simply attributed to muscle weakness and lack of exercise [76,100,101]. Periodic Dual energy x-ray absorptiometry analysis (DEXA) to monitor bone density in patients with SMA, is recommended yearly. There was consensus among experts that Vitamin D blood levels and intake should be monitored at least annually and supplements should be given in the presence of low levels or of osteopenia. In the case of frequent fracture, review may be given to use of bisphosphonates.

3. Conclusions

The recommendations reported in this first part provide an overview of what should be considered standard of care for SMA. The paper highlights the importance of a multidisciplinary approach and of the role of the neurologist/pediatric neurologist in coordinating, together with the families, the various aspects of care.

In all the aspects of care included, there was often not enough published evidence and the recommendations were the results of what was available from the literature and experts' opinion, following a well-established Delphi method to classify consensus and appropriateness of assessments and interventions. The working groups identified the aspects that constitute optimal care but considering that some of the recommendations may not be easily applicable in centers or countries with less resources, an effort was made to identify assessments or interventions that constitute the *minimal care* that families should expect to find in any neuromuscular centre.

The second part of the two-part paper will focus on other aspects of care, such as pulmonary and acute care, involvement of other organs, medications and ethical issues.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2017.11.005.

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Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics

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Abstract

This is the second half of a two-part document updating the standard of care recommendations for spinal muscular atrophy published in 2007. This part includes updated recommendations on pulmonary management and acute care issues, and topics that have emerged in the last few years such as other organ involvement in the severe forms of spinal muscular atrophy and the role of medications. Ethical issues and the choice of palliative versus supportive care are also addressed. These recommendations are becoming increasingly relevant given recent clinical trials and the prospect that commercially available therapies will likely change the survival and natural history of this disease.

Keywords: Spinal muscular atrophy; Care; Pulmonary; Acute; Nutrition

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1. Introduction

This is the second part of a two-part document aimed at updating the standards of care recommendations published in 2007 [1]. Included here is an update of some of the topics included in the earlier publication, such as respiratory management, but also topics that were only described briefly in the original publication, such as acute care, other organ involvement and ethical issues. Recent clinical trials [2,3] and the approval in December 2016 by the United States Food and Drug Administration, and subsequently in May 2017 by the European Medicine Agency, of the first drug for SMA have led to include a review of 'medication' in order to provide the state of art on the medications that have been used in the last decade, and a brief update on the new therapeutic approaches that are becoming available. This update also takes into consideration how the impact of new therapies is changing the attitude of families and physicians toward a more proactive approach, especially in type 1 spinal muscular atrophy (SMA). As with the first part, this update includes the results of dedicated working groups of experts in each topic, who, after a thorough review of the literature, used a Delphi analysis process to identify areas where evidence could be extrapolated from the literature and establish whether consensus could be reached among experts. Details of the methodology used are available in the first part and in a recent workshop report [4].

2. Pulmonary management

It is well known that spinal muscular atrophy has an impact on the respiratory system that is dependent in large part on the type of SMA or more precisely the severity of loss of muscle function [5].

3. Non-sitters

3.1. Assessment

The focus of the clinical assessment should be a physical examination (Table 1). Screening non-sitters for respiratory failure should include assessment with pulse oximetry and capnography (end tidal CO2 (EtCO2) or transcutaneous CO2 (TcCO2)) when awake), and using sleep study or pneumogram with CO2 recording when there is even minimal suspicion of hypoventilation. Data from the literature and expert opinion supports using a sleep study to confirm when a patient has sleep disordered breathing or respiratory failure and needs to use non-invasive positive pressure ventilation (NIV) [6].

Clinic visits are recommended initially for every 3 months for non-sitting patients with SMA.

3.2. Intervention

Over the last decade, the approach to treating the pulmonary manifestations of SMA has shifted from a reactive approach, of starting treatment to support airway clearance and ventilation only when there is a clear indication, to a proactive approach of introducing these therapies earlier in the disease process [7]. (Fig. 1). A respiratory therapist should be involved to initiate and support assisted airway clearance and respiratory range of motion therapy.

3.3. Airway clearance

Manual chest physiotherapy combined with mechanical insufflation–exsufflation (e.g., Cough Assist® or VitalCough®) should be the primary mode of airway clearance therapy and should be made available to all non-sitters (Table 1). Because of the importance of aggressive management of respiratory illnesses [6,8–12], airway clearance techniques should be introduced proactively in patients based on either clinical assessment of cough effectiveness or by measuring peak cough flow (not a routinely performed test in infants) [6]. When initiating cough assist devices, the insufflation and exsufflation pressures should be increased gradually to 30–40 cm H2O of positive or negative pressure, respectively [10], or instead increase them to the maximal tolerated pressure.

In the absence of significant parenchymal lung disease with small airway obstruction and air trapping there is no significant risk of pneumothorax in using the cough assist. While there is the potential of aerophagia and gastric distention in using the cough assist, this risk and the subsequent risk of aspiration can be mitigated in GTube venting to prevent gastric distention.

While there are case reports suggesting the use of mechanical insufflation or NIV to help prevent chest wall distortion [10,13,14], there was less consensus whether this is always a reasonable expectation and on the specifics of how to best accomplish this (supplementary Table S1).

Oral suctioning with a mechanical suction pump and catheter is a critical part of airway clearance in non-sitters and should be used with any patient with an ineffective cough.

The high frequency chest wall oscillation (Vest) therapy does not improve clearance of secretions in the setting of an ineffective cough or improve clearance of secretions.

3.4. Ventilation

Non-invasive positive pressure ventilation (NIV) should be used in all symptomatic infants [8–10,14,15], and in non-sitters prior to signs of respiratory failure, to be "prepared" for respiratory failure, prevent/minimize chest wall distortion, and palliate dyspnea.

Continuous positive airway pressure (CPAP) should not be used to treat chronic respiratory failure, but may be used with caution temporarily to help maintain resting lung volume (functional residual capacity (FRC)) in younger patients who are unable to synchronize with the ventilator in NIV mode, and who are not markedly hypercapnic. This applies also to weak non-sitters. It should be recognized that CPAP may fatigue SMA patients and could interfere with weaning from full time use.

Interface selection and fitting to the patient by an experienced clinician is strongly recommended, as was using at least two comfortable interfaces with different facial contact points, and using a nasal interface initially. In non-sitters there is strong support for initiating NIV using clinical titration with focus on correcting gas exchange and reducing the work of breathing.

Tracheotomy ventilation is an option in selected patients in whom NIV is insufficient or fails, or if there is no effective

Table 1
Pulmonary assessment, intervention and management recommendations.

	Assessment	Intervention	Care considerations
Non-sitters	Physical examination Assessment of hypoventilation (End tidal CO2) Sleep study or pneumograms in all symptomatic patients or to determine if a patient needs to initiate NIV Clinical assessment of gastroesophageal reflux	Support airway clearance Oral suctioning Physiotherapy/respiratory therapy should be implemented immediately: Manual chest therapy Cough insufflator/exsufflator Support ventilation with bilevel NIV in symptomatic patients	Assessments should be performed at least every 3 months initially, then every 6 months Supporting airway clearance with oronasal suctioning, physiotherapy/respiratory therapy and cough assist is critical to all non-sitters with ineffective cough Ventilation should be started in all symptomatic patients. Some experts recommend using it before documented respiratory failure to palliate dyspnea. This should be judged on individual basis NIV should be initiated in observing the patient clinically for adequate gas exchange or during a sleep study. NIV interfaces should be fitted by skilled physiotherapists selecting two interfaces with different skin contact points.
		Nebulized bronchodilators in patients with asthma or a positive bronchodilator response Customary immunizations, palivizumab through 24 months, influenza vaccination annually after 6 months of age	Mucolytics should not be used long-term
Sitters	Physical examination Spirometry (when possible depending on age and cooperation) Sleep study or pneumograms in all patients with even minimal suspicion of symptoms of nocturnal hypoventilation Assessment of gastroesophageal reflux	Support airway clearance Physiotherapy/respiratory therapy should be implemented immediately: Manual chest physiotherapy Cough insufflator/exsufflator Support ventilation with bilevel NIV in symptomatic patients	Assessments should be performed every 6 months Supporting airway clearance is critical to all patients with ineffective cough Ventilation should be started in all symptomatic patients. Some experts recommend using it during acute respiratory illnesses to facilitate discharge. NIV should be initiated during a sleep study or observing the patient clinically for adequate gas exchange. NIV interfaces should be fitted by skilled physiotherapists selecting two interfaces to alternate skin contact points.
		Nebulized bronchodilators in patients with suspicion of asthma Customary immunizations, annual influenza and pneumococcal vaccination	Mucolytics should not be used long-term
Ambulant	Clinical examination with review of cough effectiveness and detailed search for signs of nocturnal hypoventilation	Supportive care when needed Customary immunizations, annual influenza and pneumococcal vaccination	Evidence of weak cough or recurrent infections or suspicion of nocturnal hypoventilation should prompt referral to a pneumologist

interface for providing ventilation. This should be a decision focused individually on the clinical status, prognosis, and quality of life based on discussion with the family.

3.5. Medications

Nebulized bronchodilators should be available if there is suspicion for asthma. Nebulized mucolytics, 3% or 7% hypertonic saline or dornase-α (Pulmozyme®) should not be used long-term as there is no evidence to support its use. Furthermore, if 3% or 7% saline is used beyond the therapeutic need it can thin secretions of normal viscosity thereby increasing secretion burden. Glycopyrrolate should be used with caution to treat hypersalivation with great care to adjust the dose to attain the proper effect, and avoid over drying of secretions, which may contribute to the development of mucus plugs. There was no consensus for the injection of botulinum toxin into the salivary glands or other methods to reduce production of oral secretions. Palivizumab should be given during RSV season as determined by regional RSV activity through the first 24 months of life, and influenza vaccination should be administered annually after 6 months of age. Gastroesophageal reflux should be searched for and treated when present.

4. Sitters

4.1. Assessment

The focus of the clinical assessment should be a physical examination supported by clinical assessment of cough function. For sitters and standers, there is consensus that all patients able to perform spirometry should do so during each visit.

There was no clear consensus on the value of peak cough flow measurement or when a sleep study should be performed in the management of sitters. A sleep study should always be performed, however, in symptomatic patients or when there is even a minimal suspicion of nocturnal hypoventilation to determine when a patient has sleep disordered breathing or respiratory insufficiency and needs to use bilevel NIV [6].

Clinic visits are recommended, every 6 months for sitters.

5. Intervention

5.1. Airway clearance

Manual chest physiotherapy combined with mechanical insufflation-exsufflation (e.g., Cough Assist® or VitalCough®) should be made available to all patients with an ineffective cough. It should be introduced proactively in patients using either clinical assessment of cough effectiveness or by measuring peak cough flow [6]. The issues related to settings are similar to those described for non-sitters.

5.2. Ventilation

Similar to non-sitters, non-invasive positive pressure ventilation (NIV) should be used in all symptomatic patients [8–10,14,15]. The best approach is individualized to each patient's need and quality of life. A sleep study should be used to determine when a patient has sleep disordered breathing or respiratory failure and needs to use bilevel NIV, and to titrate settings [6]. (Fig. 1)

As reported for non-sitters, continuous positive airway pressure (CPAP), with rare exceptions, should not be used.

The need for tracheostomy ventilation is less frequent than in non-sitters but in some weak sitters bilevel NIV can be insufficient or fail. As for non-sitters this should be a decision based on clinical status and discussion with the family and patient, if age-appropriate.

5.3. Medications

Nebulized bronchodilators should be available if there is high suspicion for asthma or a clear clinical improvement after administration. Nebulized mucolytics should not be used long-term. Annual influenza and pneumococcal immunizations should be administered per standard pediatric recommendations for patients with chronic neuromuscular conditions.

6. Walkers

6.1. Assessment

Most ambulant patients with SMA type 3 have normal pulmonary function, but with a small decline noted over a 4-year span in one natural history study [5,16]. Nonetheless, the clinical assessment of these patients should include careful review of cough effectiveness with an upper respiratory infection, and search for any symptoms of sleep apnea or hypoventilation (snoring, arousals, morning headaches, daytime somnolence). The presence of any such concerns should prompt an assessment by a pulmonologist with consideration of pulmonary function testing and sleep study. Pre-operative assessment is also important.

6.2. Intervention

No pro-active interventions are indicated for ambulant patients with SMA. Supportive care should be provided when there are specific concerns identified in the clinical assessment. Immunizations are the same as for sitters.

6.3. Acute care management

Acute care for children and adults with SMA expands upon the vigilant respiratory and multidisciplinary care recommended for outpatient management. Individuals affected by SMA are particularly vulnerable to acute respiratory decompensation, related to community-acquired infections, aspiration, and impaired

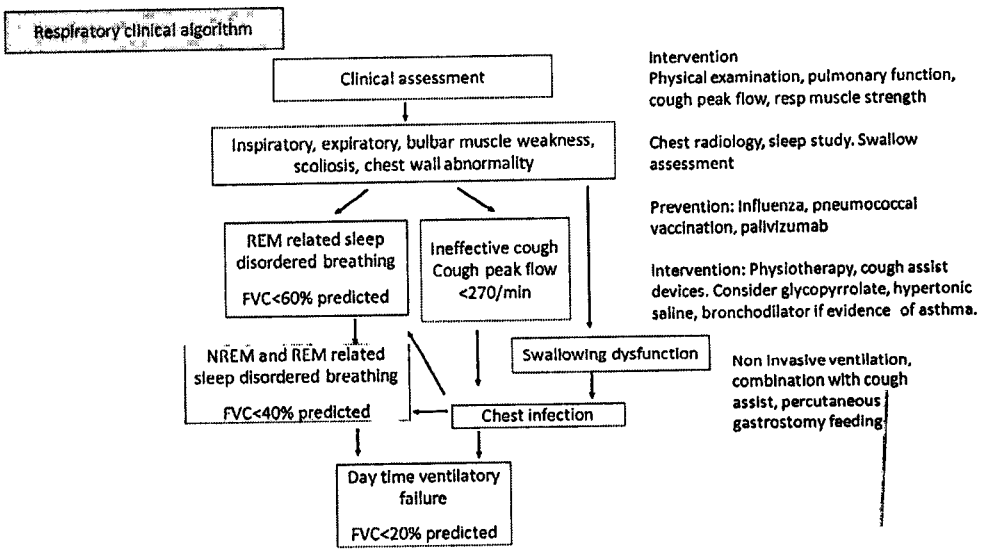

Fig. 1. Respiratory clinical algorithm.
(REM: rapid eye movements; NREM, non-REM; FVC: forced vital capacity)

secretion clearance [1,17,18]. Baseline diffuse muscle weakness is often exacerbated during illness. Associated increased metabolic demands with insensible fluid losses necessitate additional consideration of appropriate nutritional support and avoiding fasting [19–21]. Acute hospitalization may be required to support those with SMA experiencing the range of routine illnesses (e.g., viral respiratory infection, gastroenteritis with dehydration, and appendicitis among other acute processes), unanticipated bone fracture management, labor and delivery for women with SMA, and scheduled surgical procedures (e.g., gastrostomy tube placement, femoral osteotomies, and spinal instrumentation along with other preventative strategies, supportive interventions, or symptom management). Extensive consideration is required, whether admission is planned or unanticipated at the individual's primary neuromuscular care hospital or other institution (Table 2). The following considerations were devised mainly for non-sitters and sitters but some aspects may also be applied to weak ambulant type 3 children and adults who also often present some degree of respiratory impairment or nutritional issues and are at higher risk during acute illness (supplementary Table S2).

6.4. Assessment and management of acute illness at home

Individualized anticipatory care plans should be developed and include review of vital signs (e.g., oxygen desaturation and tachycardia) and symptom parameters and prompting escalation of care with specific recommendations for airway clearance, ventilation, nutrition, hydration, antibiotics, and emergency contact measures (Table 2).

Patient-specific protocols should be created based upon community resources, emergency medical services, and hospital capacity to provide for children and adults with SMA and other neuromuscular conditions.

When appropriate, families should be provided with homecare technology for monitoring respiratory function and providing related support, such as augmented secretion clearance, bilevel NIV to prevent hospitalization, and to optimize status prior to presentation. This equipment, when available, should be, brought by the family for possible use during transport.

As part of the anticipatory care, discussions with families about the options for both chronic and acute respiratory care should occur early in the disease course and written anticipatory resuscitation statements prepared with the family should be available for any professional involved in the transport or in the emergency room. Similarly, families should have a list of medical needs and neuromuscular providers including pulmonology/respirology.

Criteria for presentation to emergency care should include severity of acute clinical signs and symptoms in relation to capacity and limitations of homecare technology and providers.

Table 2
Acute care goals, intervention strategies and management recommendations: Home care and transportation.

Home care setting	Individualized anticipatory care plans should be developed and outline: • airway clearance, • ventilation, • nutrition, • hydration, • antibiotics, • emergency contact measures	Augmented secretion clearance, bilevel NIV, and oxygen supplementation should be provided to prevent hospitalization and/or optimize status prior to presentation Local emergency services should be made aware of the individual's needs in advance.
	General assessment and review of signs and symptoms	Respiratory assessment and support should be of highest priority independent of hospitalization indication
	Criteria/thresholds for presentation to emergency care	Criteria should include severity of clinical signs and symptoms in relation to capacity of homecare providers (nursing and family), limitations of homecare technology (support and monitoring)
	Communication for EMS and acute care providers	Families should have a summary of medical needs, list of primary providers, care protocols, and written anticipatory resuscitation statement available.
Community first responders transportation	Community first responders	EMS should be provided by staff with advanced cardiac life support or equivalent certification and who have the capacity to provide noninvasive and transtracheal ventilation for types I and II individuals.
	Modality of transportation	Mode of transportation between home and acute care facility should be considered on a case-by-case basis
	EMS triage	Presentation to the closest facility should be considered based upon the individual's degree of illness, distance from a tertiary care facility, availability of pediatric transport team, environmental considerations, and goals of care.
	Hospital level	Children and young adults with SMA I or II should be hospitalized at a tertiary care center, whether scheduled or emergent.
	Personal medical equipment during transport	The family should bring home equipment (e.g., NIV, cough assist device, mask interfaces, suction machine, oximeter, gastrostomy adaptors) for use during transport.

(NIV: non-invasive ventilation (bi-level positive air way pressure, not continuous positive airway pressure): EMS: emergency medical services, SMA: spinal muscular atrophy).

6.5. Transport from home to a medical facility considerations and emergency department evaluation

Hospitalization care considerations should include site or level of care, degree of illness, and goals of care including need for respiratory protocols, nutrition and hydration. Non-sitters and sitters should be triaged to tertiary care centers with SMA expertise. Presentation to the closest facility should be considered based upon the goals of care, distance from a tertiary facility, availability of pediatric transport team, and other aspects such as environmental considerations.

Engagement of the neuromuscular team providers during acute care is critical.

Emergency medical services should be provided by certified staff who have the capacity to provide the most appropriate level of ventilation and cardiac and respiratory life support.

Mode of transportation between home and acute care facility should be considered on a case-by-case basis involving the neuromuscular team.

6.6. Medical care site/hospital capacity considerations

Respiratory assessment and support should be of highest priority [22–25] (Table 3). Management should include proactive measures including optimizing use of bilevel positive airway pressure (i.e., NIV, not CPAP) respiratory support with a backup respiratory rate (delivered via noninvasive measures, tracheostomy, or endotracheal tube) and augmented secretion clearance prior to empiric oxygen supplementation.

Oxygen supplementation should not be provided empirically in the absence of NIV or without monitoring CO2 gas exchange. Oxygen supplementation should not be withheld, but weaned to minimal provision prior to extubation and not employed in lieu of positive pressure ventilatory support.

The multidisciplinary team (neuromuscular and respiratory) should be contacted to assist with acute care protocols, involving the physician, generally the neurologist or pediatric neurologist, who is aware of the disease course and potential issues [26,27]. Family should be involved [28,29].

Table 3
Acute care goals, intervention strategies and management recommendations: Hospital, and sedation/anesthesia.

Hospital	Goals of care	Goals of care, including resuscitation status, health care proxy (when age appropriate), indications and role of tracheostomy tubes, and other interventions, should be specified prior to the need for acute care. If not, the consultant teams should be engaged to facilitate discussion with the acute care team and family. Oxygen supplementation should not be provided empirically in the absence of bilevel NIV.
	Respiratory Care Protocols	Early and aggressive respiratory protocols should be implemented. Emphasis should include proactive measures, noninvasive supports use of positive pressure and augmented secretion clearance prior to empiric oxygen supplementation.
	Augmented secretion clearance	Augmented secretion clearance should be the priority during acute respiratory illness.
	Respiratory support in the Emergency Room	Noninvasive respiratory supports should be instituted early.
	Role of the consultant team	Acute care providers should contact consultant providers (e.g., neuromuscular, respiratory) to assist with acute care protocols.
	Endotracheal intubation	Threshold for endotracheal intubation should be established at the outset of an admission. Difficult airway status should be considered based upon mandibular contractures, limited neck mobility, positioning restrictions and other factors.
	Extubation criteria	If pulmonary consolidation was demonstrated on radiograph, re-expansion should be established prior to extubation. NIV should be implemented as transitional support following extubation. Oxygen supplementation should be weaned to minimal provision prior to extubation and not employed in lieu of positive pressure ventilation.
Sedation and Anesthesia	Pre-anesthetic/sedation evaluation	Sedation and anesthesia should be provided at a tertiary care center familiar with SMA management. Consultation with respiratory providers, consultant team, and an anesthesiologist familiar with SMA should be obtained prior to sedation or general anesthesia. Discussions should include options of noninvasive and invasive airway support.
	Pre-anesthetic studies	A low threshold for deferring elective/non-emergent sedation/anesthesia should be considered during intercurrent illness across all SMA types. Cardiology screening, polysomnograms, and nutritional assessment might be considered as part of a pre-anesthetic evaluation Respiratory supports (i.e., NIV and cough assist) might be introduced prior to sedation and anesthesia to optimize preprocedural standing and for desensitization.
	Sedation/anesthesia	A monitored setting should be considered. Monitoring should include capnography.
	Post-sedation and anesthesia management	Aggressive secretion clearance measures (cough assist when intubated and extubated) should be integral to post-anesthetic care. Excessive oxygen supplementation in lieu of positive pressure and extubation to NIV should be avoided.
	Analgesia provision	Opiate-based analgesia should be considered as part of routine post-procedural management. Regional analgesia might be considered for all SMA types.

(NIV: non-invasive ventilation (bi-level positive air way pressure, not continuous positive airway pressure); SMA: spinal muscular atrophy).

As reported in the Nutritional Care Section, during acute illness, fasting should be avoided to prevent metabolic acidosis, hyper/hypoglycemia or fatty acid metabolism abnormalities [20,21,30–32]. Adequate hydration and electrolyte balance are imperative.

Attention should be paid to the risk of aspiration, when orally feeding a weaker child during illness.

Criteria establishing the threshold for endotracheal intubation should be established taking into account several factors including limited neck and mandibular mobility, and positioning restrictions and patient and family preference.

Extubation criteria and procedure should be established (see supplementary Table S3).

There is no clear evidence to support empiric use of antibiotics or volume resuscitation (except for sepsis management in the general population) during acute illness or to guide viral testing or other diagnostics. For these issues, providers should consider presentation characteristics, the presence of indwelling devices and history of recent surgical interventions, and recurrent antibiotics.

Integration of physical and occupational therapy, psychosocial services, speech-language pathologist, palliative care services and Endocrinology consultants can contribute to other aspects of care such as skin care or bone fracture risk.

6.7. Hospital discharge considerations

Discharge planning should begin shortly after admission to identify goals with the patient/family, inpatient team, and primary care providers. Planning should consider threshold for discharge, need to augment outpatient services, follow-up care, and indications for urgent re-hospitalization. Threshold for discharge based on medical status will depend on the comfort and skill of family and outpatient medical care team.

6.8. Preprocedural screening [33], anesthesia/sedation consideration [34,35] and pain management

Polysomnograms and nutritional assessment may be considered as part of a pre-anesthetic evaluation. Cardiology screening is not recommended, unless there is a concern for cardiac dysfunction in older individuals or conditions unrelated to SMA. Difficult airway status should be considered based upon mandibular contractures, limited neck mobility, positioning restrictions and other factors. A low threshold for deferring elective/non-emergent sedation/anesthesia should be considered during intercurrent illness across all SMA types. Opiate-based analgesia should be considered as part of routine post-procedural management with anticipation of providing appropriate NIV and cough assistance.

Regional analgesia may be considered for all SMA types and may allow for lower amounts of systemic analgesics with subsequent effects on respiratory drive and intestinal motility. Practical consideration must be taken into account when evaluating for epidural catheter placement in context of pre-existing scoliosis. Monitoring during procedural sedation and anesthesia should include capnography to complement oximetry, as apneic or hypopneic oxygenation should be avoided.

Additional recommendations not addressed in the Delphi survey include consideration of delivery of novel gene-targeted therapies and other interventions for individuals with SMA. For example, provision of repeated intrathecal drug therapies such as recently approved antisense oligonucleotides will require extensive planning for developmentally appropriate and safe care, including procedural sedation, interventional radiology support, and potential orthopedic considerations. The anticipated emergence of gene replacement with viral vectors and other disease/symptom modifying agents may also require extensive acute care supports. Understanding that the natural history of this condition and recognized phenotypes will be altered should prompt all providers (acute, chronic, hospital-based, or community) to engage accordingly in informed discussions and adjustment of the acute care paradigm.

7. Medication, supplements and immunizations

Until recently no drug treatment had proved to be able to influence the disease course of SMA. A Cochrane review published in 2012 reported six randomized placebo-controlled trials on treatment for SMA using creatine, phenylbutyrate, gabapentin, thyrotropin-releasing hormone, hydroxyurea and combination therapy with valproate and acetyl-L-carnitine [36,37]. None of these studies showed statistically significant effects on the outcome measures in participants with SMA types 2 and 3. Others have reported using other possible therapeutic approaches, such as albuterol, a beta-adrenergic agonist that showed promising functional improvements in open label studies [38,39].

Despite the lack of evidence from randomized placebo-controlled trials, some of these drugs, especially albuterol, are often used in some countries in clinical practice in sitters and ambulant patients.

Antibiotics or medications/supplements for bone health, such as vitamin D and calcium and bisphosphonate, or drugs for gastroesophageal reflux, were recommended with the exception of vitamin D, rarely used prophylactically, and mainly used if needed/deficient. These are discussed in the sections dedicated to bone health and nutrition.

Annual influenza and pneumococcal immunizations, as reported in the pulmonary section, were strongly recommended.

At the time the consensus process was completed, none of the drugs involved in clinical trial had completed the regulatory process and were commercially available. Nusinersen (Spinraza™), an antisense oligonucleotide that had completed phase 3 clinical trials in both type 1 and type 2 SMA [3,40,41], received recent approval both by the United States Food and Drug Administration and by the Agency for Medicines Agency in Europe for the treatment of all SMA types and has become commercially available in several countries. While the early patient and family clinical outcomes have been very favorable, because nusinersen is intrathecally administered, there is a required institutional infrastructure to provide administration and post-procedural monitoring in a reliable way. In addition the cost of the medication has made long term insurance company approval uncertain.

Olesoxime, a neuroprotective drug, has completed a phase 3 trial in patients with type 2 and 3 SMA, but the primary endpoint was not met. Secondary endpoints and sensitivity analyses indicate that olesoxime might maintain motor function in patients with SMA [42]. Other approaches, such as small molecules aiming to increase SMN protein level or *SMN1* gene replacement using viral vector, are also being used in clinical trials with promising preliminary results [43] and in the next few years the scenario is likely to rapidly change.

8. Other organ system involvement

SMA is primarily a motor neuron disease but the deficient SMN protein is ubiquitously expressed in all cells throughout fetal and post-natal development [44–46]. Therefore, there is ongoing discussion as to what extent other tissues might be affected in patients with SMA. Several animal models and some case reports or small case series report involvement of other organ systems, such as peripheral nerve, brain, muscle, heart, vasculature, and pancreas (for review see [47–50]). While the involvement of other tissues might have implications for therapeutic approaches, only a minority of patients with SMA show clear clinical manifestation of other organ involvement.

Hemodynamically relevant cardiac defects have been reported in very severely affected infants with SMA type 1. Recent reviews of the literature [50,51] identified a number of cases with congenital heart defects such as atrial or ventricular septal defects. All of these patients showed the severe neonatal onset, also indicated as type 0, with respiratory distress at birth. They all had only a single copy of *SMN2* [51]. In long-term survivors with type 1 SMA receiving ventilatory support, 15 of 63 patients (24%) had severe, symptomatic bradycardia, suggesting a possible concomitant autonomic dysfunction [52].

Cardiac involvement in contrast is much less frequent in types 2 and 3 SMA. There are some reports of heart rate abnormalities in type 3 SMA [53,54]. Recent studies performed in types 2 and 3 SMA, suggested that there is no need for regular cardiac surveillance in type 2 and type 3 patients as it is highly unlikely that these patients will develop obvious clinical, ECG or echocardiographic signs of cardiomyopathy [33,55].

As reported in the part on nutritional care, occasional cases of pancreatic dysfunction including diabetes and alterations in glucose metabolism have been reported in SMA patients [56]. Hyperleptinemia has been identified in SMA patients with types 1, 2 and 3 [57]. Mitochondrial dysfunction has been described in patients and human neuronal cell lines [21,58,59].

There was consensus among the experts that specific surveillance testing for other organ involvement should generally be based on clinical symptoms and is thus not necessary in most patients. Possible exceptions are the exclusion of cardiac defects in severely affected infants with SMA type 1 and monitoring of glucose metabolism in all types of SMA. Despite immobilization of many patients with SMA prophylactic anticoagulation is not deemed necessary in the absence of additional risk factors.

As intrathecal administration of nusinersen principally targets motor neurons [40], concerns have arisen that other non-central nervous system tissues may subsequently demonstrate symptoms or signs of dysfunction due to deficiency of SMN protein. Motor impairment may be alleviated while other symptoms arise. It is recommended that patients treated with nusinersen be monitored for these potential systemic concerns.

9. Ethical considerations

The application of palliative care along with its attendant ethical challenges was the focus of an international interdisciplinary group that included clinicians, bioethics researchers, parents and patient representatives, and pediatric palliative care specialists.

The previous version of the standards of care guidelines [1] highlighted the lack of consensus and the controversies on palliative versus interventional approaches. In the absence of therapy a number of families perceived the interventional approach, especially tracheostomy, as placing quality of life in conflict with duration of life, prolonging suffering rather than relieving the burden of disease [26,52.60.61]. The previous committee reached consensus that while there was no moral imperative to any therapy, there was a deep responsibility to present care options in a fair and balanced manner, providing accurate information that the choice for palliative or interventional supportive care was not an exclusive binary choice.

The update of the literature review provided little additional hard evidence and no consensus regarding standards of palliative care as applied to SMA [62–65]. The working group was, therefore, still unable to establish a consensus for palliative care and could only acknowledge the substantive ethical issues that must attend care decisions in the context of SMA, now also in the light of the most recent therapeutic approaches. The group identified 3 key areas for future analysis: 1) The concept of palliative care as applied to SMA, 2) Patient management and decision-making, 3) Managing expectations.

Although the concept of palliative care has been defined and re-interpreted many times there is a need to regard this as an ongoing reflexive process especially when applied to contexts like SMA that are not static [66]. SMA in all of its degrees of severity does not fit a model of a condition with a relentlessly ingravescent course [67,68]. The recent availability of new therapies has created substantial reasons to hope for changes in prognosis, but several issues are in need of further clarification before a move to a standard for palliative care in SMA can be achieved [40,41], including the need to address the meaning of palliative care for the SMA community. Despite recent trends that have emphasized the role of palliative care to focus upon improving quality of life, with a point of entry well 'upstream' within the disease trajectory, there is still an association of palliative care with end of life care. There is therefore a need to support a change of culture, which sees palliative care as having a role alongside the treatment of chronic debilitating conditions that have a long prognosis. A key challenge is thus to dismiss the dichotomous model, which sets active treatment against palliative care in favor of a model of complementarity. Ethical challenges will doubtless still persist, requiring both clinical evidence and good judgment to manage. One such concern is the challenge of managing the burden of care when the

'therapeutic ratio' between side-effects and benefits must be balanced. Second is managing the phases of transition across the disease trajectory points at which advancing disease signals a transition in favor of palliative care and the cessation of life-extending treatments [69]. The challenge of managing expectations in this fluid context, especially where expectations are shaded by many conflicting opinions, adds further complexity to the task of establishing a standard of care. Resource limitations and cultural differences need also to be considered especially as variable access to resources across the globe will mean that inequalities are inevitable.

New issues about the choice of palliative care in patients enrolled in clinical trials are also emerging [70]. A recent survey among physician investigators, clinical evaluators, and study coordinators from different countries endorsed the concept that having a predefined degree of nutritional and ventilation support was warranted in this context.

10. Conclusions

Spinal muscular atrophy presents with a diverse range of phenotypes of motor impairment and related comorbidities. Effective and efficient management of the patient with SMA requires coordination of multiple clinical specialists to address both current concerns and anticipated ones. These updated standard of care considerations have been developed to provide current expert opinion on necessary care and, where appropriate, optimal management. When reviewing the results, we were surprised by the discrepancy between the literature and the Delphi analysis. Although many advances in multiple aspects of care have been made, and these had a tremendous impact on survival, onset and severity of complications, the literature reporting evidence was scanty. Very few studies provided a level of evidence based on an appropriate design and most papers reported clinical observations and small series. In contrast, despite the paucity of evidence based recommendations, for each topic there was a large expert consensus on many components of SMA care. For many aspects, such as the introduction of early spinal surgery and of cough machine support, most, and often all the experts were convinced of the impact of these recommendations on changing natural history. In these cases it was felt that although large randomized studies would have been preferable to assess more systematically their efficacy, the impact on natural history before and after their introduction was sufficient to recommend their inclusion in common practice. While this lack of evidence based papers makes it difficult to obtain an accurate estimate of the level of efficacy of individual aspects of care, the unequivocal and recent improvements in survival in type 1 and in the onset of progression in all SMA types validate the impact, collectively, of implementing these interventions.

The ultimate goal of these guidelines is to strive continually in improving quality of life and reducing burden of disease for these patients. While many of these considerations are technology driven, they all begin with a focus on a patient's clinical symptoms and signs and related risk factors. Recommendations are now based upon the current functional status of the patient: non-sitter, sitter and walker. Patient and parental autonomy and ethical dimensions must be respected. These guidelines should thus be applied with attention to individual patient concerns and complexities rather than as strict doctrine. Individual probative issues to consider include patient age, general medical status and extent of supportive care, local availability of clinical expertise, extent of health care provisions, and new treatment options. With the emergence of the first approved medication for treatment of patients with SMA, it is particularly important to meld optimal care with treatments that fundamentally alter the natural history of the disease. This effort identified questions that remain in many areas of supportive care for patients with SMA and will prompt future research. Further research is also needed on other aspects, such as psychiatric and emotional health, or on other aspects related to optimization of daily functioning. As the great majority of the aspects of care are related to the most severe phenotypes that have pediatric onset, further work is also needed to address issues related to the older population, including teenagers and adults. Further work is also needed to identify new models to support families and physicians to improve local care and reduce the number of visits and admissions to tertiary care centers.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2017.11.004.

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ADIS INSIGHT REPORT

Nusinersen: First Global Approval

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Abstract Spinal muscular atrophy (SMA) is a rare autosomal recessive disorder characterized by muscle atrophy and weakness resulting from motor neuron degeneration in the spinal cord and brainstem. It is most commonly caused by insufficient levels of survival motor neuron (SMN) protein (which is critical for motor neuron maintenance) secondary to deletions or mutations in the *SMN1* gene. Nusinersen (SPINRAZA™) is a modified antisense oligonucleotide that binds to a specific sequence in the intron, downstream of exon 7 on the pre-messenger ribonucleic acid (pre-mRNA) of the *SMN2* gene. This modulates the splicing of the *SMN2* mRNA transcript to include exon 7, thereby increasing the production of full-length SMN protein. Nusinersen is approved in the USA for intrathecal use in paediatric and adult patients with SMA. Regulatory assessments for nusinersen as a treatment for SMA are underway in the EU and several other countries. This article summarizes the milestones in the development of nusinersen leading to this first approval for SMA in paediatric and adult patients.

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

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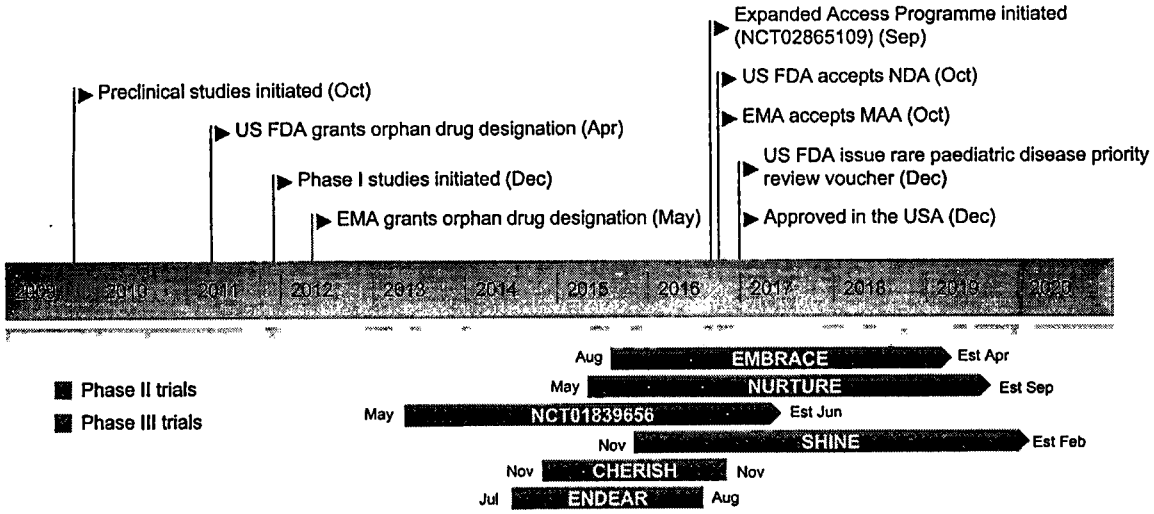
1 Introduction

Spinal muscular atrophy (SMA) is a rare (incidence of <0.02%) autosomal recessive disorder characterized by muscle atrophy and weakness resulting from motor neuron degeneration in the spinal cord and brainstem [1–3]. It is most commonly caused by deletions or mutations in the *survival motor neuron 1* (*SMN1*) gene located on chromosome 5q that result in insufficient SMN protein levels [1–4]. *SMN1* and the nearly identical *SMN2* gene encode SMN protein, which is critical for the maintenance of motor neurons [1–3]. *SMN1* encodes the majority of full-length SMN protein; 90% of *SMN2* messenger ribonucleic acid (mRNA) transcripts exclude exon 7 and thus encode a truncated SMN protein that is rapidly degraded, with only 10% of transcripts encoding full-length SMN protein [1, 3, 5]. Therefore, the number of copies of the *SMN2* gene in the genome partially determines the severity of SMA, with more copies associated with less severe forms [1]. Such understanding in the pathogenesis of SMA has led to the development of therapeutic approaches beyond symptomatic and supportive care [1, 2]. One such approach is the use of an antisense oligonucleotide to modulate the splicing of *SMN2* mRNA, thereby increasing the production of full-length SMN protein [1].

Nusinersen (SPINRAZA™) is a modified antisense oligonucleotide designed to treat SMA caused by chromosome 5q mutations that result in insufficient SMN protein levels [6]. In December 2016, nusinersen was approved by the US FDA for use in paediatric and adult patients with



Key milestones in the development of nusinersen for the treatment of spinal muscular atrophy

SMA [7]. The recommended dose is 12 mg, administered intrathecally by, or under the direction of, a healthcare professional experienced in performing lumbar punctures [6]. Treatment should be initiated with four loading doses (with the first three loading doses administered at 14-day intervals and the fourth administered 30 days after the third loading dose), with maintenance doses administered once every 4 months thereafter [6]. Regulatory assessments for nusinersen as a treatment for SMA are underway in the EU, Australia, Canada and Japan [8].

1.1 Company Agreements

In August 2016, Biogen exercised its option to license the global development, manufacturing and commercialization rights for nusinersen from Ionis Pharmaceuticals [8, 9]. Ionis will receive a US$60 million milestone payment based on the US FDA's approval of nusinersen, and is eligible to receive tiered royalties (up to a percentage in the mid-teens) on any potential sales of nusinersen [8].

2 Scientific Summary

2.1 Pharmacodynamics

Nusinersen is a modified 2′-*O*-2-methoxyethyl phosphorothioate antisense oligonucleotide that binds to a specific sequence in the intron, downstream of exon 7 on the *SMN2* pre-mRNA [6, 10]. This modulates the splicing of the *SMN2* mRNA transcript to include exon 7, thereby increasing the production of full-length SMN protein [1, 10].

In vitro and in transgenic animal models of SMA, nusinersen increased the inclusion of exon 7 in *SMN2* mRNA transcripts and the production of full-length SMN protein [6]. Moreover, in an analysis of autopsy-derived thoracic spinal cord tissue preparations, exon 7 was included in 50–69% of *SMN2* mRNA transcripts from three infants with SMA who were exposed to nusinersen as part of a phase II trial (Study CS3A; NCT01839656) [see Sect. 2.3] compared with 15–26% of *SMN2* mRNA transcripts from four untreated infants with SMA and three infants without SMA [11]. This corresponded to a significant ($p = 0.0198$) 2.6-fold increase in full-length *SMN2* mRNA transcripts in nusinersen-treated infants compared with untreated infants with SMA. Generally similar levels of *SMN2* mRNA transcripts containing exon 7 were also seen in multiple brain regions of infants with SMA who were exposed to nusinersen. Nusinersen exposure also appeared to increase SMN protein levels, with an image analysis of the thoracic spinal cord tissues demonstrating a significant ($p < 0.0001$) increase (of 64%) in SMN protein staining intensity (as assessed by mean optical density) in the large neurons of three infants treated with nusinersen compared with two untreated infants [11].

Immunohistochemical staining of the autopsy tissues from Study CS3A revealed that nusinersen was distributed in motor neurons (and vascular endothelial cells and glial cells) throughout the central nervous system (CNS) [11]. Moreover, the concentration of nusinersen in the (cervical, lumbar and thoracic) spinal cord was >10 μg per gram of spinal cord (which is above the targeted therapeutic range in CNS tissue of 5–10 μg/g where pharmacological activity is expected) [11, 12].

No increase in the incidence of cardiac adverse reactions associated with delayed ventricular repolarisation was seen in infants receiving nusinersen compared with those receiving a sham procedure in a randomized, double-blind, multinational, phase III study in 121 patients with SMA (ENDEAR; NCT02193074) [see Sect. 2.3] [6]. Fridericia-corrected QT (QTcF) prolongation (>500 ms) and a change from baseline in QTcF of >60 ms were observed in 5% of infants treated with nusinersen [6].

2.2 Pharmacokinetics

Following intrathecal injection, nusinersen was distributed from the site of administration [cerebrospinal fluid (CSF)] in motor neurons (and vascular endothelial cells and glial cells) throughout the CNS, according to autopsy data from three infants exposed to nusinersen in Study CS3A [11]. Nusinersen was cleared from the CSF into the systemic circulation consistent with normal CSF turnover, with CSF concentrations still quantifiable 15–168 days after dosing, indicating prolonged CSF and CNS tissue exposure to nusinersen [11].

Compared with trough CSF concentrations, trough plasma concentrations of nusinersen were relatively low following intrathecal injection [6]. The median time to maximum plasma concentration (C_{max}) values ranged from 1.7–6.0 h and nusinersen exhibited approximately dose-proportional mean C_{max} and area under the concentration–time curve values up to a dose of 12 mg [6]. Autopsy data from the three infants exposed to nusinersen in Study CS3A revealed that nusinersen was also identified in peripheral tissues (e.g. kidney, liver, skeletal muscle), which is consistent with its clearance from the CSF into the systemic circulation [6, 11].

Nusinersen is metabolised via exonuclease (3′- and 5′)-mediated hydrolysis [6]. The estimated mean terminal elimination half-life in the CSF and plasma is 135–177 and 63–87 days, respectively. The primary route of elimination for nusinersen and its chain-shortened metabolites is thought to be via urinary excretion. Only 0.5% of the administered dose was recovered in the urine at 24 h [6].

There were no apparent correlations between age or total bodyweight and CSF concentrations seen in a phase I trial (Study CS1; NCT01494701) assessing the pharmacokinetics of single doses of nusinersen 1–9 mg in 28 patients with type 2 or 3 SMA, suggesting that fixed doses are appropriate in paediatric patients [13]. Nusinersen is not a substrate for, or an inducer or inhibitor of, cytochrome P450 enzymes [6].

Features and properties of nusinersen

Alternative names	ISIS 396443; ISIS-SMN_{Rx}
Class	Antisense oligonucleotides; spinal muscular atrophy gene therapies
Mechanism of action	Increases the inclusion of exon 7 in *SMN2* mRNA transcripts and thus the production of full-length SMN protein
Route of administration	Intrathecal
Pharmacodynamics	Binds to a specific sequence in the intron, downstream of exon 7 on the *SMN2* pre-mRNA, thereby modulating the splicing of the *SMN2* mRNA transcript to include exon 7 and enhancing the production of full-length SMN protein
Pharmacokinetics	Distributed from the site of administration (CSF) into motor neurons throughout the CNS; cleared from the CSF into the systemic circulation consistent with normal CSF turnover; CSF concentrations still quantifiable 15–168 days after dosing, indicating prolonged CSF and CNS tissue exposure; median time to C_{max} values ranged from 1.7–6.0 h; estimated mean terminal elimination half-life is 135–177 days (CSF) and 63–87 days (plasma)
Most frequent adverse events	Lower respiratory infection, upper respiratory infection, constipation
ATC codes	
WHO ATC code	N07 (other nervous system drugs)
EphMRA ATC code	N7 (other CNS drugs)
Chemical name	RNA, [2'-*O*-(2-methoxyethyl)](*P*-thio)(m5U-m5C-A-m5C-m5U-m5U-m5U-m5C-A-m5U-A-A-m5U-G-m5C-m5U-G-G)

C_{max} maximum plasma concentration, *CSF* cerebrospinal fluid, *CNS* central nervous system, *mRNA* messenger ribonucleic acid, *SMN* survival motor neuron

2.3 Therapeutic Trials

2.3.1 *Infantile-Onset Spinal Muscular Atrophy (SMA)*

An improvement in motor milestones [as assessed by the Hammersmith Infant Neurological Exam–Part 2 (HINE-2)] (primary endpoint prespecified for the interim analysis [14]) was achieved by significantly more patients receiving nusinersen ($n = 52$) than a sham procedure ($n = 30$) [40 vs. 0%; $p < 0.0001$], according to an interim analysis of data from ENDEAR [6]. Moreover, 63% of nusinersen recipients and 3% of sham procedure recipients demonstrated an improvement from baseline of ≥4 points in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) total score, and 4 and 40% of patients, respectively, demonstrated a worsening from baseline of ≥4 points in the CHOP-INTEND total score (data not statistically controlled for multiple comparisons at the interim analysis) [6]. Based on the results of the interim analysis, the ENDEAR study was stopped, with the participating patients able to transition into an open-label phase III extension study (SHINE; NCT02594124) [14].

ENDEAR is a randomized, double-blind, multinational, phase III study in which 121 patients with symptomatic SMA (who had an onset of symptoms before 6 months of age and who were aged ≤7 months at the time of the first dose of study medication) received nusinersen 12 mg intrathecally on days 1, 15, 29, 64, 183 and 302, or a sham procedure [6, 7, 10]. The interim analysis was conducted on data from infants receiving nusinersen ($n = 52$) or a sham procedure ($n = 30$) who had completed at least 183 days of treatment, died or withdrawn from the study [6]. The median duration of therapy was 261 days. The primary endpoint assessed seven different areas of motor milestone development, with each (depending on the milestone) having a maximum score of between 2–4 points; the total maximum score was 26. A responder was defined as a patient with a ≥2-point increase (or a maximal score of 4) in the ability to kick (consistent with an improvement by ≥2 milestones), or a ≥1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking (consistent with an improvement by ≥1 milestone). Patients were classified as a responder if they exhibited improvement in more motor milestones categories than worsening. CHOP-INTEND, a secondary outcome measure, is designed to assess motor function in patients with infantile-onset SMA [6].

According to an interim analysis of data from Study CS3A, treatment with nusinersen 12 mg dose equivalent was associated with significant mean improvements from baseline to last visit in developmental motor milestones (as assessed by the HINE-2 total score) [$p < 0.0001$], motor function (as assessed by the CHOP-INTEND total score) [$p = 0.0013$] and compound muscle action potential amplitude of the ulnar (377% or 0.62 mV; $p = 0.0103$) and peroneal (742% or 1.56 mV; $p < 0.0001$) nerves [11]. Significant mean improvements from baseline to last visit in developmental motor milestones ($p = 0.0002$) and motor function ($p = 0.008$) were also seen in the combined patient cohort (i.e. patients from the 6–12 and 12 mg dose equivalent groups). Compared with a natural history case series of infants with type 1 SMA ($n = 23$; who had a mean reduction in the CHOP-INTEND total score of 1.27 points per year) [score ranges from 0–64 points], 12 of the 14 patients receiving nusinersen 12 mg dose equivalent and 14 of 18 patients in the combined patient cohort had a mean increase from baseline to last visit in the CHOP-INTEND total score of 15.2 and 11.5 points, respectively. Moreover, in the nusinersen 12 mg dose equivalent group, a score of >40 (which is rarely observed in symptomatic patients with type 1 SMA with two *SMN2* gene copies) was seen in none of the 13 patients with two *SMN2* gene copies at baseline and in 7 of the 13 patients at the last visit. The median age at death or permanent ventilation had not been reached at the time of the interim analysis (data cut-off date 26 January 2016), with a Kaplan-Meier survival curve of patients with two *SMN2* gene copies ($n = 17$) diverging from a natural history case series ($p = 0.0014$) [11].

Study CS3A is a noncomparative, dose-escalating phase I study [11]. Patients in this study (who were aged 3 weeks to 7 months and had a *SMN1* homozygous gene deletion or mutation and an onset of SMA symptoms between 3 weeks and 6 months) received loading doses of nusinersen 6 mg ($n = 4$) or 12 mg ($n = 16$) dose equivalents on days 1, 15 and 85 and then 12 mg dose equivalents on day 253 and every 4 months thereafter. Patients in the 6–12 mg dose equivalent group ($n = 4$) had been followed for 9–32 months and had received 4–9 doses of nusinersen, while patients in the 12 mg dose equivalent group ($n = 15$) had been followed for 2–27 months and had received 2–8 doses of nusinersen [11].

The results from ENDEAR are supported by those from open-label, uncontrolled studies in patients with symptomatic SMA (who were aged 30 days to 15 years at the time of the first dose of study medication) and in presymptomatic patients (who were aged 8–42 days at the time of the first dose of study medication) [6]. The findings from ENDEAR and the open-label studies demonstrate the effectiveness of nusinersen across the range of SMA patients, and potentially support the early use of nusinersen [6].

Key clinical trials of nusinersen in spinal muscular atrophy

Drug(s)	Phase	Status	Location(s)	Identifier	Sponsor
Nusinersen	I	Completed	USA	NCT01494701 (Study CS1)	Ionis Pharmaceuticals, Inc.
Nusinersen	I	Completed	USA	NCT01780246 (Study CS10)	Ionis Pharmaceuticals, Inc.
Nusinersen	I	Ongoing	USA	NCT02052791 (Study CS12)	Ionis Pharmaceuticals, Inc.
Nusinersen	I/II	Completed	USA	NCT01703988 (Study CS2)	Ionis Pharmaceuticals, Inc.
Nusinersen	II	Ongoing	Multinational	NCT02386553 (NURTURE)	Biogen Ionis Pharmaceuticals, Inc.
Nusinersen	II	Ongoing	Germany, USA	NCT02462759 (EMBRACE)	Biogen Ionis Pharmaceuticals, Inc.
Nusinersen	II	Ongoing	Canada, USA	NCT01839656 (Study CS3A)	Ionis Pharmaceuticals, Inc.
Nusinersen	Expanded Access	Available	Multinational	NCT02865109	Biogen
Nusinersen	III	Stopped to permit patients to transition into NCT02594124	Multinational	NCT02292537 (CHERISH)	Ionis Pharmaceuticals, Inc.
Nusinersen	III	Stopped to permit patients to transition into NCT02594124	Multinational	NCT02193074 (ENDEAR)	Ionis Pharmaceuticals, Inc.
Nusinersen	III	Recruiting	Multinational	NCT02594124 (SHINE)	Ionis Pharmaceuticals, Inc.

2.3.2 *Later-Onset SMA*

A significant ($p = 0.0000002$) between-group difference of 5.9 points favouring nusinersen over a sham procedure was seen in the mean change from baseline to 15 months in motor function [as assessed by the Hammersmith Functional Motor Scale Expanded (HFMSE) score; primary endpoint] (+4.0 vs. −1.9 points), according to a prespecified interim analysis of data from CHERISH (NCT02292537) [9]. CHERISH is a randomized, double-blind, multinational, phase III study in which 126 non-ambulatory patients with later-onset SMA (including those who had an onset of signs and symptoms at >6 months of age and who were aged 2–12 years at screening) received nusinersen ($n = 84$) or a sham procedure ($n = 42$). HFMSE is designed to assess motor function in children with SMA; a change of ≥3 points is considered clinically meaningful. Based on the results of the interim analysis, CHERISH was stopped, with the participating patients able to transition into SHINE [9].

2.3.3 *Presymptomatic SMA*

Interim data ($n = 13$) from NURTURE (NCT02386553) showed that infants with genetically diagnosed, presymptomatic SMA who were treated with nusinersen for up to 1 year achieved motor milestones in timelines more consistent with normal development than what is observed in the natural history of patients with type 1 SMA [9, 15]. At the time of the interim analysis, all patients were alive and did not require respiratory intervention (primary endpoint) [15]. NURTURE is an ongoing 30-month open-label, multinational, phase II study in presymptomatic infants (who were up to 6 weeks of age at the time of the first dose of nusinersen) to determine if therapy with nusinersen would prevent or delay the onset of SMA symptoms [9]. The primary endpoint was defined as time to respiratory intervention (i.e. invasive or non-invasive ventilation for ≥6 h per day continuously for ≥7 days, or tracheostomy) or death [15].

2.4 Adverse Events

Nusinersen had an acceptable safety profile in patients with SMA participating in ENDEAR [15]. The most frequently reported adverse events [occurring in ≥20% of nusinersen recipients and with a ≥5% higher incidence in the nusinersen group (n = 80) than the sham procedure group (n = 41)] were lower respiratory infection (43 vs. 29%), upper respiratory infection (39 vs. 34%) and constipation (30 vs. 22%) [6]. It is worth noting that nusinersen recipients had a higher incidence of paradoxical breathing (89 vs. 66%), pneumonia or respiratory symptoms (35 vs. 22%) and requirement for respiratory support (26 vs. 15%) than sham procedure recipients at baseline. Serious adverse reactions of atelectasis occurred more frequently in nusinersen than sham procedure recipients (14 vs. 5%). No adverse events were considered to be related to the study medication [15]. In this study, 41 and 19 patients were exposed to nusinersen for ≥6 and ≥12 months, respectively [6]. Among patients with normal or above normal platelet levels at baseline [$n = 56$ (nusinersen) and 28 (sham procedure)], 11% of nusinersen recipients and 0% of sham procedure recipients developed a platelet level below the lower limit of normal. No patient had a platelet count of <50,000 cells/μL or developed a sustained low platelet count despite continued exposure to the study medication.

Elevated urine protein levels occurred in 33% of 51 nusinersen recipients and 20% of 25 sham procedure recipients (median treatment exposure 7 months). There were no elevations in serum creatinine or cystatin C levels. Nusinersen therapy may result in a reduction in growth (as measured by height), according to observations in infants. Whether this effect is reversible upon cessation of treatment is as yet unknown [6].

Nusinersen was well tolerated in infants with SMA participating in Study CS3A, according to an interim analysis [11]. No safety concerns were identified. Adverse events, most of which were mild or moderate, were reported in 100% of 4 patients in the 6–12 mg dose equivalent group and 100% of 16 patients in the 12 mg dose equivalent group. Serious adverse events occurred in 75 and 81% of patients in the respective groups, with all considered by the study investigators to be unrelated or unlikely to be related to the study medication. The most common serious adverse events were respiratory distress or failure, or respiratory infections, which are common in infants with SMA. No clinically significant or nusinersen-related changes in CSF safety or electrocardiogram parameters, laboratory assessments, neurological examination findings or vital signs were reported, apart from one mild event of transient, asymptomatic neutropenia and one mild event of vomiting (both of which were considered by the study investigators to be possibly related to nusinersen) [11].

In an open-label study in infants with symptomatic SMA, one patient receiving nusinersen developed severe hyponatraemia requiring salt supplementation for 14 months [6]. According to the US prescribing information [6], cases of rash have been reported in nusinersen recipients.

Nusinersen demonstrated a favourable safety profile in CHERISH [9]. The majority of adverse events were considered to be common events in the general population or related to either the disease itself or the lumbar puncture procedure. No patients discontinued the study [9].

The most frequently reported adverse events in open-label studies in later-onset patients (who were aged 2–15 years at study entry; $n = 56$) were headache (50% of patients), back pain (41%) and post-lumbar puncture syndrome (41%) [6]. The majority of these events occurred within 5 days of the lumbar puncture. Other adverse events were consistent with those seen in ENDEAR. In a study in patients with later-onset SMA ($n = 52$; median treatment exposure 34 months), 69% of patients had elevated urine protein levels. There were no elevations in serum creatinine or cystatin C levels [6].

Interim data from NURTURE suggest no new safety concerns with nusinersen treatment [9]. Adverse events (all of which resolved) considered possibly related to nusinersen were experienced by three infants. There were no discontinuations from treatment or withdrawals from the study [9].

Several phase I [Study CS1, Study CS10 (NCT01780246) and Study CS12 (NCT02052791)] and phase Ib/IIa (Study CS2; NCT01703988) trials have assessed the safety and tolerability of nusinersen 1–9 mg. Where reported (Study CS1 [13] and Study CS2 [16]), no safety/tolerability concerns were identified.

The immunogenic response to nusinersen was evaluated in 126 patients who had baseline and post-baseline anti-drug antibody (ADA) assessments [6]. Treatment-emergent ADAs developed in five (4%) patients; in three patients the ADAs were transient and in two they were considered to be persistent. There are currently not enough data to evaluate an effect of ADAs on the pharmacokinetics, efficacy or tolerability of nusinersen [6].

2.5 Ongoing Clinical Trials

There are several ongoing phase I (Study CS12) and phase II [Study CS3A; EMBRACE (NCT02462759); NURTURE] trials of nusinersen for the treatment of SMA. EMBRACE will be assessing the safety and tolerability of nusinersen in patients with SMA who are not eligible to participate in ENDEAR or CHERISH. An open-label phase III extension study (SHINE) evaluating the long-term safety, tolerability and efficacy of nusinersen in patients with SMA who had previously participated in investigational studies (including ENDEAR and CHERISH) was initiated in October 2015. This noncomparative, multinational study will recruit approximately 274 patients (aged 13 months to 21 years) who will receive nusinersen 12 mg every 4 months.

3 Current Status

Nusinersen received its first global approval on 23 December 2016 for the treatment of SMA in paediatric and adult patients in the USA [6].

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