An evaluation of carrier screening for spinal muscular atrophy against the National Screening Committee criteria

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1. Introduction

There is not currently a screening programme in the UK for spinal muscular atropy (SMA). However, recently attention has been given to the condition, with contradictory statements in the US from the American College of Medical Genetics (ACMG), which issued guidance in 2008 stating that carrier testing should be offered to all couples regardless of race or ethnicity before conception or in early pregnancy [1], and the American College of Obstetricians and Gynaecologists (ACOG) which issued an opinion paper in 2009 stating that prenatal screening for SMA is not recommended at this time [2].

This paper reviews the evidence for a carrier screening programme for SMA in the general population in England. A literature review for evidence from 1990 onwards was conducted, details of which can be found in appendix 1. 3,190 potential references were elicited. These titles were further reviewed for relevance, giving 474 references for review. The evidence from these papers forms the basis of this review.

2. The condition

2.1 The condition should be an important health problem

SMA is the second most common fatal autosomal recessive disease (after cystic fibrosis). One study in North East England found a disease incidence of 1 in 24,119 live births, and carrier prevalence estimates of between 1 in 76 and 1 in 111 [3]. Other studies have estimated carrier prevalence to be between 1 in 34 in a study in France [4] to 1 in 54 in the United States general (pan-ethnic) population [5].

SMA is a neuromuscular disease, characterised by degeneration of alpha motor neurons in the spinal cord which results in progressive muscular weakness and paralysis [6].

SMA varies in terms of age of onset and severity of symptoms according to the type of SMA. These are classified into 4 types, which are summarised in table 1.

Table 1 – Classification of spinal muscular atrophy

	Age of onset	Maximum function achieved	Prognosis	SMN copy number
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated, no survival beyond the first months after birth	-
Type 1 (severe)	0-6 months	Never sits	If untreated, life expectancy <2 years	One or two copies of SMN2 in 80% of patients
Type 2 (intermediate)	7-18 months	Sits but never stands	Survival into adulthood	Three copies of SMN2 in <80% of patients
Type 3 (mild)	>18 months	Stands and walks	Survival into adulthood	Three or four copies of SMN2 in 96% of patients
Type 4 (adult)	10-30 years	Stands and walks	Survival into adulthood	Four or more copies of SMN2

Source: Mercuri et al. Childhood spinal muscular atrophy: controversies and challenges. 2012[6]

Type 1 SMA, also known as Werdnig-Hoffman disease, is characterised by a severe generalised muscle weakness and hypotonia at birth or within the first 3 months, and death from respiratory failure normally occurs within the first 2 years [1]. Infants are so weak that they are never able to maintain a sitting posture [7]. Children with type 2 are able to sit but not stand or walk unaided [1] but can survive past adolescence [6], with length of survival greatly influenced by the quality of clinical care [7]. Type 3 and 4 are milder forms – type 3 onset occurs during infancy and the patient learns to walk unaided, and type 4 occurs later (aged 10-30) and the patient survives to adulthood. Although these classifications exist, the clinical course is highly variable and is more of a continuous spectrum [8].

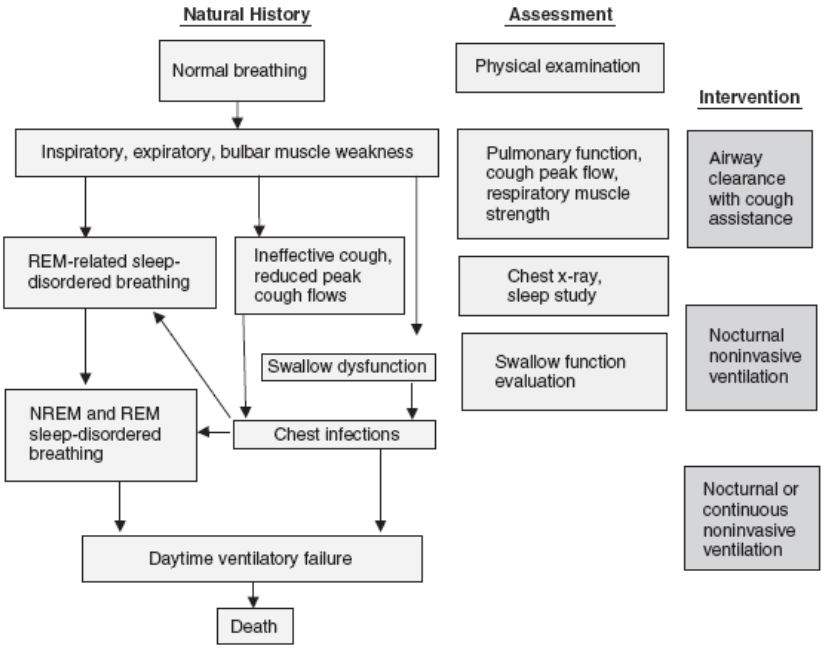
2.2 The epidemiology and natural history of the condition, including development from latent to declared disease should be adequately understood and there should be a detectable risk factor, disease marker, latent period, or early symptomatic stage

Pulmonary disease and respiratory capacity problems are a major cause of morbidity and mortality in SMA types 1 and 2 and may occur in a small proportion of type 3 [9, 10]. Pulmonary compromise is caused by a combination of inspiratory and expiratory muscle weakness. The key respiratory problems of SMA have been summarised as follows [9]:

1. Impaired cough resulting in poor clearance of lower airway secretion
2. Hypoventilation during sleep
3. Chest wall and lung underdevelopment
4. Recurrent infections that exacerbate muscle weakness

The natural history of pulmonary problems in SMA and the assessments at each stage are summarised in figure 1, as given in the Consensus Statement for Standards of Care in Spinal Muscular Atrophy [9].

Figure 1 – summary of the natural history of pulmonary problems assessment and intervention in spinal muscular atrophy



Source: Wang et al. Consensus statement for standard of care in spinal muscular atrophy, 2007[9]

Other complications of SMA are: spine deformity [11], where muscle weakness limits motor function of trunk and upper and lower extremities, resulting in contracture formation, spinal deformity, limited mobility and activities of daily living [9]; sleep disordered breathing [12]; and gastrointestinal and nutritional issues including feeding and swallowing problems, gastrointestinal dysfunction, growth and undernutrition or overnutrition problems [9, 13]. All of these can have a significant impact on quality of life.

As shown in table 1, survival for patients with SMA is limited. Studies conducted in 1995 and 1997 [14, 15] found survival probabilities at 1, 2, 4, 10, and 20 years to be 32%, 18%, 8%, and 0% respectively for type 1 patients and 100%, 100%, 98% and 77% respectively in type 2 patients.

A more recent study conducted in 2004 [8] further assessed survival pattern of infants with SMA and found that for type 1 the survival probabilities at 1, 2, 4, 10, and 20 years were 50%, 40%, 30%, 30% and 30% respectively, and for type 2 for the same years they were 100%, 100%,

100%, 92% and 92% respectively. However numbers in the study were small, with just 22 SMA type 1 patients and 26 SMA type 2 patients.

One study [16] found that patients born in 1995-2006 had significantly increased survival compared to those born in 1980-1994. Those born in the more recent cohort analysed had a 70% reduction in the risk of death compared to the earlier cohort. However when controlling for demographic and clinical care variables, year of birth was not associated with age at death whereas ventilation for more than 16 hours and use of mechanical insufflation-exsufflation device and gastronomy tube feeding showed a significant effect in reducing risk of death.

These increasing survival rates, particularly for the severest forms of SMA, could be due to improved respiratory care, specifically better airway clearance and breathing support, as well as improvement in nutritional status [17]. In addition it has been suggested that survival differences between countries may reflect differences in access and attitudes to mechanical ventilation [17].

In terms of groups that are more at risk of developing SMA, two studies conducted in the USA have analysed carrier status by ethnicity and found some difference in prevalence of carrier status in different ethnic groups [5, 18]. In the first study, carrier frequencies were found as follows: 1 in 37 in Caucasian; 1 in 46 Ashkenazi Jew, 1 in 56 Asian, 1 in 91 African American, and 1 in 125 in Hispanic groups. In the second study the overall frequency in the population was found to be 1 in 54, with 1 in 47 in the Caucasian population; 1 in 67 in the Ashkenazi Jewish population; 1 in 59 in the Asian population; 1 in 68 in the Hispanic; 1 in 52 in the Asian Indian; 1 in 72 in the African-American population.

While there are case studies and smaller prospective studies of severe SMA, there are no large prospective studies of treatment interventions so knowledge of disease progression with treatment is limited [9]. The first consensus for standard of care was published in 2007[19] (see section 4 on treatment).

2.2.1 Genetics

It is only in relatively recent years, since the 1990s, that a greater understanding has been achieved of the genetics of SMA [20-23] and the link has been made to a specific gene,- mapped to a specific chromosome, responsible for spinal muscular atrophy [21]. From this, a rational basis for diagnostic criteria could be developed [7].

SMA is caused by mutations of the survival motor neuron (SMN) gene. The gene has been found to be on the "5q13" location on the human chromosome. There are two almost identical SMN genes that are present in this location; the SMN1 gene – which it is now known is the SMA causing gene – and the SMN2 gene. SMN1 has 9 exons (the protein coding region of the DNA). There are a number of genotypes that have been established in those that are affected with SMA, as follows.

In approximately 95% of affected patients, the SMN1 exon 7 (or both exon 7 and 8) is homozygously absent in the patient through either deletion of the SMN1 gene or through it converting to another form [1, 21, 22].

If the SMN1 gene undergoes conversion (as oppose to deletion) the SMN1 is replaced by a copy of SMN2. This SMN2 gene copy differs from SMN1 in that it does not have exon 7 in its transcript. In these cases SMA occurs because without exon 7, SMN2 does not have the same protein coding [1].

Studies have shown that the SMN2 copy number influences the severity of the disease [24, 25], as the small number of full length transcripts caused by SMN2 mean a milder type 2 or 3 disease is produced when the copy number of SMN2 is increased – i.e. SMN2 goes some way to counteract the absence of SMN1 but not completely, making the form of disease milder.

Homozygous deletion or conversion of SMN1 is estimated to occur in approximately 96% of type 1, 94% of type 2, and 88% of type 3 SMA patients [23]. Further studies have found variations of these proportions, summarised by Wirth et al [26] to be in the range 92-100% for type 1, 82-100% in type 2 and 78-100% for type 3. These discrepancies may be partly to do with differences in ethnic origin, or misdiagnosis, but are thought to be due to true differences between the three phenotypes. However there does appear to be overlap between the different estimates.

A further genotype has been identified as having one exon 7 deletion and a small mutation on the other allele in SMN1 [27]. Around 6% of patients have been determined to fit into this group [21, 26], with either "de novo" mutations – i.e. mutation events that are new to a family - or inherited intragenic mutations. Gene dosage tests (section 3.1.2) have allowed for cases in which patients with SMA have one SMN1 copy and mutation on the other allele to be identified and the mutations analysed [26]. Three intragenic mutations have been identified in a number of correlating studies [21, 23, 26, 27], whereas others differ to these, for example showing a complete deletion of exon 5 and 6 on the chromosome. 3.4% of patients with SMA have been

found to have this type of mutation [26]. Around 2% of SMA cases have been found to arise from “de novo” mutation events [28, 29]. It is suggested that this relatively high rate of de novo mutation may account for the high carrier rate in the population, and is thought to be owed to the large number of repeat sequences in the area on the chromosome leading to unequal crossovers and recombination events [1].

A final genotype option is for a carrier to possess one chromosome with two copies of SMN1 and another chromosome with zero copies [1]. Studies have found different estimates of the prevalence of this genotype in carriers, ranging from 4% [27] and 4.8% [25], 5.5% [30], and 7% [31]. Due to the quantity of SMN1 genes being the same as for a non-carrier, this would mean that carriers with this genotype would be incorrectly identified as not being carriers in a standard carrier test [32].

This knowledge of the genetics of the disease has lead to molecular diagnosis and determination of carrier status to be possible, although with some limitations (section 3).

2.3 All the cost-effective primary interventions should have been implemented as far as practicable

As far as currently known, SMA is not a disease that can be prevented through primary interventions. Parents that have previously had an SMA baby can undergo genetic testing leading to informed reproductive choice and possibly prevent further cases.

2.4 If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood including the psychological implications

No papers were found in this review regarding the natural history or psychosocial implications of carrier status.

3. The test

3.1 There should be a simple, safe, precise and validated screening test

Deletion methods were developed and used as a diagnostic tool for detection of homozygous deletion of SMN1 exon 7 (and 8) and can be used to confirm diagnosis in a patient with SMA symptoms or for prenatal diagnosis [33]. However it has limitations as a carrier test, as it cannot distinguish carriers and non-carriers since both would be expected to have a negative result [34]. Likewise, methods that detect the ratio of SMN1 to SMN2 are not suitable for carrier analysis as they do not account for the possibility of more than one SMN1 gene on a chromosome [27].

The method to determine carriers was developed by McAndrew [27, 35] and is known as gene dosage analysis [34]. Polymerase chain reaction (PCR) assay is used to detect gene copy numbers in SMN1 and SMN2 relative to a reference of the cystic fibrosis trans-membrane regulator therefore enabling identification of carriers by quantifying the number of SMN1 and SMN2 genes [27].

Initially, sensitivity and specificity were found to be 95.8% and 97.6% respectively [26]. Difficulties were found in distinguishing between 1 and 2 SMN1 copies in about 6% of tests on carriers and non-carriers, meaning that some carriers who have chromosomes carrying two SMN1 copies (4%) would not be identified and leading to a 4% false positive result [26].

A number of real-time PCR assays which allow the amplification of only one SMN copy have since been developed, building on this method and increasing its efficiency and accuracy [25, 36-38].

One study [25] combined and analysed results from other PCR studies [26, 27, 37] and concluded that in 2.4% of healthy chromosomes, two SMN1 copies were found, meaning that 4.8% of carriers would be misinterpreted as non-carriers on the basis of the direct gene dosage test. This would mean a sensitivity of 95.2%. In addition, 1.7% of carriers have intragenic mutations (3.4% of patients with SMA show compound SMN1 mutations - plus intragenic mutations) which reduces the sensitivity to 93.5% for a person from the general population.

More recently, other methods have also been developed for gene quantification which could be used in carrier testing, such as combining capillary electrophoresis and mass spectrometry [39], multiplex ligation-dependent probe amplification (MLPA) [30, 40, 41], and denaturing high-performance liquid chromatography (DHPLC) [41, 42] .

MLPA has been shown to be a versatile and fast technique for determining different nucleic acid sequences in a single reaction, with the same specificity as real-time PCR [40]. DHPLC was found to be accurate in differentiating carriers of SMA except for the 4% who have 2 SMN1 copies in the same chromosome [42].

However despite progression with these methods in terms of the technical efficiency and technique, there are limitations to current carrier testing methods.

This is still the case with the newer developments and more efficient methods. Individuals within the population identified as carriers who have a partner with two SMN1 copies carry a residual risk of having SMA affected offspring of about 1:3000, due to the chance the partner has two SMN1 copies on one allele [30]. In cases such as this, it may be possible to further reduce risk by testing the parents of the apparently normal spouse for their carrier status. Depending on the genotype of the parents, the partner could be determined to have a 50% chance of being a carrier. This could bring the sensitivity up to 95% [30]. Further testing of family members in linkage analysis such as this can improve sensitivity, but is more expensive, requires additional resources and logistics and is not always feasible [26].

In summary, the limitations and challenges of dosage analysis for carrier testing are the following [30, 36]:

1. 2. Two or more SMN1 copies can be located on a single chromosome. These carriers will have a negative result in testing, and so a normal result in carrier testing in the general population does not completely rule out a carrier status
2. SMN1 de novo mutations occur in approximately 2% of SMA patients (1% of parents). This configuration will not be detected through gene dosage analysis.
3. Small intragenic mutations in the SMN1 gene have been described in about 3-4% of patients, i.e. 1-2% of carriers. When paired with SMN1 deletion, this genotype cannot be identified by quantitative analysis of SMN gene copies

A study [5] found the sensitivity of carrier detection in the African American population to be 70.5%. This decreased carrier detection rate is thought to be due to an increased frequency of the genotype with 2 SMN1 copies on one allele in this population, and means that a higher frequency of carriers would not be detected in this group by gene dosage analysis. Whether the same findings would apply to British populations is not known from the evidence in this review.

There is also evidence that in the general population there are individuals with an SMN1 copy number of 0 who are asymptomatic or mildly affected [29, 43], which means there is a risk of false positives in this testing method due to these individuals being misclassified as carriers of a deletion/gene conversion within the SMN1 gene. Through further testing these individuals can be reclassified but there their associated risk is not fully known at present [5].

3.2 The distribution of the test values in the target population should be known, and a suitable cut-off level defined and agreed

Cut off values were not often or consistently reported in the literature.

In the earlier study by McAndrew [27], which looked at ratios rather than the quantifying methodology now introduced, ratios were assigned to indicate normal or carrier status of SMN1 and SMN2 against a cystic fibrosis gene standard. For SMN1/standard the ratios for carrier status were determined as 0.28±.06 and for SMN2 to the standard as 0.29±.06, whereas for normal status the respective ratios were determined as 0.67±.08 and 0.62±0.06.

A further study [37], using fluorescent PCR and the retinoblastoma gene as the standard, used a ratio of under 0.75 for carriers and over 0.75 for non-carriers. This study reported a sensitivity of 95.3% in the general population having the limitations as discussed previously of certain genotypes not being picked up by the test, and a specificity approaching 100% (95% confidence interval 87-100%).

More recently, a study using PCR real time methods clearly specific non-overlapping ranges that distinguish between one, two and three SMN1 copies: 0.2 to 0.5 “real time values” for 1 copy; 0.8 to 1.4 for 2 copies; and 1.8 to 2.5 for 3 copies [44]. Another study using a real time PCR approach using Tagman technology [36] stated the quantification dosage value range for carrier status in the study to be 0.6 to 1.2.

A further study [30], using MLPA, used cut-offs of the ratio of relative peak areas for each sample compared to a control sample of 0.3-0.7 for a single copy, 0.71-1.35 for two copies, and >1.35 for three or more copies. The author stated that the computer generated a trimodal, bell-shaped distribution around the values of 0.5, 1.0, and 1.5, corresponding to 1, 2, and 3 copies of SMN1 exon 7, but that appropriate cut offs need to be determined for the test to be used in a clinical setting. The author states that there is no clear demarcation between the three peaks and no clear cut off values exist – leading to possible false positives or false negatives. The study determines a sensitivity of 90% for the methods used.

3.3 The test should be acceptable to the population

A number of studies have looked at the acceptability of prenatal testing and subsequent diagnosis of SMA, and have demonstrated varied results.

In one prospective study [41], of 2,262 partners or spouses that were requested to be screened following carrier status being determined in their pregnant partners, 224 persons either refused to participate or could not be traced. At approximately 10%, this is a relatively high number and suggests challenges in this element of a screening programme.

A further study on the American population suggested that approximately half of those offered accepted carrier testing for SMA, and of those that accepted 98.7% responded favourably to the experience [45]. Results of a carrier screening pilot programme implemented in Israel showed that of women that were already being offered screening for cystic fibrosis and fragile X, 93% requested SMA testing as well [30]. This is a much higher percentage than in the American study. However the population in Israel differs to the general population in both the United States and the UK, and the acceptability of the test in the population may differ.

There is a need to ensure couples are adequately educated regarding the disease and test if they are to be offered screening for SMA. In line with this, the ACOG state one of their reasons for not currently supporting population screening for SMA to be that educational materials and methods need to be addressed before a programme can be initiated [2].

3.4 There should be an agreed policy for further diagnostic investigation of individuals with a positive test result and the choices available to those individuals

If two parents are found to be carriers of SMA, there is a 25% chance that the foetus will have SMA, a 50% chance that the foetus will be a carrier, and a 25% chance it will be unaffected. In this scenario, the couple would be offered genetic counselling and diagnostic testing.

Before 1995, linkage analysis and genetic analysis was the only way of diagnosing SMA prenatally, and is based on analysing close flanking informative DNA markers [46-49]. This type of analysis was usually only possible with parents who had previously had a type 1 SMA baby, and DNA samples of siblings and parents are isolated and analysed with markers for the appropriate chromosome region [49].

Methods have since progressed, and prenatal diagnosis can be undertaken using amniotic fluid or chorionic villi [41], or maternal blood [50, 51], using the same deletion or gene dosage methodologies as previously discussed including DHPLC [52, 53] and PCR assay [46, 54, 55].

These methods have been used in combination with linkage analysis [42, 46, 56]. Prenatal diagnosis can also pick up non-homozygous deletion cases, because over 95% of cases of SMA are deletion type, one of the parents is very likely to be a carrier of a deletion which can be detected by the ratio of fragments after enzyme digestion. The other normal-like parent carrying a non-deletion allele can then also be determined. Accurate pre-natal diagnosis can then be performed after determining the mutation [46].

Many of the prenatal diagnosis studies presented information on only a small number of women. A summary of results obtained is shown in table 2.

Table 2: Summarised results of studies performing prenatal prediction

	Shuan-Pei et al, 1999 [46]	Savas et al, 2002 [54]		Chen et al, 2007 [56]	Shaw et al, 2008 [53]	Su et al, 2011 [41]	Ben-Sachar et al, 2011 [30]
		Group A – molecular basis of disease known in family	Group B – Molecular basis of disease not known in family				
Method	Linkage analysis, non-isotope SSCP*, and PCR-RFLP**	Direct deletion analysis of SMN1 by restriction digestion		PCR-RFLP, DHPLC***, and linkage analysis	DHPLC***	DHPLC*** and MPLA****	MPLA****
Number of prenatal diagnoses performed	26	44	24	11	5	43	17
Number tested positive	5	8	2	4	2	12	1
Number tested negative	21	36	22	7	5 (2 normal, 3 carriers)	31 (8 normal, 23 carrier)	16
Number terminated	5	8	1	4	2	11	1
Number actually affected	5	Not stated	Not stated	7	Not stated	not stated	Not stated
Number actually unaffected	12 normal, 9 carrier	21 tested and verified	11 tested and verified	4	5	Not stated	16

* single-strand confirmation polymorphism; ** polymerase chain reaction-restriction fragment length polymorphism; *** Denaturing high performance liquid chromatography; **** Multiplex ligation-dependent probe amplification

It can be seen from this table that in more than half of these studies the actual diagnosis of those that tested positive was not clearly reported. The studies by Chen at al and Shuan-Pei et al were the only studies in which it was clearly stated that the test result was reconfirmed in the fetus or born child. However, it is the nature of this type of test that in terminated fetuses this will only ever be a re-confirmation of genotype, rather than being able to confirm phenotype or classification of SMA. This is a limitation to these studies and to the available evidence.

The diagnostic methods do have limitations. Absence of a deletion will not completely rule out the possibility of an affected child [46], due to some of the genetic complexities we have seen in section 2.2.1. The genotype in which there are 2 SMN1 genes on one allele will not be identified, as well as a small number of unaffected individuals with a homozygous deletion or conversion event [29, 43]. This could lead to false positives and possibly unnecessary terminations. The susceptibility of the SMA locus to de novo mutations is also a concern [46]. A further limitation is that it is not possible to inform two carriers of the SMA type their offspring is likely to have [41, 43].

With these complicated results, it is important that comprehensive, sound genetic counselling is given. Couples must receive adequate and balanced information both pre-test and post-test [41].

In one prospective cohort study [41], genetic counselling involved a team of medical geneticists, genetic counsellors, social workers, and pediatric neurologists. The counselling involved 3 stages: pretest counselling prior to carrier testing in which the study was explained using brochures and information including information on SMA, carrier frequency, inheritance, etc; interpretation of results, given after a woman was found to be a carrier, and alongside her partner being asked to undergo carrier testing and following this if they were subsequently both found to be carriers, and post-test counselling giving an explanation of the results following prenatal diagnostic testing, if positive informing them of the different management decisions available and asking permission to perform genetic testing on any other children. Within this study 91.5% of participants at high risk decided to undergo prenatal diagnostic procedures.

3.5 If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

As described in section 3.1.2, a screening programme would use gene dosage analysis to quantify the SMN1 and SMN2 gene copies, and therefore determine carriers with homozygous deletion or conversion of the SMN1 gene, or those with heterozygous deletion and a mutation where possible. However, as previously discussed there are difficulties in detecting heterozygous mutations and also those cases in which there are two SMN1 genes on one allele.

4. The treatment

There is currently no effective treatment available for SMA and no cure; management consists of preventing or treating the complications [57]. However, the field of research is very active, with translational research clinical trials ongoing [58].

The Cochrane Collaboration have conducted recent reviews on treatment available for SMA, one for type 1 and a further review for types 2 and 3 [59, 60].

The review for type 1 SMA [59, 60] found there to be extremely limited evidence of effective drug treatments for type 1 SMA. Only one small randomised trial was found and the review concludes that no drug treatment is shown to have a significant efficacy for SMA type 1.

The review for SMA type 2 and 3 found more results [60], assessing 6 randomised controlled trials. However, no evidence was found of a significant effect on the disease course when patients with SMA types 2 and 3 were treated with creatine, phenylbutyrate, gabapentin, thyrotropin releasing hormone, hydroxyurea, or combination therapy with valproate and acetyl-L-carnitine. None of the studies were completely free of bias but the evidence was sufficient for the review to conclude that there is still no known efficacious drug treatment for SMA types 2 and 3, and confirm the view that current management involves controlling or treating the complications of the disease.

A consensus statement on standard of care in SMA has also been published [9], following the formation of the International Standard of Care Committee for Spinal Muscular Atrophy 2005. The consensus statement was published following an acknowledgement of wide variation in care due to family resources, medical practitioners' knowledge, and regional and cultural standards. The consensus statement addresses care areas according to three functional levels of the patient: non-sitter; sitter; walker. The areas of care covered by the statement are: pulmonary care; gastrointestinal and nutritional; orthopaedic care and rehabilitation; and palliative care.

In terms of pulmonary care, the main recommended steps are given in figure 1, section 2.2, and the summarising recommendations given in the paper are as follows:

1. Referral for respiratory care evaluation and discussion of options should occur shortly after diagnosis, including evaluation of cough effectiveness, observation of breathing, and monitoring gas exchange.
2. Chronic respiratory management includes providing methods for airway clearance including mechanical insufflation-exsufflation or manual cough assist and non-invasive ventilatory support. Routine immunization also recommended
3. Discussion with families about the options for respiratory care and identifying the goals for chronic and acute respiratory care should occur early in the disease course and contine in an ongoing dialogue
4. Acute respiratory illness management requires increased airway clearance and secretion management techniques using mechanical insufflation-exsufflation or manual cough assist, increased respiratory support, nutrition and hydration management and a low threshold to start antibiotics
5. Perioperative evaluation of respiratory status ideally by a pulmonologist

There are ethical issues with the respiratory aid options available for type 1 patients. Both non-invasive ventilation and tracheostomy can prolong survival in SMA patients [61]. Tracheostomy can prolong survival to over 20 years in some cases but patients with tubes do not develop the ability to speak and lose all ability to breathe from the point of the tracheostomy, as well losing useful movement in the extremities [62, 63]. Non-invasive options develop the ability to communicate verbally and maintain some autonomous breathing ability, and have significantly fewer hospitalisations that those with tracheostomy [61] however is much more labour intensive for care providers [63]. With decision making difficult for families, it is recommended they are presented with all options and supported by a knowledgeable and compassionate team [64].

The consensus statement advises optimal management of gastrointestinal and nutritional problems to be by a multi-disciplinary team of physicians, speech therapists or occupational therapists, dieticians and paediatric surgeons, and this approach should greatly improve survival and quality of life.

The consensus recommends that infants with SMA should have appropriate evaluation for their presenting musculoskeletal and functional deficits and should be offered independent mobility and activities of daily living. Wherever possible walking should be encouraged with appropriate assistive devices and orthotics.

With respect to palliative care, the Consensus Statement acknowledges that some therapies may be perceived as placing quality of life in conflict with duration of life, prolonging suffering rather than relieving the burden of diseases, and optimal clinical care should be mindful of potential conflict of therapeutic goals.

Some of the new treatments that are under development are based around increasing the amount of SMN protein produced by SMN2 genes through promoter activation or reduction of exon 7 alternative splicing – or both - to manage the severity of the disease [65, 66]. These approaches are very much still in development, but work is being undertaken investigating appropriate biomarkers [65], and potential therapeutic compounds [66].

4.1 There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

There is currently no cure for SMA, and treatment options are limited to managing the symptoms. Therefore the aim of an antenatal carrier screening programme such as this is to

allow informed reproductive choice [67], thereby giving parents the option to terminate an affected foetus through informed choice.

4.2 There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

As above, the aim of an antenatal carrier screening programme would be to offer informed reproductive choice and the option of termination in all affected cases.

4.3 Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

As we have seen, there is currently no cure for SMA and treatment options are limited to managing the symptoms. The Cochrane Collaboration reviews [59, 60] on drug treatment have shown that no drug treatments currently have strong evidence of effectiveness, and the Consensus Statement on care [9], has demonstrated that evidence of effective treatment and management is limited.

5. The screening programme

5.1 There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at informed choice, there must be evidence from high quality trials that the test accurately measures risk. The information provided about the test and its outcome must be of value and readily understood by the individual to be screened

There have been no randomised controlled trials on screening for SMA. However there have been a small number of population studies [30, 41] looking at carrier screening for SMA.

One of these is based on the experiences in Israel, in which they assessed the feasibility of introducing SMA screening as part of the antenatal screening programme between March 2007 and August 2009 [30]. Within the study, SMA carrier testing had a cost to the parent of between $25 and $100. The programme had high uptake, at 93% suggesting individuals valued and accepted the screening test. All carriers detected in the programme were given detailed genetic counselling and were made aware of the disease characteristics and patterns and reproductive options. Prenatal diagnosis was performed for six cases during the study period, and all fetuses were found to be unaffected. The study concludes that screening for SMA is acceptable and feasible in the Israeli population. However no analysis was conducted on the cost-effectiveness of the programme. The evidence from this study is also limited in that no affected fetuses were identified.

The second population-based cohort study was conducted in Taiwan between 2005 and 2009 [41]. This was a nationwide programme recruiting pregnant women from primary care clinics. 107,611 women were screened. No information is given in the study regarding uptake rates or ease of recruitment into the study. Within the methodology, genetic counselling was given at pre-test, for interpretation of results, and post-test. Within the study, 47 carrier couples were identified as high risk of having SMA-affected offspring. Of these, 43 went on to have prenatal diagnosis. 12 were found to be high risk of SMA and 11 of these were terminated. It is not clear from the study that the diagnosis of those fetuses terminated were confirmed. The study concludes that SMA screening should be incorporated into prenatal care. However, again no analysis of costs was included in the study. It is not clear from the literature whether screening for SMA has now been incorporated into the screening programme in Taiwan.

5.2 There should be evidence that the complete screening programme is clinically, socially, and ethically acceptable to health professionals and the public

There was limited evidence found within this review as to whether a screening programme for SMA would be ethically acceptable to health care professionals and the public. However two guidance documents from the USA give health professionals' views, demonstrating that to some it is ethically acceptable and to others not at this time [1, 2].

The American College of Obstetrics and Gynaecology issued a statement in which population screening for SMA is not recommended [2], indicating that it is not ethically acceptable at this time. One issue raised was the need for development of appropriate educational materials for both patients and primary care staff, as well as the importance of laboratory standards.

However the American College of Medical Genetics issued a statement recommending that all couples should be offered screening for SMA [1].

One study [68] looking at parents' perspectives of genetic counselling for spinal muscular atrophy found many respondents to report negative experience with genetic counselling, possibly because it occurred at the time of diagnosis or shortly after which is a difficult period emotionally. The results highlight the difficulty in genetic counselling in a complicated and sensitive disease, and the importance of the timing and method and consistency of such counselling in order for it to be acceptable to the population.

5.3 The benefit of the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures, and treatment)

A conclusion regarding this cannot be made from the evidence available. However, the area is complex and in order to limit psychological harm it is clear from the evidence that a screening programme such as this would need to have clear and consistent genetic counselling to support any decisions.

5.4 The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole. Assessment against this criterion should have regard to evidence from cost benefit and/or cost-effectiveness analyses and have regard to the effective of available resources

One of the main issues raised in the ACOG opinion paper regarding SMA screening is a lack of pilot screening programmes to allow for better analysis of the programme, and cost effectiveness analyses [2]. Since the publication of the paper, a small number of cost analyses have been published. These papers do not show a screening programme for SMA to be cost effective.

One study [69] created a decision analysis model, and concluded that universal screening for SMA is not cost-effective. The results of the analysis found that a universal screening programme would reduce the number of cases of SMA by 80%, and that the remaining 20% would be accounted for by false negatives and de novo mutations. However this does not seem to correlate with the 93% sensitivity in testing we have seen elsewhere. The model estimated the costs of caring for an affected child from best available proxies in the literature, for mild and severe disease including respiratory support costs. A lifetime cost for a child with severe disease as estimated at $322,126, with a range of $50,000 to $2,000,000 considered in sensitivity analysis, and for mild disease $819,762, with a range of $500,000 to $3,000,000 considered in sensitivity analysis. The authors state as a limitation that there is limited evidence regarding the costs of having a child with SMA. However through sensitivity analysis, the authors found the model to be robust to the ranges of cost and utility estimates and that the cost estimates had little impact on the overall findings.

The model in the study predicts that at a cost of $425 per test, prenatal screening for SMA would on average cost an additional $40 million per 100,000 women, and 12,594 women would need to be screened at a cost of $5 million to prevent 1 additional case of SMA. The authors considered maternal QALYs only in their analysis. Utilities were estimated for the possible outcomes; 0.92 for pregnancies that ended in fetal loss, 0.78 for women who have a child with severe disease for a period of 2 years and then 0.92 for fetal loss, and 0.81 for mild disease based on an estimate for Down's syndrome. From this the authors calculated incremental cost

effectiveness of offering prenatal screening for SMA and cost per QALY. They found prenatal screening for SMA not to be cost-effective, with an incremental $4.9 million per QALY gained.

This study lacked any information on patient preferences, to consider that not all carriers may choose to go on to fetal diagnosis or termination once an affected pregnancy is identified. However with these factors taken into account, screening would become less cost effective. The study concludes that carrier screening is not cost effective across all populations, however it might be cost-effective to screen in specific high risk groups. Although we have seen [5, 18] that there are no specific ethnic groups that appear to be at greater risk, prevalence is higher in women who have a family history. The authors suggest that cascade screening may therefore be cost-effective in these groups.

A further decision analysis model was developed to compare the cost-effectiveness of routine screening for SMA via mutations in the SMN1 gene [70]. However it was not possible to assess full details of the model as only the abstract of this study was available. In the model, probability and cost estimates were determined from published literature, and key assumptions were a sensitivity of 95%, specificity of 99% and carrier rate of 1/50. It was not clear from the information presented whether the model took into account costs of care for an affected child. The model predicted that in whole population screening in an "idealised" scenario, in which 100% of women accepted screening testing and termination, 85.2% of cases would be identified with a cost per case of $1,112,007. A "real world" scenario was also modelled, in which <100% of couples accepted screening, subsequent testing and termination (although the actual percentages used were not given). Using this scenario, the model predicted only 28.09% of SMA cases would be detected, and preventing 8.15 cases per 1,000,000 women – with a cost of $10,804,515 per case prevented. In the ideal scenario – i.e. the best case scenario – the cost per QALY gained was $585,919, whereas in the "real world" scenario the cost per QALY gained was $5,616,811. The conclusion from the information presented is that antenatal screening for SMA does not appear to be cost effective.

Although the figures presented in these two models differ greatly, neither show a carrier screening programme for SMA to be cost-effective.

5.5 All other options for managing the condition should have been considered to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available

There is currently no cure for SMA and treatment is to manage the condition and its complications.

5.5 There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

This is not been considered as part of this review

5.6 Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

This is not been considered as part of this review, although for a screening programme to be implemented it would require substantial staffing infrastructure and resources, particularly with regard to laboratory testing and genetics services.

5.7 Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

This is not been considered as part of this review

5.8 Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

In this review, a screening population of the general population has been assessed – i.e. all pregnant women. There is no evidence of particular ethnic groups that should be targeted [5, 18, 19]. However, screening an entire prenatal population, rather than specific high risk groups, through genetic analysis, raises logistical, educational, and counselling issues [2].

5.9 If the screening is for a mutation, the programme should be acceptable to people that would be identified as carriers and to other family members

This is covered elsewhere, see section 3.3.

6. Conclusion

This analysis of the evidence for a population-wide carrier screening programme for SMA against the National Screening Centre Criteria indicates that a screening programme is not recommended at this time. The key reasons for this are as follows:

- Available evidence suggests that a carrier screening programme for SMA would not be cost effective – the estimated costs per QALY and costs per case prevented are very high.

- There are limitations to the screening test currently available. Although the sensitivity and specificity are relatively high, there are specific mutation groups that would not be identified with the common tests. However, these do make up a very small percentage of cases. Cut off values for screening tests also seem to be unclear from the literature.
- The molecular genetics of SMA are complicated, and would require a very considered and consistent approach to patient education and genetic counselling if a programme were to implemented, particularly with regards to explanation of risk and assisting with informed decisions for the parents
- There is limited available evidence from pilot studies, and no larger trials have been conducted
- There is limited information on the acceptability of a programme to health professionals and to the public

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Appendix 1 – Literature review search strategy

Knowledge update on screening for spinal muscular atrophy (SMA)
Paula Coles, Information Scientist
July 2012

BACKGROUND: In 2012, two Cochrane reviews were published on the treatment of SMA.

Wadman *et al*. Drug treatment for spinal muscular atrophy type I (Review). *Cochrane Database of Systematic Reviews* 2012; Issue 4
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006281.pub4/abstract

Wadman *et al*. Drug treatment for spinal muscular atrophy types II and III (Review). *Cochrane Database of Systematic Reviews* 2012; Issue 4
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006282.pub4/abstract

The literature searches for these two systematic reviews started from 1991 onwards "...because at that time genetic analysis of the SMN1 gene became widely available and could establish the diagnosis of SMA."

Therefore, it was decided the searches for this review against the UK NSC screening criteria would be run from 1990 onwards.

SOURCES SEARCHED: Medline (OvidSP), Embase, PsychINFO, Cinahl, Web of Science and the Cochrane Library.

DATES OF SEARCH: January 1990 – June 2012

SEARCH STRATEGY: Medline (OvidSP)

1. "Spinal Muscular Atrophies of Childhood"/ (805)
2. Werdnig-Hoffman.tw. (71)
3. Wohlfart-Kugelberg-Welander.tw. (26)
4. spinal muscular atroph$.tw. (2955)
5. 1 or 2 or 3 or 4 (3235)
6. exp Prenatal Diagnosis/ (55806)
7. 5 and 6 (113)
8. (screen$3 or detect$3 or test or tests or testing).tw. (2697635)
9. Mass Screening/ (74725)
10. 8 or 9 (2714689)
11. (pregnan$ or antenatal$ or prenatal$).tw. (383010)
12. exp Pregnancy/ (668112)
13. 11 or 12 (755152)
14. 5 and 10 and 13 (114)
15. 7 or 14 (168)
16. (prevalen$ or inciden$ or epidemiolog$).tw. (1021832)
17. incidence/ or prevalence/ (300527)
18. Prognosis/ (321321)
19. disease progression/ (85988)
20. "Quality of Life"/ (99953)
21. quality of life.tw. (120104)
22. prognosis.tw. (201461)
23. outcome$.tw. (743513)
24. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (2201963)
25. 5 and 24 (446)
26. therapeutics/ or drug therapy/ (39985)
27. exp treatment outcome/ (548073)
28. treat$.ti. (941506)
29. therapy.ti. (387564)
30. Respiration, Artificial/ (35463)

31. (respiratory support or ventilator assistance or mechanical ventilation).tw. (23918)
32. Palliative care/ (36424)
33. 26 or 27 or 28 or 29 or 30 or 31 or 32 (1805643)
34. 5 and 33 (245)
35. 15 or 25 or 34 (748)
36. limit 35 to yr="1990 -Current" (694)

Similar searches were also carried out in Embase, PsychINFO, Cinahl, Web of Science and the Cochrane Library.

All searches carried out on 25 June 2012

Medline	694
Embase	1018
Cochrane Library	52
PsycINFO	200
Cinahl	226
Web of Science	1000
Total	3190

Inclusions and exclusions

The above search strategies retrieved 3190 references in total. After duplicate references were removed a total of 1854 potentially relevant references were left. The title and abstracts of the remaining citations were scanned for relevance to screening for spinal muscular atrophy, focussing on all the aspects of the UK NSC criteria:

- The condition – the focus was on SMA Types I, II and III as Type IV is mild and does not manifest until adulthood if at all.
- The test – all types of testing/screening were included
- The treatment – any treatments tested in humans were included. Animal/experimental trials were excluded
- The screening programme – all types of screening were included

475 references were deemed to be relevant

Systematic reviews and meta-analyses	15
Non-systematic reviews	24
The condition *Reviews (4)* *Epidemiology (21)* *Clinical features (13)* *Natural history (9)* *Survival (8)* *Outcomes (6)* *Muscle strength/mobility (11)* *Quality of life (8)* *Respiratory problems (8)*	117

Cognitive function (7) *Cardiac problems (8)* *Feeding/swallowing problems (6)* *Fracture/dislocation (4)* *Sleeping problems (3)* *Spinal deformity (2)* *Urinary incontinence (1)*	
Genetic analysis Genotype in relation to phenotype/disease severity	41 33
Genetic testing/diagnosis Pre-implantation genetic diagnosis Carrier testing Prenatal diagnosis/prediction Non-invasive prenatal diagnosis Newborn screening Newborn and carrier screening	11 15 14 46 10 1 3
The treatment *Reviews (18)* *Respiratory management (52)* *Pharmacotherapy (33)* *Scoliosis (12)* *Physiotherapy/strength training (9)* *Palliative care/life-support (6)* *Gastrostomy (3)* *Miscellaneous (3)* *Technical devices (1)* *Genetic counselling (1)*	138
The screening programme	6
Total	474