2025

Public Consultation Summary Document

Newborn Screening for Spinal Muscular Atrophy in Australia and Aotearoa New Zealand

Public consultation summary document

Organisation /Individual	Feedback	Changes made	Oversight Committee review
[*redacted*]	The report appears very comprehensive. One area that could be bolstered is the role of clinical genetics in SMA and other genomic newborn screening. If this is not adequately included then the genetic support for genomic newborn screening will be diminished at the expense of the direct and indirect family. We are somewhat biased at [*redacted*] given our model mostly means that a genetic counsellor usually joins the paediatric neurologist at the first appointment. I think it would be useful to have a genetic counsellor as a member of the working group to contribute to this component of the pathway. I don't think the genetics aspects of newborn screening are being adequately considered. Many of the psychosocial supporting clinicians provided by the MDT do not feel confident addressing the genetic questions that families inevitably have (reproductive carrier testing, pattern of inheritance, implications to other siblings and the wider family, complexities around and facilitating carrier testing and implications to future offspring and reproductive testing). A genetic counsellor can provide	The GDG has already been formed and therefore this feedback cannot retrospectively be actioned. The role of clinical genetics services and genetic counsellors have been expanded in the background of section 5 which now reads "With their role expanding in a new therapeutic era, genetic counsellors can now provide information not only on the genetics of a condition but work in conjunction with neurology specialists to facilitate understanding of treatment timing, delivery and follow-up. Dependant on health expertise and confidence in disclosing sensitive results to families, other programs have leveraged the experience of trained genetic counsellors or nurses, particularly in regional and remote areas. "	Agree

	support and provide detailed knowledge around the genetic aspects of an SMA diagnosis. These questions are usually raised at the same time of the diagnosis disclosure and access to a genetic counsellor (F2F or via telehealth) is an essential component of care to support the family through a very stressful time.	Genetic counsellors fulfil a vital role in providing support and addressing the genetic questions that families inevitably have as pertains to a diagnosis of SMA (i.e. on reproductive carrier testing, pattern of inheritance, implications to other siblings and the wider family, complexities around and facilitating carrier testing and implications to future offspring and reproductive testing).(214) Whilst many jurisdictions have conjoined clinical genetics and neurology services to facilitate genetic support at the time of diagnosis, for families living in jurisdictions without these shared services, early referral to clinical genetics centres for review is deemed important 5.1.1. The designated paediatric neurologist, receiving the screen positive SMA result, should coordinate with other relevant healthcare practitioners to develop a family-centred plan for screen positive disclosure, including delegation of roles for who is best placed to facilitate this process. **Information Box** Dependent on child and family circumstances, it may be appropriate for a designated healthcare practitioner with support from the paediatric neurologist through telehealth to disclose a screen positive result to the family. The designated healthcare practitioner will vary between health jurisdictions and may include general practitioners, paediatricians, neonatologists, specialist nurses and/or genetic counsellors. 7.2.2. The number of healthcare practitioners at the first clinic visit for diagnostic evaluation (following screen positive disclosure) should be limited to those necessary for information disclosure and may include the information provider (usually a paediatric neurologist or paediatrician), and ideally support from a healthcare practitioner which may include clinical geneticists and/or genetic counsellors, nurse specialists and/or medical social work and/or psychological services.	Agree

	I can see that referral recommendations to clinical genetic services are present but they appear optional or something that can be addressed later issue which is not our experience.	The recommendation has been revised and is a high priority Recommendation 8.5 Consensus recommendation Families of newborns diagnosed with SMA through newborn screening programs should be offered referral to, and review for genetic counselling and cascade testing (which may include referral to clinical genetics services).	
[*redacted*]	Congratulations on this, it's a great draft. I do however have two concerns: • **Genetic Counsellors (GCs) should be mentioned as specific health care practitioners in the guideline** o Families value the education and psychosocial support routinely provided by after a NBS screening diagnosis per our pathway here at [*redacted*]. [*redacted*] is a Genetic Counsellor who did a study comparing our SMA NBS cohort with the Metabolic NBS cohort from [*redacted*]who do not receive genetic counselling. The results demonstrated the benefit of genetic counselling after a NBS diagnosis. [*redacted*] o There are numerous GCs in Regional Settings available to support local Medical Practitioners when disclosing the diagnostic results. This has not been mentioned in this document and I feel that it needs to be. A regional GC is the	The role of genetic counsellors has been further highlighted through the Guideline in view of the feedback in the following sections. Background section 5: Dependant on health expertise and confidence in disclosing sensitive results to families, other programs have leveraged the experience of trained genetic counsellors or nurses, particularly in regional and remote areas. The role of genetic counsellors and clinical geneticists have been reinforced throughout the recommendations Practice Standards 5.1.1. The designated paediatric neurologist, receiving the screen positive SMA result, should coordinate with other relevant healthcare practitioners to develop a family-centred plan for screen positive disclosure, including delegation of roles for who is best placed to facilitate this process. **Information Box** Dependent on child and family circumstances, it may be appropriate for a designated healthcare practitioner with support from the paediatric neurologist through telehealth to disclose a screen positive result to the family. The designated healthcare practitioner will vary between health jurisdictions and may include	Agree

		ideal person to provide follow up support and education for the family, as well organising cascade testing and advice for future pregnancies. This would be done by a GC rather than a Clinical Geneticist, as is the case in our pathway.	general practitioners, paediatricians, neonatologists, specialist nurses and/or genetic counsellors. 7.2.2. The number of healthcare practitioners at the first clinic visit for diagnostic evaluation (following screen positive disclosure) should be limited to those necessary for information disclosure and may include the information provider (usually a paediatric neurologist or paediatrician), and ideally support from a healthcare practitioner which may include clinical geneticists and/or genetic counsellors, nurse specialists and/or medical social work and/or psychological services. 7.2.4. Families receiving a diagnosis of SMA for their newborn, through a newborn screening program should be provided with the contact details of a designated healthcare practitioner who can direct a response to their queries. **Information Box** The designated healthcare practitioner will vary between health jurisdictions and may include but are not limited to paediatric neurologists, paediatricians, clinical geneticists, genetic counsellors or specialist nurses. Recommendation 8.5 Consensus recommendation Families of newborns diagnosed with SMA through newborn screening programs should be offered referral to, and review for genetic counselling and cascade testing (which may include referral to clinical genetics services).	

	Aside from these points, I think it is a very exciting to see this come together. Congratulations again on a wonderful document! **At least one GC should be present on the Guideline Development Group** Given the importance of the role, the Guideline Development group would benefit from a GC's detailed subject-specific knowledge in the area.	The GDG has already been formed and therefore this feedback cannot retrospectively be actioned. However, the public feedback system has targeted a number of genetic peak bodies for feedback.	Agree
[*redacted*]	The feedback from one colleague was to please replace "New Zealand" with "Aotearoa New Zealand" in all documents P25 of the Guideline "… internationally developed SoC for SMA.." - References 25 and 26 are quoted. I wondered whether specifically for SMA the reference 50 and PMID: 29305137 (which is not listed as a reference at all) would be more appropriate. P59 of the Guideline - there are two recommendations 10.15 and two recommendations 10.17 – 1 of each should be 10.14 and 10.16, respectively. Page 106 Fig 4 – SMN2 produces 6 hexagons worth of full length SMN protein in a healthy individual but only 3 in a SMA patient – not sure what this is meant to indicate? Again, my respect and congratulations for your amazing work!	Aotearoa has been added All references are now aligned These recommendations have been reconfigured and realigned The Figure has been redesigned to be representative	Agree Agree Agree

[*redacted*]	[*redacted*] in the Newborn Bloodspot Screening (NBS) decision-making pathway, which ensures national consistency in partnership with states and territories 2. Spinal Muscular Atrophy (SMA) is a condition listed for screening as part of the NBS program 3. Children born in [*redacted*] with SMA would be cared for in partnership with sub-specialists based at institutions such as [*redacted*].	No changes required	Agree
[*redacted*]	Health and Social Policy Branch has reviewed the draft Guideline and do not have any specific feedback. [*redacted*] is committed to participation in the national process underway to achieve national consistency for NBS, and I commend you and your team on your work to support these principles. I look forward to reading the final version of the guideline when published.	No changes required	Agree
[*redacted*]	Upon review of both the National Recommendations for Newborn Screening in Spinal Muscular Atrophy in Australia and New Zealand Guideline Document, as well as the National Recommendations for Newborn Screening in Spinal Muscular Atrophy in Australia and New Zealand Administrative and Technical Report, there were noted areas of repetition that may be truncated or condensed to enhance accessibility and readability. Specifically, but not exhaustively:	As per NHMRC guidance, grading process is preferable in both documents	

	1.Grading the direction and strength of evidence-based recommendations Page 85 Page 84 While not a word-forword repetition, suggest limiting to one document 2.Stakeholder consultation activities – systematic observation form evidence on page 89 Systematic observation forms to collect expert evidence on page 77 Text repeated wordfor-word 3.Healthcare practitioner survey (modified Delphi process) Page 91 Page 79 Text repeated word for-word		
[*redacted*]	[*redacted*] supports the implementation of the National Recommendations for Newborn Screening in Spinal Muscular Atrophy guideline.	No changes required	Agree
[*redacted*]	• P21 whilst I agree that 'back up gene' is not an ideal term for SMN2, to me the phrase 'nearby related gene' is a bit confusing, so I wonder if it would be clearer to say 'related gene… located near SMN1'? • P25 Population – I know it is mentioned further on, but I wonder whether it would be good to mention early in the document that SMA affects all populations/ethnic groups (albeit at varying frequencies) • I note that you have varyingly referred to absence/loss of SMN1 as 'deletion' throughout the document • I suggest that you are consistent	This has been corrected and now reads related gene, located near SMN1. This has been incorporated and now reads Guideline purpose, scope, population and settings: Whilst incidence and prevalence varies between groups, SMA affects all ethnic populations. Whilst the screening assays are targeted at biallelic deletion of exon 7 in SMN1 and have thus remained the same, where appropriate, absence of exon 7 on SMN1 has been added.	

	• In most places throughout the document I think it is most correct to avoid the term deletion – as this implies mechanism for the loss of SMN1, whereas the testing that we do is just quantitative and only tells us whether SMN1 is present, not how it was lost. I understand that a significant proportion of patients are thought to have lost their SMN1 through gene conversion rather than deletion per se • Suggest using loss, absence, deficiency.	This has been changed	Agree to all feedback
	• Suggest adding 'clinical' to geneticist throughout the document (where that Is what you mean!) – including the diagram	The word clinical has been incorporated throughout the document.	
	• P39 I think it would be useful to add that sometimes testing of parents is suggested to try to work out why there is a false positive or uninterpretable result	This has now been added as a good practice point which reads Implementation Guidance 4.2.2. Blood samples from parents for *SMN1* quantification purposes should be considered to understand the aetiology of a false positive or uncertain result for the newborn.	
	• P42 – I think the term 'responsible medical practitioner' is ambiguous – I presume you mean responsible for the patient rather than someone not irresponsible!	This has now been changed to designated healthcare practitioner throughout the document.	
	P46 – there are a few places where you say 'venous sampling for SMN1' – I don't think this makes sense? Should be it venous sampling for quantification of	Now changed and reads	

	SMN1? – and then similarly, venous sampling for determination of SMN2 copy number?	Recommendation 6.1 Consensus recommendation The following assessments should be completed immediately as part of the diagnostic and clinical evaluation of the newborn, who screens positive for SMA. • Neurological examination. • Venous sampling for quantification of *SMN1* exon 7 on whole blood. • Venous sampling for determination of *SMN2* copy number on whole blood OR repeat dried blood spot for confirmation of *SMN2* copy number.	
	• P100 – in 1st paragraph – you mention the scenario of two sequence variants – but they need not necessarily be homozygous – is more correct to say 'biallelic sequence variants' (could be homozygous or compound heterozygous).	This has now been altered.	
	• P114 I think the more correct term is 'reproductive genetic carrier screening' (but noting that the MBS uses 'testing' not screening)	This has now been changed to reproductive carrier testing.	
	• P117 last paragraph & p119 – I don't think the sequence variant needs to be in exon 7 – there are recurrent variants in exons 1,3 & 6 in particular	Please see ICER comments	
	P161 you mention the phrase 'done incorrectly' - I am not sure that this is a binary thing - right or wrong – I suspect it is better to reword this in a way that says we want to deliver this devastating news in the most	This has been changed and now reads in the background of Section 5:	

	constructive/least traumatic way possible rather than correct vs incorrect • I note the use of the term 'allied therapist' in several places throughout the document – I am more familiar with - 'allied health therapist/specialist/professional'? • I wasn't sure whether I was looking in the right place for ref 24, 25 and 26 below – which don't appear to match the numbered ones at the end of the document	*The evidence reported that some families felt that the information given at this juncture set the tone of the healthcare journey and could challenge family perception, engagement and trust in care thereafter* The term has now been rewritten as allied health therapist throughout the document. The references have been realigned	
[*redacted*]	Section 5: Disclosing a screen positive result to families [*redacted*] recommends that written information, either as a standalone document or by referral to a website, is provided to parents immediately following the disclosure phone call. This information should be available in an accessible format and in different languages. The 2021 Census shows that a language other than English is used in 28% of households in [*redacted*] (Cultural diversity: Census, 2021 | Australian Bureau of Statistics (abs.gov.au)). We suggest the written information provided to families includes plain language information for recommendation	Additions have been made to reflect the feedback The GDG highlighted the need to standardise information provision (through verbal and written means) and highlight signs and symptoms of clinical deterioration, to mitigate clinical risks to the child. This now reads Practice standard 8.3.4. Families may require support with therapeutic decision making and resources may be made available to them (including as appropriate referral to medical specialists, social work, clinical geneticists and genetic counsellors, psychology, and/or patient advocacy groups) to facilitate this process. Written information as a standalone document or direction to a well-curated, reliable and up to date website should be provided to families that will inform them on the potential benefits, risks, uncertainties of SMN augmenting treatments and the need for long term surveillance. The information should be in an accessible format and ideally provided in different languages.	

	5.10 advising families to contact the medical practitioner if the following are noted in the newborn/infant: change in movement, feeding, or breathing pattern, change in voice or weak cry, increased fatigue without increased activity, decline or loss of function in previously attained motor ability or failure to show progress in expected motor ability, abdominal breathing and/or failure to thrive. It is unlikely that parents will be able to remember or assess clinical signs without written resources and accessible support from a health professional. Alternatively, this recommendation may need to be simplified to alerting a health professional if parents have any concerns about their newborn rather than listing the clinical signs which may be too burdensome for newborn parents who have received a positive screening result. Section 3: Confirming the diagnosis of spinal muscular atrophy. We recommend the timeline for diagnostic results is clearly stated in the guidelines. For example, results are required such that treatment can begin by 6 weeks of life, if this is consistent with the evidence provided below in Section 3. The timelines appropriate for completion of all diagnostic tests for SMA (including SMN1 and SMN2 copy number) should be as short as possible, without compromising the accuracy of the process. This is emphasised by the fact that children diagnosed and started on SMN augmenting treatment by 6 weeks of life have a higher probability of following normal motor development trajectories, independent of SMN2 copy number. Therefore, time to diagnosis and	Practice standard 5.2.2. Healthcare practitioners should instruct families **and provide them with written information** as to when immediate contact is required to facilitate urgent clinical review for their screen positive newborn/infant. Circumstances include • Change in movement, feeding, or breathing pattern. • Change in voice or weak cry. • Increased fatigue without increased activity, decline or loss of function in previously attained motor ability or failure to show progress in expected motor ability. • Abdominal breathing and/or failure to thrive. • In case of an acute event that requires hospitalisation Recommendations 3.3. Diagnostic results for *SMN1* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory. Recommendations 3.4. A diagnosis of SMA (including *SMN1* and *SMN2* copy number results) should be available to clinical services as quickly as possible. This should be completed within 30 days of birth to enable timely treatment. **Information Box** The timings included in Recommendations 3.3 and 3.4 define the **maximum** time for diagnostic result availability in keeping with processes that are feasible and sustainable across Australia and Aotearoa New Zealand. However, it is noted that the shortest time to diagnostic results (as a pathway to early treatment), confers the	

	subsequent treatment appears to be a substantial modifier of health outcomes for these children. Section 4: Managing uncertain, false positive and false negative screening results We suggest that lessons or insights derived from the 'root cause analyses' of false positive/false negative or uncertain results are shared between Australasian Newborn Bloodspot services so that common issues and errors can be identified. This would be in addition to the knowledge exchange activities described below in Section 4. The Guideline Development Group (GDG) highlighted the need to undertake knowledge exchange activities across Australasia of the limitations of newborn screening for SMA, to emphasise the necessity for prompt referral to clinical services for symptomatic children due to the potential for false negative cases (due to the inherent limitations of the target assay, human/system error or probe binding issues). Section 7: Information provision to families during the diagnostic evaluation of a screen positive newborn and after confirming the diagnosis of SMA We recommend nationally consistent and up to date information is available to all families who receive a screen positive newborn result and a diagnostic positive result based on the evidence below from Section 7. The evidence showed that families struggled to find sources of information other than their doctor and the GDG acknowledged that clinics could leverage local and national support groups to augment information provision.	maximum clinical benefit for the affected child, and processes should be coordinated and implemented to keep this interval as short as possible. Implementation Guidance 4.2.3. Lessons or insights derived from the case review of false positive, false negative or uncertain results should be shared across Australasian Newborn Bloodspot services so that issues and errors can be identified as part of quality improvement. Section 7 background: Families often describe a period of information seeking between screen positive disclosure and diagnosis, associated with feelings of distress and confusion. Well curated and reliable sources of information at screen positive disclosure are considered vital to bridge the information gap and provide accurate counsel. Recommendation 7.2 Consensus recommendation Families receiving a diagnosis of SMA for their newborn, through a newborn screening program, should be directed to high quality and reliable educational	

		resources that reflect the contemporary care landscape and are nationally consistent.	
	The GDG highlighted through clinical experience and consensus that a tailored program of information provision was required, paced and adjusted according to the preferences and circumstances of the family. We recommend there is a smooth process to transition the newborn from screening, diagnosis and post diagnosis across clinical care, with information and resources and psychosocial support throughout. The process should 3 Guideline Feedback recognise each family will be at different stages of understanding the information and be tailored to each families' unique needs based on the information below from Section 7. The evidence showed that there are gaps in current practice in communication, information and support available to families. Benefits of high quality, accurate and tailored information provision were considered by the GDG to encompass many levels including improving therapeutic decision making for families and clinicians, improving access to appropriate support, increasing family wellbeing and satisfaction with care and empowering families to be active participants and engage in the healthcare process for their child.	Recommendation 7.2 Consensus recommendation Families receiving a diagnosis of SMA for their newborn, through a newborn screening program, should be directed to high quality and reliable educational resources that reflect the contemporary care landscape and are nationally consistent. Practice standard 7.2.1. Clinical services should provide families with information that is compassionate, accurate and tailored to their information needs and preferences. Information provided may include information on the (genetic) cause and clinical implications of SMA, next steps and approximate timelines to confirm a diagnosis, information on psychosocial supports (including referral to social work services), and/or psychology and/or advocacy services.	
	Section 8: Delivering the diagnosis and supporting families as they receive the diagnosis of SMA Consistent with Section 7 and recognising the intent of the GDG in addressing the psychological and support needs of families, we recommend all families either have a	Practice standard 8.3.4. Families may require support with therapeutic decision making and resources may be made available to them (including as appropriate referral to medical	

	psychosocial support healthcare professional present at the appointment or receive a phone call offering psychosocial support to the family after the results disclosure. Section 10: Treatment planning and initiation for newborns and infants diagnosed with SMA through newborn screening programs We suggest that written information or website information is provided with Recommendation 10.9 where medical practitioners will explain to families and document the potential benefits, risks, uncertainties of SMN augmenting treatments and need for long term surveillance. This information must be available in accessible format and in different languages. The recommendations 10.15 onwards refer to the newborn diagnosed with SMA "through newborn screening" where this terminology has not been used in the other recommendations. It is unclear whether the clinical recommendations apply to newborns diagnosed with SMA regardless of whether it is through newborn screening or clinically following a negative newborn screen. Guideline impact For [*redacted*], and likely other jurisdictions, the guideline will alter the diagnostic pathway, shifting it from a clinical diagnosis triggered by clinical signs to a newborn screening triggered diagnosis. The implementation of additional newborn and reproductive screening will increase the demand for both reproductive counselling and pre-implant genetic testing. Barriers and facilitators of implementation recommendations Barrier to implementation: Lack of appropriate resources for patients/families. For example,	specialists, social work, clinical geneticists and genetic counsellors, psychology, and/or patient advocacy groups) to facilitate this process. Written information as a standalone document or direction to a well-curated, reliable and up to date website should be provided to families that will inform them on the potential benefits, risks, uncertainties of SMN augmenting treatments and the need for long term surveillance. The information should be in an accessible format and ideally provided in different languages. This is now acknowledged in the dissemination and implementation plan These barriers and facilitators have been added in the implementation and dissemination sections	

	the Australian SMA advocacy and support group website will need resources specific for families when a positive screening result and diagnostic result is received. Spinal Muscular Atrophy: Causes, Symptoms, & Treatment (smaaustralia.org.au). Facilitator of implementation: Jurisdictional consistency in implementation is preferable, and identification of a mechanism for key stakeholders in each jurisdiction to coordinate and provide consistent communications will support successful implementation of the recommendations across screening, diagnostic and post diagnosis care. Overall feedback The title of the guideline does not reflect the breadth of the content. Suggest the title includes reference to 'diagnosis' and 'post diagnosis' in addition to screening to ensure it captures the attention of the appropriate stakeholders beyond the newborn bloodspot screening laboratories. This will align with the Executive Summary, 'to span the entire healthcare journey of the newborn'. Technical report No feedback Family fact sheet No feedback Additional feedback The draft guidelines recommend five yearly review and update. We suggest adding an option to review the guideline should new practice changing evidence become available.	Title unchanged on recommendation of the SAC, Reworded and now states The Guideline should be reviewed in 5 years of publications or sooner if the screening, diagnostic or clinical landscape changes in the interim, updated to reflect and respond to new evidence from research, clinical practice and changes in community needs, values and preferences.	
[*redacted*]	<u>Guideline document</u>		

	Really good. Obviously very thoroughly researched, proof read and edited. Few notes.		
	On page 20, states: “Decentralisation of newborn screening in Australia and New Zealand may give rise to regional differences in newborn screening programs”New Zealand has a centralised NBS programme. Not sure if they are trying to say it that it’s not centralised across the two countries? May be better to say: “Decentralisation of newborn screening in Australia and a separate system in New Zealand may give rise to regional differences in newborn screening programs”	This has now been amended and reads Decentralisation of newborn screening in Australia and a separate system in New Zealand may give rise to regional differences in newborn screening programs	Agree
	On page 21: “In 2022 and 2023, the federal governments of Australia and New Zealand respectively…”Federal government is not a term used in NZ. Would suggest deleting the word federal to just say: “In 2022 and 2023, the governments of Australia and New Zealand respectively”	This has been deleted and reworded as per suggestion	Agree
	On page 25: “It is made to be flexible and adapted to conform with available resources and capacity on a state/territory level across Australia and New Zealand.”Would suggest: “It is made to be flexible and adapted to conform with available resources and capacity on a state/region/territory level across Australia and New Zealand.	This has been deleted and reworded as per suggestion	
	On Page 54: “Recommendation 9.9.Consensus based recommendation. We suggest that newborns undergo neurophysiological assessments within a reasonable time of diagnosis, including collation of compound muscle	The variability of access to equipment and personnel to complete these assessments has been acknowledged in the Guideline and no change required	Agree

	action potential (CMAP) +/- electromyography (EMG), to obtain predictive information on disease course. Strength of recommendation Conditional, Grade 2C ” [*redacted*] Technical report • Previous comments about the executive summary in the other document regarding inclusive language [*redacted*] is all true in this one too. • Under Risk Assessment pg 103: A further risk not mentioned that could be consider that’s no specifically mentioned is that the introduction of genetic testing to the NBS programme may lead to disengagement with the overall NBS programme, particularly for indigenous populations who may have additional concerns around data sovereignty of genetic information and implications [*redacted*]. This could be considered in the context of point 3 “the risk of widening health inequalities across Australia”. Also both point 2 and 3 should be “… across Australasia”. • Under Dissemination and Implementation plan pg 105: No mention of implementation in NZ. Add a sentence “In New Zealand this is overseen by the national Newborn Metabolic Screen Programme”. Otherwise all good.	This has been addressed in the implementation plan (barriers and risks to implementation) This has been added Sentence added	

[*redacted*]	<u>General feedback</u> Clinical services have already absorbed 3 SMA treatments, increased patient numbers due to survival, increased complexity in treated symptomatic patients, coordination of care, coordination of treatment programs and support and managing the care. NBS programs have also increased demand for clinical services, critically urgent review and initiation of treatment & the intense monitoring post treatment. There has been no additional resourcing of services to support the increased clinical workloads. It remains challenging to provide SOC to patients with NM disorders. To implement the SOC for NBS screening programs, clinical services need additional funding to build capacity, workforce, succession planning. <u>Screening feedback</u> Health literacy ... non English speaking backgrounds, cultural considerations, Temporary Visa status - NBS offered to all infants, regardless of Medicare status and eligibility, however access to care and PBS funded treatments is restricted. Families may not be able to afford access to care or genetic testing, genetic counselling etc. How is this managed in other NBS programs? <u>Diagnostic feedback</u> Variability between in states for Tier 2 testing SMN1 & SMN2 confirmatory testing timeframes.	-Resourcing has been addressed in the implementation protocol. The Guideline is intended to inform and guide but does not replace clinical reasoning or acumen. It is linked with and thus do not replace the National Screening Policy Framework (34) and internationally developed Standards of Care for SMA.(35, 36) It is made to be flexible and adapted to conform with available resources and capacity on a state/region/territory level across Australia and Aotearoa New Zealand. As such, it has been developed within the current health policy framework of these two countries and the parameters of the Guideline do not specifically address reimbursement pathways for children with SMA (diagnosed through newborn screening) who are not eligible for subsidised or publicly funded health services or treatments. While the SAC recognises the geographical differences between states, this Guideline has been developed as a best practice protocol for NBS for SMA.	

	[*redacted*] for 2nd tier .. - 7-10 days turn around. Much quicker for other states - [*redacted*] [*redacted*]- logistics with timely access to care and confirmatory testing - will likely cause delays - maybe outside of the recommended timeframe of 7-10 days. <u>Clinical feedback</u> Our local experience has shown that whilst NBS is done on most patients, however not all have Medicare. 50% of NBS this year. Immigration /Visa status impacts access to clinical care and treatment options. Hospital systems, service demand/capacity restraints. Impact on clinical services .. demand, survival, critical timeframes , clinical services struggle to juggle and absorb workload to provide diagnostic, treatment and ongoing clinical care. Clinical services need additional resourcing / staff to deliver services. SMA care has changed dramatically in the last decade, however clinical resourcing & funding of service has not responded to this demand. <u>Guideline potential implications</u> Improved awareness and understanding.	Addressed in Scope: The Guideline is intended to inform and guide but does not replace clinical reasoning or acumen. It is linked with and thus do not replace the National Screening Policy Framework (34) and internationally developed Standards of Care for SMA.(35, 36) It is made to be flexible and adapted to conform with available resources and capacity on a state/region/territory level across Australia and Aotearoa New Zealand. As such, it has been developed within the current health policy framework of these two countries and the parameters of the Guideline do not specifically address reimbursement pathways for children with SMA (diagnosed through newborn screening) who are not eligible for subsidised or publicly funded health services or treatments.	

	Consumer expectations ... logistical and systematic barriers which impact the delivery of clinical services. Recognition for the importance of SMA care, timely access to treatment. Hopefully - appropriate resourcing of services, additional funding, capacity building, succession planning <u>Barriers and facilitators</u> Inequity in care still exist - Treatment eligibility - no Medicare - can't access PBS funded treatments, can't access NDIS supports to meet SOC recommendations. Insurance status - variability ... SMA treatments are high cost, they won't necessarily be covered by insurance. Family who have NO private health insurance and no Medicare. Challenges - NBS positive, confirmatory genetic testing, unable to access treatments; family with no insurance to cover treatment or care. Will State based health systems absorb the cost, how do we advocate for compassionate access to treatments ?		

[*redacted*]	<u>General feedback</u> Slide - What is NBS for SMA Blue circle Please correct 2 spelling errors "manging" to managing and "screeing" to screening	-Changes made according to feedback	

[*redacted*]	General feedback fantastic, well thought out Clinical feedback Recommendation 9.5 (referral to genetic counselling) does not seem to incorporate an understanding that some areas of mainstreaming genetic counselling is growing and it may not necessarily be a 'clinical genetics unit' that provides this counselling. There may be genetic counsellors within the neuromuscular multi-D team who will provide this. Would it be easier to say refer for genetic counselling and cascade testing (which may include referral to a clinical genetics unit)???	Recommendation 8.5 Consensus recommendation Families of newborns diagnosed with SMA through newborn screening programs should be offered referral to, and review for genetic counselling and cascade testing (which may include referral to clinical genetics services).	

[*redacted*]	General feedback • On review, the guideline appears comprehensive and aligns with the work by policy makers in states and territories and the Commonwealth. • Keen to understand how these guidelines when finalised will be disseminated, promoted and used to support SMA integration into newborn bloodspot screening (NBS) – noting it is already part of NBS programs across the country. Assume this will be via s/t and hospital networks to reach clinicians, consumers etc?	An implementation and dissemination document has been provided as a separate file and is also incorporated into the Guideline document	

[*redacted*]	General feedback We have sought expert clinical feedback on the guideline. The advice is, while the recommendations are reasonable, they are mostly not of direct relevance to GPs.	-no change needed [*redacted*]	

[*redacted*]	General feedback The consensus-based recommendation grading system detailed on pg 90 (i.e., 1A-2C) would be useful to include in the 'list of recommendations' on pg 28 to help understand the grading for these recommendations, and minimise confusion with the evidence-based recommendation grading system. Screening feedback A few recommendations are a little redundant and/or may overlap with other guidance already available/applicable to all NBS conditions, e.g., Recommendation 1.1 is national policy in Australia that has already occurred through an alternative recommendation pathway and has already been implemented, and Recommendation 1.8 – does this duplicate existing guidance on taking bloodspots prior to transfusions? Also, if this recommendation is targeted at sample collection staff it differs from almost all of the other recommendations and it is not clear that this is a key audience for the guidelines. The use of the term “screen positive” is used differently in different parts of the guidelines and wording may need to be clarified – Recommendation 1.7 refers to the “screen positive” result being communicated as just the SMN1 result, which does	The grading system has been removed to reduce confusion and a prioritisation system (high, moderate and low priority) has been assigned to consensus recommendations based on GDG review and evidence. Whilst recommendation 1.1. is true, the SAC felt that it was still important to keep within the Guideline as other jurisdictions (outside of Australasia) continue to assess saliva and whole blood to implement NBS for SMA. Recommendation 1.8. is now a practice standard 1.3.3. If blood transfusion in the neonate is considered, the dried blood spot should be taken prior to transfusion aligning with processes with the National Policy Framework for Newborn Screening. The wording has been corrected accordingly. Recommendation 1.3. Consensus recommendation	

	not align with the definition in Recommendation 2.3 being both the SMN1 and SMN2 results defining a "screen positive".	A screen positive result should be communicated to clinical services when the *SMN1* screening result is available (independent of the availability of *SMN2* copy number) on screening assays.	

[*redacted*]	General feedback Thank you for such a comprehensive guideline and for thinking so deeply about the experience of patients and families. The only feedback I would like to give and have considered is the inclusion of referring or at least making families aware of the existence of SMA Australia, and other support organisations like Genetic Support Network of Victoria and Genetic Alliance Australia. We have learnt that unless this is explicit it is often overlooked. Section 9 I believe is where this would be most relevant.	The SAC has discussed this feedback and felt it is not prudent to incorporate specific advocacy group names. We have titled these within an umbrella term of support organisations, with the clinician role to identify the most appropriate in terms of the family's needs and preferences. This has been added into the definition section of the Guideline under the title 'The definition of advocacy services' and states the GDG recognised that a variety of international, national and jurisdictional services exist for children with SMA and their families. For the purpose of the Guideline these have been grouped under the terminology of advocacy services. We leave it to the discretion of relevant healthcare practitioners to direct families to the most appropriate services based on individual needs and preferences.	

[*redacted*] GUIDELINE DOCUMENT -See next box for Tech report	Screening feedback • **The definition of newborns, infants and children with SMA (pg 25, 100).** The Reading the Guideline the Population sections of the guideline outline that NBS for SMA could occur after the defined period for newborns (<= 28 days), expanding the NBS testing period out to 12 months of age. We note that the Guideline Development Group (GDG) defined the cohorts of newborns and infants with children. Although this seems to contrast with recommendation 3.8, regarding diagnostic *SMN1* results being delivered within 30 days of birth, we recognize, as outlined in the	No changes required.	

	Guideline, that in some circumstances this timeframe may not be logistically practical. • Recommendation 1.2 As outlined in the guidelines, recommendation 1.2 reflects that 95% of newborns with SMA is due to homozygous deletion of exon 7. The other 5% is made up of a compound heterozygote genotype, biallelic pathogenic sequence variants or SMA not due to SMN protein deficiency. This approach is consistent with other countries including Canada (Groulx-Boivin et al., 2024). As outlined in the guidelines, patients affected by SMA not picked up by newborn screening would follow the normal clinical pathway. We anticipate future review of the guidelines would include a consideration of ways to incorporate this 5% group into newborn screening, particularly as testing technologies advance. • Recommendation 2.4 (pg 33,130) We recognize the complex question regarding timing of result disclosure of an *SMN1* positive screening result in relation to the result of determination of *SMN2* copy number. The reasons outlined in the guidelines for this decoupling reflect that *SMN2* copy number determination is not a confirmatory test; as a prognostic marker is not absolute and can vary depending on the methodology used. Clinical presentation is the absolute measure of disease severity. The approach adopted by the guidelines is balanced regarding the timing of the *SMN1* screening result which still incorporates guidelines on the utility of *SMN2* copy	We have added this change No changes required.	

	number as a prognostic marker (recommendation 2.1, 2.2, 2.3, 2.4, 2.5, 2.6). Diagnostic feedback **General comment on technique of screening.** As noted in Mercuri et al., (2018), 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). The guideline summarized a study by Tavares et al., (2023) that concluded real-time PCR methodologies are accurate and cost effective. This study used MLPA as the confirmatory second test. In a systematic review of NBS programmes for SMA, Cooper et al., (2024) found that most programmes used RT-PCR or RT-qPCR as the index test method, with most programmes using MLPA as the confirmatory test. We agree with the need for flexibility in the guidelines including of the technique employed – to allow for the possibility of advances in technology associated with testing. As mentioned in the guidelines, the accreditation for tests will be governed by the usual regulations for diagnostic laboratory clinical testing accreditation. • Recommendation 3.4 (pg 35, 140)	No changes required. No changes required. No changes required.	

	We strongly agree with the need of orthogonal validation utilizing a different methodology for diagnostic testing. This will aid in the robustness of the test overall and decrease the chance of false positives. This was evident in the systematic review of newborn screening programmes by Cooper et al., (2024) with in most programmes, the index test method being RT-PCR and the confirmatory test MLPA (refer to Table 1, Cooper et al., 2024). • Recommendation 3.8 We strongly agree with the need for timely screening and diagnostic results, given the implications for clinical care. Newborn screening directly addresses issues relating to delayed diagnosis in the absence of screening (Nishio et al., 2023 review; Lin et al., 2015). The recommended turnaround time of the diagnostic tests should be regularly reviewed with new advances in methodology. Our understanding is that 30 days is feasible in terms of current timelines – approximately 2 weeks for *SMN1* NBS and 8-10 days for *SMN2* copy number determination. • Recommendation 3.9 We agree with this statement, particularly in relation to accurately detailing the method for copy number determination. Additionally, the number of repeats >4 is important for informing phenotype severity (Prior et al, 2020). The information regarding methodology is also important in terms of false positives and negatives. We encourage these conventions to be incorporated	No changes required. This has been reinforced by the addition of a statement which now reads The Guideline should be reviewed in 5 years of publications or sooner if the screening, diagnostic or clinical landscape changes in the interim, updated to reflect and respond to new evidence from research, clinical practice and changes in community needs, values and preferences. This is particularly pertinent as evolving screening, and diagnostic assays change the time to confirmation of SMA.	

	into internal diagnostic laboratory policies regarding SMA testing and reporting. <u>Clinical feedback</u> • Recommendation 5.3 / 8.2 / 9.7 / 10.10 / In the guidelines and literature there is a strong emphasis on the need for a multidisciplinary approach to the management of SMA patients. Part of this relates to access to specialised neurology services and clinical genetics services when SMA patients are referred for further genetic testing. We note the access to such services can be challenging in outer regional, remote and very remote parts of Australia which creates issues of equity of access for all Australians including Aboriginal and Torres Strait Islander patients in remote areas. For example, Best et al., (2021) identified barriers of access to clinical genetics and genomics, including current service model designs which centre on urban areas, and limited investment in rural areas. Workforce capacity and capability were also raised including the lack of capacity to engage with genetics specialists. A study by Baazeem et al., (2023) found most tertiary hospitals in Australian cities were in major centres (72% in Sydney for NSW; 82% in Melbourne for VIC; 57% in Brisbane for QLD). We encourage investigation of Telehealth as one possible solution for access to specialist neurology services (as indicated in Recommendation 5.3 and Recommendation 8.2 where travel is not feasible. A recent study (Marne et al., 2023) evaluated a neurology outreach programme to aid in paediatrician training in neurology via	No change required	

	video-conferencing and was found to be both accepted and effective. In relation to health access for Aboriginal and Torres Strait Islanders, there are general barriers that contribute to health inequities, including lack of transport, waiting times and a lack of culturally appropriate health information and materials (Australian Institute of Health and Welfare 2024). We note in the recent Health Technology Assessment Policy and Methods Review Recommendation 1: Creating a more equitable system for First Nations peoples and Recommendation 2: Providing equitable access to medicines for paediatric patients. • Recommendation 9.5 [*redacted*] supports this recommendation and that referral occurs in a timely fashion. This is consistent with current practice, where referral to a specialist genetics service can provide families with expert advice regarding cascade screening testing and recurrence risk. Involvement of genetic counselling at the time of SMA diagnosis is consistent with the 2017 International Standards of Care for SMA (Mercuri et al., 2018). It should be noted that the role of genetic counsellors in SMA has adapted in the new therapeutic era (Serra-Juhe et al., 2019). Clinical geneticists and genetic counsellors will play important roles in collaboration with neurology specialists in terms of providing information around treatment options and timing, how treatment will be delivered and follow-up of patients. Additionally, at the appropriate time, information and advice surrounding future reproductive options can be discussed.	We thank the reviewer for these insights and have incorporated these barriers to equity in the dissemination and implementation plan. These excellent points have been incorporated into the Guideline on the expanding role of genetic counsellors. This now reads: With their role expanding in a new therapeutic era, genetic counsellors can now provide information not only on the genetics of a condition but work in conjunction with neurology specialists to facilitate understanding of treatment timing, delivery and follow-up. Dependant on health expertise and confidence in disclosing sensitive results to families, other programs have leveraged the experience of trained genetic counsellors or nurses, particularly in regional and remote areas.	

	• Recommendation 11.11 – comment on treatment options for infants with 4 SMN2 copies As outlined on pg 200 of the Guidelines document, at the time of writing, pre-symptomatic children with 4 or more *SMN2* copies do not have access to approved and reimbursed treatments. This contrasts with an international consensus treatment algorithm (Glascock et al., 2020) which was inclusive of such infants. We note pt 4 of the 'Evidence gaps and future directions' relates to the management of newborns with SMA and 4 or more *SMN2* copies and the need for an increased evidence base for informed decisions regarding the risks and benefits of early treatment. <u>Potential Guideline Impact</u> • Comment on likelihood of workforce issues for neurologists, GPs, genetic counsellors, laboratory diagnostic staff. In Queensland, an SMA newborn screening program has been in operation since May 2023 and it is anticipated that 6 individuals a year would be identified by the program, on average. Based on 2022 figures (D'Silva et al., 2022) and 300,000 births per year in Australia, one would expect 26-30 individuals per year affected by SMA. Given the complex nature of a multidisciplinary approach, workforce issues could be a barrier to successful implementation (as outlined on pg 198 of the National Guidelines). To mitigate such barriers, education of diagnostic laboratory workforce in terms of importance of turn-around-times for *SMN1* confirmation and *SMN2* copy number determination will be important. Regarding training, page 161 notes: "Non-specialist medical practitioners who may reasonably be expected to perform result disclosure where appropriate may	No changes required.	

	require a process of training and education on SMA and implications of a screen positive result for optimal information provision". This may include Indigenous **Health Liaison Professionals** (IHLPs) but potentially other professionals in the Indigenous health workforce. <u>Overall feedback</u> We strongly support the proposal for guidelines to be **flexible** (pg 24, pg 25) which aligns with existing guidelines including the National Screening Framework and internationally developed Standards of Care for SMA. This is particularly relevant giving the likely ongoing advancements in treatment for SMA. We also support the proposed strategies for Guideline evaluation (pg 206/207) including the need for update of guidelines in a rapidly evolving landscapes, further investigation of barriers and enablers to implementation and acknowledgment of jurisdictional differences in adoption of the guidelines. In terms of the length of time for review – five years is suggested. This timeline seems appropriate; however, we envisage that any major changes in treatment or diagnostic methods may warrant an out-of-session review. As these are the first implementation of the guidelines, a 1-year 'fit-for-purpose' review could be of benefit. This would allow for adjustments based on any feedback from those stakeholders who are utilising the guideline or identify any key gaps that might have only been highlighted once the guideline was used in the practical sense. We note that the 2016 NHMRC standards for guidelines state in section 6.1: Be informed by well conducted systematic reviews, however a timeframe is not given. <u>Broader feedback on relationship between NBS and RCS.</u>	A sentence has been added to incorporate Indigenous Health professionals within an education and training model, within the future directions section; education and training for relevant medical practitioners in rural and regional areas. The need for a flexible approach to review of document is noted in the Future directions section which now reads: The Guideline should be reviewed (at maximum) in 5 years of publications or sooner if the screening, diagnostic or clinical landscape changes in the interim, updated to reflect and respond to new evidence from research, clinical practice and changes in community needs, values and preferences.	

	Pg 114 of the guidelines references the inclusion of SMA1 (and fragile X and cystic fibrosis) as a condition screened via reproductive carrier screening (RCS) (Medicare item number 73451). This will allow couples more information regarding their reproductive decision making in the context of SMA. The guideline document indicates the complementation of the two programs – this may warrant further comment and linking to guidelines for reproductive carrier screening as they become available. Potential bi-directional impacts of reproductive and newborn screening programs for certain conditions may include cost effectiveness, and awareness and education of the different health practitioners, including the strengths and limitations of screening programs in identifying conditions like SMA. <u>Possibility of generally streamlining Guidelines.</u> Due to the structured nature of their development there is some overlap between specific guidelines and the opportunity of streamlining. As an example, recommendation 8.4 and 8.5 concerning diagnostic results disclosure. We suggest such streamlining could be incorporated into future reviews. <u>Recommendation 11.5</u> We are very supportive of Recommendation 11.5 and the collection of real-world evidence by neurology services after identification and management of children identified as screen positive Post implementation evaluation metrics will be important to inform future refinement of the guidelines / screening practice.	Whilst the SAC felt that comment on reproductive genetic testing was outside the scope of the current Guideline, the existence of guidelines for other screening methods for SMA was delineated in the Scope, population and setting section: Newborn screening is a public health program that fits alongside and within other public health initiatives such as reproductive carrier testing, and prenatal genetic screening. This Guideline acknowledges, compliments and does not replace existing guidelines that encompass these domains We have streamlined the recommendations accordingly.	

	<u>Aboriginal and Torres Strait Islander, Pacific Islander and/or Māori representation on the GDG.</u> It was indicated that there was no formal representation of Indigenous populations on the GDG. We suggest invitation of consultation by respective groups such as Queensland Aboriginal and Islander Health Council (QAIHC), National Aboriginal Community Controlled Health Organisation (NACCHO), Te Aka Whai Ora (Māori Health Authority). This also relates to Recommendation 7.4 (pg 48). With no formal involvement, there was no clear messaging or guidance on how the lack of representation would be addressed within the framework. The guidelines lay the responsibility for supporting families whose child has been diagnosed with SMA with the **Indigenous Health Liaison Professionals** to provide advice and be involved in how the clinical test is communicated to the family. This puts pressure on these roles/people and there are no clear recommendations for appropriate training that the IHLPs could be supported to undertake. Pg 210 refers to continued involvement of Aboriginal and Torres Strait Islander peoples in the evolving SMA research but no clear pathways identified for how this can be or should be achieved. In their current form the guidelines do not identify culturally appropriate pathways or best practice approaches to supporting Aboriginal and Torres Strait Islander families whose child has been diagnosed with SMA. We encourage the development of an Indigenous Governance Advisory Group to support ongoing guideline work.	We agree with the stakeholder perspectives that these communities should be represented in future work. We have incorporated the advice for a Consumer Group with purposive sampling from Indigenous Stakeholders to support future work in this domain.	

[*redacted*]	<u>Technical report General comment</u> As a general comment, the technical and administrative report was very useful, particularly the evidence tables for each section, for each respective recommendation. This will be a valuable	No change needed	

Tech and family fact sheet	resource for future revisions of the guidelines as the evidence base changes (for example relevant literature). <u>Family fact sheet comments</u> • The family fact sheet is an important communications tool and so Australian Genomics' community engagement team provide specific feedback to this section. This includes brief background on SMA, the guidelines process, a summary of screening, diagnostic and clinical care steps and a summary of recommendations. We suggest a further heading in slide 7 such as "Summary of screening and clinical pathway". • We also suggest mention (and link) to the Family fact sheet in the main Guidelines Document. <u>What is SMA</u> • Formatting of question mark at top and bottom • Instead of numbering each of the points, it may be better to use icons here that represent the content (e.g. a picture of someone walking/moving for point 2) • The gradient background could make it difficult for people who are vision impaired • More detail on inheritance may be warranted, for example, the sliders depicting percentage is a bit difficult to understand could use a pie chart or similar • Great explainer of the cause of SMA but there is a new term "higher copy number" introduced at the end and not explained	This title has been added. Family fact sheet now incorporated into main documents via link in the targeted secondary end users section. This has been changed Icons have been added Backgrounds have been placed in monotone for readability Changed sliders to pie charts. Added sentence "If both parents carry the gene mutation" to make clearer the linkage with % likelihood that child develops SMA The wording has been changed and now reads, 'more copy numbers of SMN2'	

	<u>What is NBS for SMA</u> • suggest changing the order of the circles – leading with what NBS is: 1. NBS aims to identify children at risk 2. This test takes a small amount of blood 3. NBS is offered to all babies 4. In Australia and NZ each health area 5. In 2022 and 2023 6. this is the first times genetic 7. Those identified during screening • Rather than "confirmatory testing" suggest " …urgently referred to confirm the results." • Formatting: Breaking up the heading at the top and bottom of the page make it difficult to read. <u>Why we need a guideline</u> • Content: The opening sentence "the intent of these guidelines…" is quite formal. Could reword to something like "These guidelines aim to provide recommendations that improve the care of newborns based on the best available evidence." • Formatting: Suggest placing text in boxes around the graphic <u>Steps page</u> • Content: 1. Steps could be reworded to the active voice e.g. Step 1 could be reworded to 'A dried blood spot is collected from the newborn for newborn screening'.	Order of circles changed according to feedback Words changed to match suggestion Heading from bottom brought under heading at top Words changed to match suggestion The SAC felt that this formatting change did not improve readability. Words changed to match suggestion	

	2. Step 2: Suggest “laboratory” rather than “reference screening” 3. Step 3: suggest removing “reference screening” and use laboratory. Spelling error: services. Could removing “screen” and replace with “positive result” 4. Step 5: Suggest simpler explanation of “diagnostic evaluation”. Spelling error: positive 5. Step 6: Suggest changing biomarkers to markers/signs. 6. Step 7: Reword ‘The family is told the results and treatment plan starts’ 7. Step 8: suggest rewording • Formatting: Icons are difficult to see. Would also make the outline of icons bolder <u>Summary page</u> • Screening box: Is there a need to mention exon 7? This has not been introduced previously. • Consider rewording of some of the Recommendations boxes, as some appear more to be explanations, rather than a summary of key recommendations. • gradient background will make it difficult for people who are vision impaired <u>Further general comments</u> [*redacted*] endorses the National Recommendations for Newborn Screening in Spinal Muscular Atrophy in Australia and New Zealand. Specific points of consideration:	Bold added to icons to ensure they are visible Co-leads feel Exon 7 is important in this context. The wording has been changed to make this style more in reflection of recommendations, linked in part to explanations to provide context. Gradient changed to single colour background	

	• Further engagement with Indigenous Health representatives and peak bodies across Australia and New Zealand. As stated previously, we suggest development of an appropriate Indigenous Governance Advisory Group to support this work.	We have reached out to the peak bodies for further consultation and have added the need for an Indigenous Advisory Group to inform further research. This now reads: the establishment of an Indigenous Advisory Group to inform future revisions and implementation of the Guideline will be a necessary future step towards equitable delivery of best care for all children with SMA across the diverse communities of Australasia.	
	• Commend recommendations that address the **potential health inequity of access** to specialist neurology services and multi-disciplinary teams in outer regional, remote and very remote areas of Australia and New Zealand.	No change required.	
	• We commend the need for **flexibility** in the guidelines given potential advancements in treatment and potentially developments in diagnostic technology. We suggest the possibility of out-of-session updates aside from the scheduled 5 years schedule for any major disruptive changes in treatment or diagnosis relating to SMA and newborn screening.	We have updated the need for a minimum 5 year review as above.	
	• We agree with the section on pg 8 regarding **evidence gaps and future directions for stakeholders**. In relation to point 1- the evolution of genomics capabilities in newborn screening, we encourage further work in this area in benchmarking various platforms including exome and whole genome sequencing. Point 2 is also a very important consideration given the challenges in determining *SMN2* copy number and variables in linking copy number to disease prediction.	No changes required.	
	• **Relationship and potential overlap between Guidelines and Implementation.** We note that there is considerable reference	An implementation document has been provided as a separate file and is located on the website, with a link provided in the Guideline document under the section of future	

	to downstream clinical management associated healthcare support that are very specific, given these are guidelines. It is not clear if a separate implementation document is planned at a separate stage.	directions; dissemination and implementation of recommendations within the Guideline.	
	• **Although not directly addressed in the guidelines, individuals residing in Australia who are not eligible for Medicare do not have the same access to newborn screening or potential treatments.** We understand reimbursement of treatment in this scenario would be reviewed on a case-by-case basis on compassionate grounds which exacerbates inequities and widens the health gap.	This has been a point considered across the feedback. In response, the SAC agrees to add an implementation point in 10.1.1 that states: in Australia and Aotearoa New Zealand treatments for SMA are subsided by the publicly funded healthcare system for children who meet eligibility criteria. Reimbursement strudtures and options for treatment vary across the two countries. For children who are not eligible to access subsided treatments on the basis of their residency status or other factors, treatment pathways require interrogation on a case-by-case basis.	
	• There are a few differences between the Australian and New Zealand health systems relevant to SMA which may impact the guidelines – for example New Zealand currently funds Nusinersen as a treatment option, from January 2023 via Pharmac, New Zealand's pharmaceutical management agency (Pharmac 2022). Risdiplam was available from May 2023.	The variations in practice and access to treatments have been added to the implementation point 10.1.1 which now reads In Australia and Aotearoa New Zealand treatments for SMA are subsidised by the publicly funded healthcare system for children who meet eligibility criteria. Reimbursement structures and options for treatment vary across the two countries. For children who are not eligible to access subsidised treatments, on the basis of residency status or other factors, treatment pathways require interrogation on a case-by-case basis.	
	• **we reinforce the potential need for revisions of the guidelines,** given most of the evidence was consensus based. This may be particularly relevant for SMA given the rapid recent advancements in treatment and technologies relating to methodology.	-No change needed	

[*redacted*]	• Equity / rural and remote context Stakeholders uniformly highlighted that timely access to treatment services and teams may not be achievable in context of the timeframes recommended. The geographical size of [*redacted*] can present challenges for families in a rural or remote setting; their ability to access services and/or receive care in a timely manner is likely to be extremely challenging when considering the recommendations. Medicare eligibility of diagnosed infants can impact the ability to access specialist services. Confirmation testing of SMA is only available [*redacted*], and presents significant risk and delay to diagnosis and care of [*redacted*] infants. For rural and remote infants and their families, several stakeholders proposed that an adjustment to recommendations should be made to promote the increase of utilisation telehealth and local clinicians in an effort to reduce the impact on the centralised service and improve equity of access and support. • Workforce [*redacted*] noted that specialised allied health services were identified as a need, however, additional capacity in nursing and medical may be required to maintain or increase service provision based on the recommendations. Particularly, specialist neuromuscular clinicians are indicated to have key roles within the recommendations, however, the availability to resource this is not realistic in terms of clinical workforce availability and	These barriers to implementation have been discussed within each recommendation (in terms of resourcing required, feasibility) and have also been explored in the implementation plan. After discussion with the GDG it was considered essential to maintain maximal timelines for completion of screening and diagnostic pathway, to facilitate best outcomes for children with SMA. The use of telehealth services has been incorporated throughout the Guideline recommendations. These barriers to implementation have been discussed within each recommendation (in terms of resourcing required, feasibility) and have also been explored in the implementation plan. The GDG acknowledged challenges to resourcing however felt the benefit of implementing the recommendations in the Guideline were in line with international standards, requiring reconfiguration of healthcare services	

	funding to resource services to the levels indicated in the recommendations • Service funding Funding for pre-screening and post-screening services does not specifically exist for newborn bloodspot screening. For post-screening services this especially presents a challenge when considering implementing the recommendations as essentially more services are being required without additional funding and resourcing to support them. • Service capacity Clinical and genetic services are currently operating at or over service capacity. If implemented, some of the recommendations will result in additional service delivery challenges to meet increased testing, family support, treatment, education, travel, and other needs. • First Nations [*redacted*] stakeholders emphasised that implementation of recommendations should include ensuring culturally appropriate and safe support for First Nations families with infants diagnosed with SMA. • Education Clinical education was highlighted as an essential component when considering implementation of the recommendations. Contemporary education for clinicians involved in pre and post-	We have addressed this in the relevant recommendations and implementation plan. We have addressed this in the relevant recommendations and dissemination and implementation plan.	

	natal conversations, diagnosis, treatment and care of infants with SMA will strengthen their ability to provide safe, informed care.		

[*redacted*]	In principle agree with all recommendations; they are mostly consistent with the model-of-care in the neuromuscular service in [*redacted*]. However, in order to continue to meet the recommendations there are some hurdles. • Equity a. [*redacted*]provides NBS for [*redacted*] – timely access to services and teams, may not be able to meet the timeframes recommended. [*redacted*]can offer telehealth for the initial conversation; however, these infants need some specific genetic and investigative blood sampling – this would be messy across health systems – challenging enough in [*redacted*]. Also, they need clinical examination by a Neurologist and physiotherapist who are specialists in SMA. The family would need to travel to [*redacted*], on short notice, within 1-2 days after NBS positive. Consideration for post-partum mothers and families is relevant given the geography of [*redacted*]. . Tier 2 genetic testing – In [*redacted*], confirmatory genetic testing needs to be sent interstate – [*redacted*] for SMN1 & SMN2 testing. Most states can offer this testing locally with a quicker turnaround time. At best these test results take 7-10 days for [*redacted*]families. This testing is essential to determine	Whilst the SAC acknowledged the timelines for screening and diagnostic results could vary across health jurisdictions, due to the neurogenetic emergency of SMA, it was considered on the whole feasible to implement these timelines. Specific recommendations have been developed to help promote equity of access to best care for children in remote and rural areas. These include the use of telehealth systems to	

	eligibility for PBS funded SMA medications. Testing and results is time critical. c. Medicare Eligibility – 50% of our patients diagnosed through NBS in [*redacted*]in 2024 have not had Medicare …. this impacts their ability to self-fund/access specialist NM services, allied health teams, and PBS funded treatments. They're also ineligible for NDIS. One family did not have private health insurance, which impacts delivering on Standards of Care (SOC) recommendations. The family does not have capacity to fund the appropriate standard of care. d. Delivering care to SMA patients has impacted the NM service significantly with no additional resourcing. There are less appointments • Specialist nursing support a. Allied health teams were noted. Clinical nurse consultants/ nurse specialists weren't specifically mentioned, however have a vital role in supporting families from screen positive, through to coordination of care, clinical advice and ongoing specialist • Resourcing / funding of NM services / access to timely care a. NBS laboratory received funding to build capacity and capability of their service, however clinical services have not had additional funding to support care and management. b. Psychological support for NBS positive – none at [*redacted*]. Our service has access to a Social Worker (SW) only, and we	support screen positive disclosure, diagnosis and clinical surveillance and treatment for children and families unable to travel to tertiary centres. This is considered outside of the scope of the Guideline and has been set out in the Scope. The SAC acknowledges this point but felt it was outside the scope of the Guideline to address. This was added as a point in Scope, which now reads "It is made to be flexible and adapted to conform with available resources and capacity on a state/region/territory level across Australia and Aotearoa New Zealand. As such, it has been developed within the current health policy framework of these two countries and the parameters of the Guideline do not specifically address reimbursement pathways for children with SMA (diagnosed through newborn screening) who are not eligible for subsidised or publicly funded health services or treatments." The barriers outlined in this comment are considered in the implementation plan. The GDG agreed that processes for result disclosures were jurisdictionally dependent, and that medical practitioners such as **genetic counsellors** nurse specialists and non-specialist medical practitioners could also be well placed to disclose and counsel on the results. For these professionals, the evidence showed that access to and advice from specialist services, enabled a streamlined and effective disclosure process. The barriers to implementation as discussed (b-e) have been discussed within relevant recommendations (in terms of resourcing required, feasibility, education and training)	

	link all families with SW, however they also have other workloads and competing clinical commitments with other teams/inpatients etc. There is also a high turnover in the SW service for Neurology, so I would advocate for a consistent team that can develop specialised knowledge in this area. The SW do an excellent job; however, the turnover of staff is less than ideal. It's difficult for them to provide psychological support if they're only in the role for a few months. c. Sustainability of services – Some states were successful in securing additional government funding. Unfortunately, our department, has absorbed the NBS workload and treatments for SMA, however this has been challenging and workloads have increased significantly. Previously, palliation was the only option for many infants born with SMA, however they are now surviving, require high-cost PBS funded medications and intensive monitoring and coordination of care. We have had a 320% increase in SMA1 since 2018 when treatments became available. This means, higher number of patients, increased complexity and acuity. If we are to consistently deliver on the SOC recommendations it will be a challenge, without impacting other aspects of the service delivery in the Neuromuscular service and patients with other neuromuscular conditions. We are a very small team, resourcing and succession planning needs to be addressed. Services need to be reviewed and resourced accordingly. We already have long wait times for CAT 2 and review appointments. Timely access to ongoing care is a challenge, clinics are overbooked, and if a patient FTAs or cancels it's a 9 month wait for a review appointment. Currently all NBS SMA and SMA treatment monitoring are done over and above other workload. Appointments are booked adhoc and overbooked. This is not a sustainable system for patients or staff.	and have also been explored in the implementation plan. The GDG acknowledged challenges to resourcing however felt the benefit of implementing the recommendations in the Guideline were in line with international standards, requiring reconfiguration of healthcare services	

	Services cannot deliver the SOC recommendations without reviewing resourcing. d. SMN2 4 copies – impact on clinical services... frequency of reviews to monitor for disease progression, puts more demand on existing appointment availability. We know firsthand as we are one of the few states with an SMN2 4 copy patient. This patient became symptomatic … and was then eligible for PBS funded treatment. So close monitoring is very important to ensure timely initiation of treatment which can change long term health outcomes. e. Workforce for NM clinics – our service is significantly oversubscribed for appointments; we've had a reduction in medical FTE attached to the service and do not have capacity to absorb the workloads. Patients diagnosed with SMA need to be seen in a specialist NM service, however managing the demand and capacity is at a tipping point. We have done extensive work to ensure optimisation of services over the last few years, yet still struggle to see patients in clinically recommended time frames.		
[*redacted*]	1. Consensus based recommendation 7.4 on page 48 of the National Recommendations for Newborn Screening in SMA states "We recommend that medical practitioners providing information to, and discussing diagnosis with, families of newborns from Aboriginal, Torres Strait Islander, Pacific Islander, Māori or other First Nations backgrounds should be aware of particular issues arising from information provision and diagnostic evaluation. The medical practitioner may elicit the advice of Indigenous Health Liaison professionals in how to best conduct these evaluations and offer families the support of Indigenous Health Liaison services at the time of diagnosis." When considering appropriate support for First Nations families, consideration should be given to providing additional cultural	- The suggested professionals have been incorporated into the relevant recommendations	

	support and sensitivity. We suggest a First Nations Nurse, Midwife or a Health Worker practitioner with a sound understanding of the Newborn Screening process be included in conversations with these families where possible. 2. Consideration should be given to providing some detail about potential sensitivities for First Nations patients. This is not to remove the need for an Indigenous Health Liaison Officer or a First Nations health professional, but to provide better guidance for the clinician's discussions and to benefit the pursuit of cultural safety in the long-term with better understanding of this issues.	-Currently there is a paucity of evidence for potential sensitivities for First Nations peoples within the remits of NBS for SMA, as considered by a targeted systematic literature review. We have aligned our implementation plan to incorporate the need for research to address these data gaps.	
[*redacted*]	1. Supportive of the DRAFT Guideline supplied. 2. Makes perfect sense that the NBS recommendations align with current evidence base given treatment advancements for SMA. 3. The biggest factor for the midwifery cohort will not be the resources in terms of education and access to expertise for post diagnostic assessments but more so the educational requirements for having discussions with parents postnatally while gaining informed consent for NBS (with SMA screening included). 4. With the addition of SMA in the NBS will there be communication and educational update provided to maternity clinicians working with families at the point of NBS screening?	No change required. See implementation plan linked to the Guideline See implementation plan linked to the Guideline	
[*redacted*]	1. Agree with the draft documents rationale for including SMA testing, as described, in the routine NBS paradigm. 2. Recommendation 1.6 is important (not reporting heterozygous state) – reporting of carrier state would have significant	No change required No change required	

	implications for genetics services given the population carrier frequency for SMA. 3. Important to emphasise that inclusion of SMA on newborn screening will increase demands on neurology and clinical genetics services. Consequently, recommendations should also be made that Hospital and Health Services should ensure these clinical teams are appropriately resourced to meet the assessment / counselling demands that will result. 4. While those with clinical SMA would have been seen eventually by these services anyway, there is likely to be a false positive load that will increase work for both services. Given the nature of the condition, these families are still likely to need robust and timely counselling	Resourcing issues are considered in the implementation plan and where relevant in the justification of each recommendation. Recommendation 4.1 Consensus recommendation For newborns with a false positive, false negative or uncertain screening result, a case review with communication and collaboration between screening, diagnostic and clinical services should be conducted to understand the aetiology of results and explained to families. Information Box Information can be provided by paediatric neurologists and/or clinical geneticists and/or genetic counsellors. Practice Standard 4.3.2. Families who receive a false negative, false positive or uncertain screening result should be provided information and psychosocial support by relevant members within the multidisciplinary team.	
[*redacted*]	• Consensus feedback 1. The document is comprehensive however at over 200 pages it may impact readability.		

	2. There are many repetitive statements, with the formatting impacting on the ease of reading the document. 3. The suggested requirement for the availability of a paediatric neurologist as the point of contact and the person for initial screening mentioned throughout may be impractical, especially in [*redacted*]. For reference, there is one paediatric neurologist in [*redacted*], but otherwise no others outside the [*redacted*]. Relying on the sole practitioner for a very large area to be available may be a quite cumbersome and risk delays in diagnoses. Currently, [*redacted*]has an effective system for following up abnormal results, involving the appropriate teams from Metabolic, Immunology or Neurology, in which the results then defer to the local delivery/paediatric centre. This works well for metabolic conditions which require very rapid management. The [*redacted*]suggests utilising the already well-established system, along with a co-referral to the paediatric neurologist as a consideration. – a query for [*redacted*]is, will the neurologist at [*redacted*] be deemed the link person for the state? 4. Page 104 – there is a spelling error, foetal should be corrected to- fetal. • Additional late feedback 1. Page 33 Recommendation 2.7 – Formatting error – needs a space inserted between the first two sentences, highlighted in yellow, for readability - We recommend that the newborn screening for SMA program will establish a clinical referral pathway for newborns who screen positive for SMA.A positive newborn screening result should be verbally relayed to a designated paediatric neurologist.	The Guideline has been reduced and streamlined to avoid repetition whilst maintaining a solid evidence base for recommendations. The emergency nature of SMA warrants specialist input and therefore the SAC maintains that a paediatric neurologist should be contacted for the screen positive result. The QLD medical team were part of the consultation process and have agreed to this recommendation. We acknowledge that work flow will vary between health jurisdictions and this has been accounted for in a slight rewording of these recommendations as follows: Recommendation 2.2. Consensus recommendation Newborn screening programs should establish a clinical referral pathway that includes simultaneous early notification of a screen positive result to a paediatric neurology specialist and local healthcare practitioner. This is the English/Australia spelling of foetal and therefore has been retained. Extra space entered between sentences	

	2. I agree group, the pathway including the handling of false positive results, should follow that already established for NBS. 3. Page 42 Recommendation 5.3 – this wording could be changed to 'responsible healthcare practitioner' instead of medical. For example, a specialist neurology nurse practitioner or genetic counsellor with support from a paediatric neurologist would be a suitable person to disclose a screen positive result, the latter not typically falling under the descriptor of 'medical' which could be taken to mean doctors only, or doctors/nurses but would typically not be used as a descriptor of allied health including genetic counsellors, who are arguably well placed to perform this role. This would also make this recommendation congruent with the following recommendation 5.4, which does reference healthcare practitioners. 4. Page 48 Recommendation 7.5 – should include clinical geneticist or genetic counsellor or genetic service. 5. Page 106 – the use of the term 'healthy individual' is not in line with best practice around the language used in disability, as it's a value laden term that many parents of children with a disability find distressing. Alternative terminology has been recommended. Equally, 'SMA patient' is better stated as Individual with SMA or Neonate with SMA or Child with SMA or Person with SMA. Recommend "person without SMA" and "person with SMA" for this section.	This has been changed to read designated healthcare practitioner. This has been added to the recommendation Changed 'healthy individuals' to 'individuals without SMA'. -All mentions of 'patient' are in the context of definitions by CLSI, or 'patient organisation' etc.	
[*redacted*]	1. There should be more consideration/emphasis for patients and families who live in more rural/remote regions of the country (e.g. rural QLD and WA, the NT) who are already at a disadvantage from receiving high quality healthcare. Most	The SAC agrees with these comments and have accounted for this in the recommendations as follows, with wording changed to incorporate the wider role of general practitioners.	Some adjustments made to account for

	families from rural QLD and WA, as well as the NT are often more than a couple hours away from their local tertiary paediatric hospital. a. Travel with a young infant, especially when they are initially diagnosed can often be challenging. b. The utilisation of telehealth and local medical resources might be an avenue to emphasise and consider. c. For example, at the initial consultation/on initial diagnosis, patient and family can be with the local paediatrician, and the paediatric neurologist can provide the initial consult via telehealth. Additionally, this method can be used to support the local paediatric team during subsequent reviews. 2. Should there be more involvement of a general paediatrician in the holistic care of these children, especially ones who live in rural/remote regions of the country, where access to a specialist multidisciplinary clinic might be challenging to access. a. Involvement of a local general paediatrician, especially at the time of diagnosis, gives these patients a local contact person, but also someone who can coordinate the patient's overall care (e.g. growth, development etc). 3. The guidelines should strongly encourage the development of a state based neuromuscular clinic (which I suspect is likely to be available in all tertiary paediatric hospitals across the country), where there can be multidisciplinary review of these patients. Additionally, these clinics should also closely liaise to regional teams (including various allied health teams) to empower them to help provide care to these patients in rural and remote regions.	Several recommendations include the use of telehealth systems to support result (screen positive and diagnostic) disclosure and post treatment surveillance (done with support and guidance of specilaists), This is considered in the implementation plan	the feedback but the recommendations are across the board centred on equity of access in regional and rural areas.

[*redacted*]	It's great to see in the evidence gaps and future directions for stakeholders' section of the Guidelines, there is reference made to broadening and deepening the evidence base of perspectives and challenges for families from rural and remote regions. We would recommend that rural and remote families are prioritised for co-design of educational resources for families.	In the future directions section we have incorporated specific mention of rural populations and their role in future co-design. "Given the unique challenges facing rural and remote regions, it remains a priority to incorporate representative voices of this population into any future co-developed evidence. Furthermore, the information gap at the point of screening, diagnosis and therapeutic decision making for families can only be filled through codesign of targeted and relevant educational resources with the child and family perspective to remain central.	
[*redacted*]	1. [*redacted*]has no comment. The guideline appears comprehensive on the topic. Recommendations noted for inclusion in the [*redacted*]g guideline (in development). 2. Note also that SMA forms part of the reproductive genetic carrier screening recommendations as per the [*redacted*]: Preconception and prenatal genetic screening clinical guideline.	-No change required. This has been addressed within the Scope section which now reads: Newborn screening is a public health program that fits alongside and within other public health initiatives such as reproductive carrier testing and prenatal genetic screening. This Guideline acknowledges, compliments, and does not replace existing guidelines that encompass these domains.	

International Peer review (via NHMRC) summary document

Reviewer One (USA)	NHMRC Comment	Developer Response
In the Plain Language Summary, it is not clearly stated that both copies of *SMN1* have exon 7 deletions in the majority of those with SMA. Also, recommend stating that approximately 4% of SMA is caused by other mutations in the *SMN1* gene and thus will be missed by the newborn screen. Being missed on the screen for those rare genotypes could also be stated when it is discussed on page 100.	Please consider this suggestion.	Suggestion has been incorporated into plain language summary which reads: Plain language summary; Background (p22) The most common form of SMA is caused by an absence of a part of both copies of the survival motor neuron 1 (*SMN1)* gene which leads to deficiency of a protein called survival motor neuron (SMN) and loss of nerve cells (motor neurons) that control muscle movement.(3) In a minority of individuals, SMA is caused by other changes (pathogenic variants) in the *SMN1* gene, which are not identified by current newborn screening methods.

		This has also been clarified in the section (p123) on the genetic basis of spinal muscular atrophy which reads SMA is caused in 95% of children by biallelic (homozygous) deletion of exon 7 of the survival motor neuron 1 (*SMN1*) gene on chromosome 5q.13.2 and as such is inherited in an autosomal recessive manner (Figure 4.).(74) Other condition-causing variants account for the remainder of genetic changes leading to SMA in (< 5%) of cases, and these are not detected by current newborn screening methods
Recommendation 2.3 does not make sense to me; those with *SMN2* copy number >4 also have SMA and should be seen by a neuromuscular specialist.	Please consider this suggestion.	This recommendation has been reviewed and removed due to the confusion caused. Recommendations now read Recommendation 1.3. Consensus recommendation A screen positive result should be communicated to clinical services when the *SMN1* screening result is available (independent of the availability of

		SMN2 copy number) on screening assays. Recommendation 2.1. Consensus recommendation *SMN2* copy number should be performed expeditiously, ideally as part of newborn screening processes using suitably validated quantitative assays but the result should not delay notification of the absence of exon 7 on *SMN1*. Implementation Guidance 2.1.1 Where *SMN2* copy number is conducted as part of newborn screening, a screen positive result will be classified as an absence of exon 7 on *SMN1* and *SMN2* copy number ≤ 4 on the dried blood spot.
Recommendation 3.6 and 3.8 – these two time windows seem long, especially for infants with two copies of SMN2 – unless there are logistical hurdles that cannot be overcome would recommend a shorter turnaround.	Please consider adding text to clarify these recommendations.	Whilst the SAC agrees with the suggestion for faster turn around times, there are substantial logistical barriers across the states and territories of Australia that can challenge these timings. These include long distances that incur logistical barriers between

		clinical and diagnostic services and the establishment of personnel and workflow to not only support NBS for SMA but also SMA carrier screening. It has been deemed that most diagnostic services can turn around results within 7 days and that the screening to diagnosis cycle can be completed ideally within the first month of life. The recommendations are therefore the most feasible as pertains to the entire national landscape. Recommendation 3.3. Diagnostic results for *SMN1* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory. Recommendation 3.4 Consensus recommendation A diagnosis of SMA (including *SMN1* and *SMN2* copy number results) should be available to clinical services as quickly as possible. This should be completed within 30 days of birth to enable timely treatment.

		Information Box The timings included in Recommendations 3.3 and 3.4 define the **maximum** time for diagnostic result availability in keeping with processes that are feasible and sustainable across Australia and Aotearoa New Zealand. However, it is noted that the shortest
Pg. 103 and Table 6: Spelling of Hoffmann.	Please amend typographical error.	This typographical error has bene rectified in p105 and the table 6
Figure 5: suggest adding concern for impact on male fertility and GI upset to risdiplam side effects. For OA: thrombotic microangiopathy.	Please consider this suggestion.	The potential risk of thrombotic microangiopathy for OA has been added to the Figure. There is limited information on male fertility for risdiplam and this suggestion has not been incorporated. However, the legend for Figure 5 has been revised to accommodate changes in knowledge and now reads The potential side effects listed are not exhaustive and accompanying product information should be adhered to for a wider discussion on potential risks. For families taking part in therapeutic decision making, risk-benefits of treatment should be discussed with a specialist, incorporating up to date knowledge.

Page 110 and Figure 6 do not match re. % of motor neurons lost at 6 months (90 vs. 95) – consistently 90 for the rest of the document.	Please consider this suggestion or add a reference to support.	The percentage is now consistent (90%) over all figures and in the document.
Page 199: extra “f” in the second to last line of the first paragraph.	Please amend typographical error.	This has been removed
Section 2 title is missing “A” in “SMA”.	Please amend typographical error.	This has been changed on P 129
Pg 127: Sentence “Similarly, access to SMN augmenting therapies…” isn’t clear.	Please consider rewording this for clarity.	This has been changed and now reads Treatment recommendations for infants with 4 *SMN2* copies are evolving, with some guidelines advocating immediate treatment whilst others are in favour of a surveillance approach for symptom onset.(138, 146-148), with access to SMN augmenting therapies in these individuals varying between countries
Pg. 128 – disagree that phenotype/genotype correlation violation is “frequently” noted, it is rare but does occur.	Please consider this suggestion or add a reference to support.	The word frequently has been removed.
Pg 155 – feeding mentioned twice.	Please amend typographical error.	The first feeding has been removed.
Pg 180 – paragraph 2 “one who” is repeated.	Please amend typographical error.	This has been changed
Pg 204 – first word “The” not “There”.	Please amend typographical error.	This has been changed
Reviewer Two (UK)		
Recommendation 2.1 “We suggest that SMN2 copy number should be performed expeditiously, ideally as part of newborn screening processes but	Please note this comment.	Comment is noted

not delay notification of absence of exon 7 on SMN1, as per recommendation 2.4." I tend to agree with this. There is a balance between seeing parents as soon as possible and having a fully informed discussion. If SMN2 copy numbers are assessed on the NBS sample, while the results may not be available at the timing of phoning to arrange an appointment, they may be available when the family are actually seen. One way to cut down delay, might be to initiate the SMN2 assay once the initial SMN1 result is known to be abnormal, rather than await confirmation of the repeat test on the NBS.		
Recommendation 2.3 is "We recommend that the definition of screen positivity for the Australian and New Zealand newborn screening for SMA program is homozygous deletion of exon 7 on SMN1 and SMN2 copy number ≤ 4 (where SMN2 copy number is conducted as part of newborn screening)." On page 127 it is stated that "As such incorporating SMN2 copy number testing on the same dried blood spot as SMN1 testing, is not required to identify newborns screening positive for SMA,...." My understanding is that reporting from the bloodspot sample will be on the basis of the SMN1 assay, irrespective of whether SMN2 copies have been ascertained or their number. If this is correct, a simpler more consistent definition would be "homozygous deletion of exon 7". If SMN2 copy numbers are performed on NBS, but the result is only available after the baby has been referred, would the child be re-designated if there were >4 SMN2 copies?	Please consider this comment or add a reference.	The feedback has been taken and the consensus recommendations changed in terms of wording: Recommendation 1.3. Consensus recommendation A screen positive result should be communicated to clinical services when the *SMN1* screening result is available (independent of the availability of *SMN2* copy number) on screening assays. Recommendation 2.1. Consensus recommendation *SMN2* copy number should be performed expeditiously, ideally as part of newborn screening processes using

		suitably validated quantitative assays but the result should not delay notification of the absence of exon 7 on *SMN1*. Implementation Guidance 2.1.1 Where *SMN2* copy number is conducted as part of newborn screening, a screen positive result will be classified as an absence of exon 7 on *SMN1* and *SMN2* copy number ≤ 4 on the dried blood spot.
Recommendation 3.6 states "We suggest that … diagnostic results for SMN1 should be available within 7-10 days of receipt of the sample by the diagnostic laboratory." My understanding is that the available technology would allow a turn around time of 3-4 days allowing for the test to be repeated. Bearing in mind the urgency of initiating treatment, do you think this recommendation might be strengthened. One could replace "suggest" with "recommend" and/or change "7-10 days" to "3-4 working days".	Consider wording change.	Whilst the SAC agrees with the suggestion for faster turn around times, there are substantial logistical barriers across the states and territories of Australia that can challenge these timings. These include long distances that incur logistical barriers between clinical and diagnostic services and the establishment of personnel and workflow to not only support NBS for SMA but also SMA carrier screening. It has been deemed that most diagnostic services can turn around results within 7 days and that the screening to diagnosis cycle can be completed ideally within the first month of life. The

		recommendations are therefore the most feasible as pertains to the entire national landscape. A commentary has been added below each recommendation to explain this Recommendation 3.3. Diagnostic results for *SMN1* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory. **Information Box** The timings included in Recommendations 3.3 and 3.4 define the **maximum** time for diagnostic result availability in keeping with processes that are feasible and sustainable across Australia and Aotearoa New Zealand. However, it is noted that the shortest time to diagnostic results (as a pathway to early treatment), confers the maximum clinical benefit for the affected child, and processes should be coordinated and implemented to keep this interval as short as possible.

Recommendation 3.8 states that "We suggest that diagnostic test results (including *SMN1* and *SMN2* copy number) should be available to clinical services within 30 days of birth." For the same reasons as above, might "suggest" be changed to "recommend" and change "30 days" to "21 days". While there may be special instances where these recommendations could not be met, for the overwhelming number of cases, it should be possible. The results of the Australian pilot (page 152) shows what can be done.	Consider wording change.	Whilst the SAC agrees with the suggestion for faster turn around times, there are substantial logistical barriers across the states and territories of Australia that can challenge these timings (which were not seen in the NSW/ACT pilot). These include long distances for travel between clinical and diagnostic services and the establishment of personnel and workflow to not only support NBS for SMA but also SMA carrier screening. It has been deemed that most diagnostic services can turn around results within 7 days and that the screening to diagnosis cycle can be completed ideally within the first month of life. The recommendations are therefore the most feasible as pertains to the entire national landscape, and align with barriers suggested through the public consultation process. A commentary has been added below each recommendation to explain this. Recommendation 3.4 Consensus recommendation A diagnosis of SMA (including *SMN1* and *SMN2* copy number results) should be available to clinical services as

		quickly as possible. This should be completed within 30 days of birth to enable timely treatment. **Information Box** The timings included in Recommendations 3.3 and 3.4 define the **maximum** time for diagnostic result availability in keeping with processes that are feasible and sustainable across Australia and Aotearoa New Zealand. However, it is noted that the shortest time to diagnostic results (as a pathway to early treatment), confers the maximum clinical benefit for the affected child, and processes should be coordinated and implemented to keep this interval as short as possible.
Recommendation 5.8 states "We suggest that a clinical review within local paediatric services, with clinical support from paediatric neurologists should be offered to screen positive newborns where access to specialist services is limited and may cause delay in diagnostic evaluation." As is emphasised, parents, quite rightly, expect to talk to someone who knows about the disease *and its treatment* and can answer their questions. If they can't, there is a real danger that they will 'surf the net' and come across inaccurate information. In the interests of time, it may not be possible to arrange an in-person consultation with a paediatric neurologist. If that is not possible, the consultation might be with local paediatric services to examine the child and take blood, with the specialist present at the same time, but	Please consider this suggestion.	The feedback has been considered and several recommendations changed in line with this Recommendation 7.1 Consensus recommendation The process of disclosing a diagnosis of SMA to families should occur with a paediatric neurologist when *SMN1* (diagnostic) confirmation is received,

remotely, to answer questions and explain the next stages. Perhaps this could be suggested as the wording could be interpreted to mean that the specialist briefs the local services, which would be a very much less satisfactory option.		regardless of the availability of *SMN2* copy number result. Implementation Guidance 7.1.1. Some newborns and families are unable to travel to paediatric neurology/neuromuscular services to receive diagnostic results. For these newborns, a designated healthcare practitioner with support from a paediatric neurologist through telehealth may disclose the diagnosis. **Information Box** The designated healthcare practitioner will vary between jurisdictions and may include a paediatrician, general practitioner, specialist nurse, neonatologist, clinical geneticist or genetic counsellor.
Recommendation 8.2 states "We suggest that ideally, diagnostic results should be disclosed to families by a specialist medical practitioner such as a paediatric neurologist." This seems a bit permissive. This is the consultation at which the treatment options will be confirmed and the parents will want to go into the practicalities. I would suggest it is essential that the parents talk to a specialist, albeit virtually. I would suggest rephrasing as "We recommend diagnostic results …."	Please consider this comment or add a reference.	We acknowledge the reviewer comment and have changed this as a priority recommendation which now reads Recommendation 7.1. . The process of disclosing a diagnosis of SMA to families should occur with a paediatric neurologist when *SMN1* (diagnostic) confirmation is received,

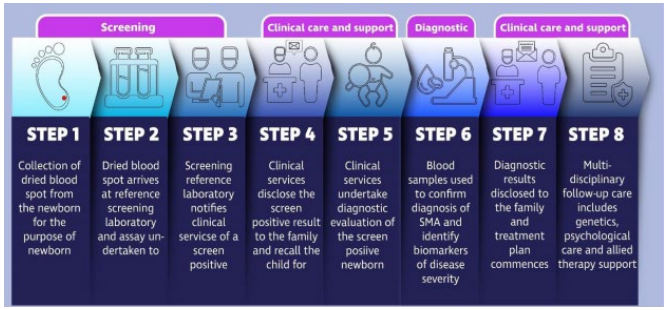
		regardless of the availability of *SMN2* copy number result.
For the reasons stated above, I would suggest that “recommend” replaces suggest in Recommendation 9.1 and Recommendation 9.2. This could be virtual in co-operation with local paediatric services.	Please consider this comment or add a reference.	The grading system for consensus recommendations have changed to reflect the feedback, the GDG have placed a high priority on these recommendations Recommendation 7.1 Consensus recommendation The process of disclosing a diagnosis of SMA to families should occur with a paediatric neurologist when *SMN1* (diagnostic) confirmation is received, regardless of the availability of *SMN2* copy number result. Implementation Guidance 7.1.1. Some newborns and families are unable to travel to paediatric neurology/neuromuscular services to receive diagnostic results. For these newborns, a designated healthcare practitioner with support from a paediatric neurologist through telehealth may disclose the diagnosis. **Information Box** The designated healthcare practitioner will vary between jurisdictions and may

		include a paediatrician, general practitioner, specialist nurse, neonatologist, clinical geneticist or genetic counsellor.
On page 134, it is stated that copy numbers >4 would not be reported. I assume that this applies where they are measured on NBS, as they would have to be reported as part of the diagnostic process. If they are not to be reported on NBS, if families are referred on the basis of the SMN1 result, but SMN2 is measured on NBS and becomes available after referral, this would have to be disclosed, would it not?	Please consider this comment.	The reviewer is correct and the differences in jurisdictional screen positive results has now been clarified in p 134 Within Australasia, the newborn screening process will differ with some jurisdictions concurrently analysing *SMN1* and *SMN2* number on the dried blood spot (reporting only those with *SMN2* copies < 4) whilst others complete *SMN2* quantification as part of diagnostic care. Thus, in some jurisdictions it is conceivable that children with copy ≥ 4 *SMN2* copies will be diagnosed through newborn screening programs.

Recommendation 10.14 "We suggest that newborns with diagnostic confirmation of SMA and who are unable to access approved and reimbursed treatments immediately, should have clinical follow-up with a minimum of 3 monthly assessments for the first two years from diagnosis, and minimum 6- monthly thereafter." This worries me considerably. If this applies to those with SMN2 copy numbers >4, I can understand, but otherwise, can it be ethical to screen for a condition when the family will not be able to get treatment?	Please consider this comment or add a reference.	We acknowledge the reviewer's ethical concerns however, as its stands Federal policy is to screen for all children with routine NBS panels (even if they are not eligible for reimbursed treatment in Australasia). The scope of this issue falls outside the Guideline and as it stands the target population is all children in Australasia. Some of these children do have access to care under private health insurance policies. The consideration for screening for newborns with 4 SMN2 copies and surveying them closely is that they are eligible for treatment as soon as symptoms appear. This was the state of play across most jurisdictions as per Glascock et al. before urgent treatment was recommended. As per the evidence base, there are still limitations to knowledge on the therapeutic window for newborns with 4 SMN2 copies. The recommendations have therefore not changed.
Reviewer Three (UK)		

For recommendation 3.6, the timeline for the diagnostic results for *SMN1* should be shortened to 2-3 days of receipt of the sample to ensure more timely treatment.	Please consider this suggestion.	Whilst the SAC agrees with the suggestion for faster turn around times, there are substantial logistical barriers across the states and territories of Australia that can challenge these timings. These include long distances for travel between clinical and diagnostic services and the establishment of personnel and workflow to not only support NBS for SMA but also SMA carrier screening. It has been deemed that most diagnostic services can turn around results within 7 days and that the screening to diagnosis cycle can be completed ideally within the first month of life. The recommendations are therefore the most feasible as pertains to the entire national landscape. A commentary has been added below each recommendation to explain this. The timings included in the Recommendation define the **maximum** time for diagnostic result availability in keeping with processes that are feasible and sustainable across Australia and New Zealand. However, it is noted that the shortest time to diagnostic results (as a pathway to early treatment), confers the maximum clinical benefit for the affected child, and processes should be

		coordinated and implemented to keep this interval as short as possible.
For recommendation 5.10, to the second paragraph: change in movement, feeding or breathing 'or in case of any acute event (e.g. respiratory difficulties) that requires hospitalization'.	Please consider this suggestion.	This recommendation has been modified and the sentence added as per reviewer recommendation.
Reviewer Four (AUS)		
P21 whilst I agree that 'back up gene' is not an ideal term for SMN2, to me the phrase 'nearby related gene' is a bit confusing, so I wonder if it would be clearer to say 'related gene… located near SMN1'?	Please consider this suggestion.	This has been changed P 23.
P25 Population – I know it is mentioned further on, but I wonder whether it would be good to mention early in the document that SMA affects all populations/ethnic groups (albeit at varying frequencies)	Please consider this suggestion.	This has been changed p29
I note that you have varyingly referred to absence/loss of SMN1 as 'deletion' throughout the document o I suggest that you are consistent o In most places throughout the document I think it is most correct to avoid the term deletion – as this implies mechanism for the loss of SMN1, whereas the testing that we do is just quantitative and only tells us whether SMN1 is present, not how it was lost. I understand that a significant proportion of patients are thought to have lost their SMN1 through gene conversion rather than deletion per se o Suggest using loss, absence, deficiency.	Please consider suggestion and use consistent language throughout documents.	This has been changed throughout the document where appropriate and we have kept the terminology consistent with 'absence of SMN1). However we have kept the terminology as 'deletion' when necessary to be consistent with terminology used in the literature to date.
Suggest adding 'clinical' to geneticist throughout the document (where that Is what you mean) – including the diagram	Consider suggestion about clinical role titles.	This has been changed throughout the document.

P39 I think it would be useful to add that sometimes testing of parents is suggested to try to work out why there is a false positive or uninterpretable result	Please consider this suggestion.	This has been revised Implementation Guidance Blood samples from parents for *SMN1* quantification purposes should be considered to understand the aetiology of a false positive or uncertain result for the newborn.
P42 – I think the term 'responsible medical practitioner' is ambiguous – I presume you mean responsible for the patient rather than someone not irresponsible!	Please consider this suggestion.	This has been changed to designated medical practitioner.
P46 – there are a few places where you say 'venous sampling for SMN1' – I don't think this makes sense? Should be it venous sampling for quantification of SMN1? – and then similarly, venous sampling for determination of SMN2 copy number?	Please consider this suggestion and edit for clarity.	This has been changed
I know you can't put everything in this quick guide, but I wonder if it would be sensible to include the words 'paediatric neurologist/paediatrician' as they are really central to the whole process? - given that you include all the multidisciplinary teams (should say clinical genetics) 	Please consider change to the quick guide.	This Figure has been changed and the legend incorporates the members of the MDT team.

P100 – in 1st paragraph – you mention the scenario of two sequence variants – but they need not necessarily be homozygous – is more correct to say 'biallelic sequence variants' (could be homozygous or compound heterozygous).	Please consider this suggestion.	This now reads The GDG considered newborn screening from the perspective of the population of *all* children born with the most common form of SMA i.e. those with a biallelic deletion of exon 7 on *SMN1* **and** those with biallelic pathogenic sequence variants (including children with a compound heterozygous genotype i.e. one allelic deletion of exon 7 on *SMN1* and a pathogenic sequence variant on exon 7 *SMN1* on the second allele, *or* homozygous sequence variants on each allele).
P114 I think the more correct term is 'reproductive genetic carrier screening' (but noting that the MBS uses 'testing' not screening)	Please consider this suggestion.	This has been changed
P117 last paragraph & p119 – I don't think the sequence variant needs to be in exon 7 – there are recurrent variants in exons 1,3 & 6 in particular	Please consider this suggestion, if correct, please edit.	We acknowledge the reviewer comment but as per the literature, the target exon for most NBS programs is exon 7. We have contextualised this by adding the following: Whilst variants in exon 1, 3 and 6 of *SMN1* are noted in individuals with SMA, leveraging the fact that 95% of individuals with SMA have an absence of exon 7, *SMN1* assays have generally targeted this genetic change, with rare studies targeting exon 7 ***and*** exon 8 loss within *SMN1*

Reviewer Five (Taiwan)			
Recommendation 2.3. We recommend that the definition of screen positivity for the Australian and New Zealand newborn screening for SMA program is homozygous deletion of exon 7 on *SMN1* and *SMN2* copy number ≤ 4 (where *SMN2* copy number is conducted as part of newborn screening).	Not sure if SMN2 copy number should be included here as a criteria. How about a baby with no SMN1 but 5 SMN2 copies? It may have some confusion especially not every screening program has SMN2 information. Such recommendation may be violated to recommendation 2.4.	Please consider this suggestion.	The wording of several recommendations have been changed in line with this feedback Recommendation 2.1. *SMN2* copy number should be performed expeditiously, ideally as part of newborn screening processes using suitably validated quantitative assays but the result should not delay notification of the absence of exon 7 on *SMN1*. AND Implementation Guidance 2.1.1 Where *SMN2* copy number is conducted as part of newborn screening, a screen positive result will be classified as an absence of exon 7 on *SMN1* and *SMN2* copy number ≤ 4 on the dried blood spot.
Recommendation 3.5 We suggest that discussions between clinical and diagnostic services (either through verbal and/or written	I suggest to add something like "should ideally occur *upon screening positive"* to better	Please consider this suggestion, if correct, please edit.	The language has been revised to reflect the feedback and now reads 3.4.1 Clinical and diagnostic services should have pre-established protocols

means), should ideally occur so that stakeholders understand…..	emphasize the urgency of screening positive to the further management.		and pathways in place upon receipt of a screen positive result that lead to rapid collection, authorisation of diagnostic tests and result notification.
Recommendation 3.6 We suggest that to enable timely treatment, diagnostic results for *SMN1* should be available within *7-10 days of receipt* of the sample by the diagnostic laboratory	If in the real-world setting that a diagnostic result comes back after 10 days, other procedures need to be taken especially for the babies with 2 SMN2 copies. Otherwise, they are getting the diagnosis at age 14(or longer) days, and may only get treatment probably after symptoms onset.	Please consider this suggestion, if correct, please edit.	This has been revised Recommendation 3.3. Diagnostic results for *SMN1* should be available as quickly as possible, and at maximum of 7 days of receipt of the sample by the diagnostic laboratory. **Information Box** The timings included in Recommendations 3.3 and 3.4 define the **maximum** time for diagnostic result availability in keeping with processes that are feasible and sustainable across Australia and Aotearoa New Zealand. However, it is noted that the shortest time to diagnostic results (as a pathway to early treatment), confers the maximum clinical benefit for the affected child, and processes should be coordinated and implemented to keep this interval as short as possible.

Recommendation 3.8 We suggest that diagnostic test results (including *SMN1* and *SMN2* copy number) should be available to clinical services within 30 days of birth.	The timeline is too long especially for a baby with 2 SMN2 copies. Such limitations should be addressed properly.	Please consider this suggestion, if correct, please edit.	Feedback through the process of public consultation shows that some states and territories will find even these timelines challenging to meet. A qualification statement has been added for the purposes of the recommendations and timelines defined. Recommendation 3.4. A diagnosis of SMA (including *SMN1* and *SMN2* copy number results) should be available to clinical services as quickly as possible. This should be completed within 30 days of birth to enable timely treatment. **Information Box** The timings included in Recommendations 3.3 and 3.4 define the **maximum** time for diagnostic result availability in keeping with processes that are feasible and sustainable across Australia and Aotearoa New Zealand. However, it is noted that the shortest time to diagnostic results (as a pathway to early treatment), confers the maximum clinical benefit for the affected child, and processes should be coordinated and implemented to keep this interval as short as possible.

Recommendation 4.1 …and openly explained to parents.	Not sure if openly to the public as well as the NBS governance is a proper suggestion. If yes, that will enhance the screening method and understanding of SMA.	Please note this comment.	Due to the rarity of the condition, disclosure of false positive, false negative and uncertain cases to the public are likely to be highly identifiable. This statement has therefore not been changed but a standard to improve the quality of the program has been added. Implementation Guidance 4.2.3. Lessons or insights derived from the case review of false positive, false negative or uncertain results should be shared across Australasian Newborn Bloodspot services so that issues and errors can be identified as part of quality improvement.
Recommendation 4.2 We suggest that families of newborns with false positive results should be given the option of returning to discuss the implications of results with members of the neurology/neuromuscular multidisciplinary team.	False positive cases should be properly counselling by clinical geneticists (or genetic counsellors), or paediatric neurologists who understand the tests well. It may not be a proper suggestion to consult a team member such as social worker about the false positive results.	Please consider this suggestion.	Recommendation 4.1. For newborns with a false positive, false negative or uncertain screening result, a case review with communication and collaboration between screening, diagnostic and clinical services should be conducted to understand the aetiology of results and explained to families.

			Information Box Information may be provided by a paediatric neurologist and/or clinical geneticists and/or genetic counsellors.
Recommendation 4.8. We recommend that parents should be supported by the multidisciplinary team, including referral to medical social services and psychology as appropriate, during the process of managing false positive, uncertain or false negative results for their newborn/infant.	It should include babies who are screening positives. (as Recommendation 10.18) Similarly, referring babies with false positives to social worker may not be necessary. (as suggestion in recommendation 4.2)	Please consider this suggestion.	The recommendation has been in part modified and now reads as a practice standard 4.3.2. Families who receive a false negative, false positive or uncertain screening result should be provided psychosocial support by relevant members within the multidisciplinary team. Information box. Multidisciplinary team members may vary dependent on health jurisdiction. Support may be provided by paediatric neurologists or paediatricians, genetic counsellors and/or clinical geneticists, social workers, psychologists, allied therapists and/or specialist nurses.
Section 4	False positives may be only confirmed after the diagnostic test. Therefore, who are not confirmed by	Please note this comment.	We have now clarified the definition of false positive and of uncertain results

	the diagnostic test should be referred as uncertain results.		Consensus based recommendation We suggest that for newborns with a false positive **or** uncertain screening result, the reasons for this should be explored with screening, diagnostic and clinical (including clinical genetic) services and openly explained to parents. False positive results are defined by individuals with a screen positive result through newborn screening who have been confirmed **not** to have SMA on diagnostic testing. Uncertain results are defined by individuals with an uncertain result on newborn screening assays, who then have definitive results on further testing of the initial dried blood spot. These are not classed as false positives as issues resolve through further testing of the initial dried blood spot, which is considered as part of the index test process
Recommendation 8.2. diagnostic results should be disclosed to families by a specialist medical	Suggest to revise as "such as a paediatric neurologist *or clinical geneticist*".	Please consider suggestion.	In keeping with challenges for clinical genetics services to facilitate diagnostic results and treatment planning at this first point of contact in Australia we have maintained recommendation 7.1 as

practitioner such as a paediatric neurologist.			is but have added implementation guidance to enhance the role and capability of clinical geneticists 7.1.1. Some newborns and families are unable to travel to paediatric neurology/neuromuscular services to receive diagnostic results. For these newborns, a designated healthcare practitioner with support from a paediatric neurologist through telehealth may disclose the diagnosis. **Information Box** The designated healthcare practitioner will vary between jurisdictions and may include a paediatrician, general practitioner, specialist nurse, neonatologist, clinical geneticist or genetic counsellor. .
Recommendation 10.2 We recommend that for newborns who demonstrate signs and symptoms of SMA (consistent with disease onset),	Please consider to specify newborns here is classified by only "diagnosis" or including newborns with "screening positive". For planning, probably screening	Please consider this suggestion and if you agree edit.	Recommendation modified and now reads Recommendation 8.1. Consensus recommendation

	positive should also trigger that discussion.		For screen positive newborns who demonstrate signs and symptoms of SMA (consistent with disease onset i.e. clinically manifest), a paediatric neurologist should discuss options for immediate treatment with SMN augmenting treatments with the family
Recommendation 10.10 …should occur in a specialist (paediatric neurology) care centre/service.	should occur in a specialist (paediatric neurology) care centre/service *with a multidisciplinary team*.	Please consider this suggestion and if you agree edit.	Modified to align with addition. Of 'within a multidisciplinary team'
Recommendation 10.15 .. should have clinical follow-up with a minimum of 3 monthly assessments for the first two years	The suggestion needs to take SMN2 copies into consideration. For babies with 2 or 3 copies, 3 monthly assessments may be too late to capture symptoms. The current version may be only good for babies with 4 SMN2 copies.(as Recommendation 11.1)	Please consider this suggestion and if you agree edit.	This recommendation has been modified to reflect this point and now reads: We suggest that newborns with diagnostic confirmation of SMA and who are unable to access approved and reimbursed treatments immediately, should have clinical follow-up with a minimum of 3 monthly assessments for the first two years from diagnosis, and minimum 6-monthly thereafter. Practice standard 8.4.3. Children who have 2 and 3 SMN2 copies who do not access treatments immediately may require more frequent surveillance, as part of an informed management plan between families and

			healthcare practitioners. The frequency of surveillance will be dependent on the child's individual biopsychosocial characteristics and should be made with consideration of their healthcare needs and family preferences.
Recommendation 11.2 .. all newborns with 4 *SMN2* copies…	Consider revise as ≥ 4 *SMN2* copies	Please consider this suggestion and if you agree edit.	This has been revised and reads Implementation Guidance 3.2.2. Redetermination of *SMN2* copy number in a different laboratory or using a different method may be considered in newborns with ≥ 4 *SMN2* copies, due to imprecision arising from *SMN2* copy number methodologies that can impact therapeutic decision making.
Reviewer Six (AUS)			
Pg 13 - Glossary – Loci not described		Please consider adding to glossary.	This has been added
Pg 15 – Glossary – definition of variant to replace mutation		Please consider adding to glossary.	This has been replaced

Pg 25 – Are the guidelines only to be used where there is availability of SMA treatments i.e. that would only be applicable in the developing world?	Please consider adding text to clarify.	As per the Scope, the Guideline is for use in Australia and New Zealand, although other countries may find it useful to refer to.
Pg 29 – Difference between B and 1B grading of recommendations?	Please consider adding text to clarify.	We have now removed this grading system for consensus recommendations to avoid confusion.
Pg 33 – last paragraph, space missing between SMA. A positive…	Please amend typographical error.	This has been changed.
Pg 35 – Recommendation 3.4 – should it include an orthogonal assay type?	Please consider suggestion.	The SAC agrees not to depict the name of assays used as these will vary on capabilities across jurisdictions and may also evolve over time.
Pg 37 – Recommendation 3.9 This is probably a NPAAC requirements though these don't apply to NZ. Perhaps in the introduction there should be reference to laboratory accreditation standards.	Please consider suggestion.	This has been added to the introduction section for section 3 which now reads (as is referenced accordingly). *As a mitigator, the development of standard operating procedures for SMN2 analysis using validated assays and completed in accredited and centralised diagnostic centres is thought to be appropriate and relevant for greater diagnostic accuracy, in line with national pathology standards*

Pg 39 – Recommendation 4.3 Should there be a recommendation for a review/repeat of the NBS testing to ensure that another child is not positive for SMA. That is specimen mix-up in NBS. Is this covered in 4.1?	Please consider suggestion.	This suggestion has been considered and added to the implementation guidance which now reads Implementation Guidance 4.2.1. A further blood sample from the newborn may be required for repeat screening and/or diagnostic testing if resolution of *SMN1* and/or *SMN2* genotype does not occur.
Pg 40 - Recommendation 4.7 This would be part of a laboratory quality system review. It should lead to recommendation that minimise the potential for this to occur again.	Please consider suggestion.	This suggestion has been considered and added to the implementation guidance which now reads 4.2.3. Lessons or insights derived from the case review of false positive, false negative or uncertain results should be shared across Australasian Newborn Bloodspot services so that issues and errors can be identified as part of quality improvement.
Pg 46 – Recommendation 6.1 The implication is that these should be separate collections. A single diagnostic collection could suffice for both SMN1 and SMN2 testing.	Please note this comment.	This recommendation has not been changed as in some jurisdictions two different samples are required as the specimens for SMN1 and SMN2 go to separate labs and has been qualified by an information box statement

		…healthcare practitioners should adhere to processes for blood collection for genetic confirmation of SMA as defined by the relevant diagnostic laboratories servicing the specified health jurisdiction.
Pg 56 – Recommendation 10.5 Is single agent treatment gene therapy?	Please consider comment and add text for clarity.	The text has been clarified and reads Recommendation 8.3. We recommend that in the absence of comparative data, currently single agent treatment i.e. monotherapy at initiation of therapeutic intervention is recommended.
Pg 58 - do 10.10 and 10.11 contradict? is 10.10 the preferred option? Is 10.11 a fallback position? These are recommendations and not "musts".	Please consider comment and if you agree, edit.	The feedback has been used to clarify the recommendations which now read Recommendation 8.3 Consensus recommendation In the absence of comparative data, single agent treatment i.e. monotherapy at initiation of therapeutic intervention

		is recommended, started within paediatric neurology treatment centre. Implementation Guidance 8.3.2. Dependent on the needs and preferences of the child and family, SMN augmenting treatments may be planned to be initiated from a non-specialist treatment centre/service, with paediatric neurology support and guidance. **Information Box** Onasemnogene abeparvovec-xioi can only be administered in designated and approved paediatric treatment centres in Australasia.
Recommendation 10.13 Is this where the guidelines comment on patients without access to funded therapy. If funded therapy is not available should these newborns be screened for SMA?	Please consider comment and if you agree, edit.	This is an ethical consideration for the NBS program as a whole. Currently, children without recourse to treatment are screened in Australasia for all conditions on the NBS panel. This has now been addressed in Practice Standard 8.2.1. When children do not have access to publicly funded treatments and healthcare in Australasia, healthcare practitioners will be proactive in

		providing care and support for the child and family.
Pg 58 – is 10.14 missing?	Please amend numbering of recommendations.	This has been rectified
Recommendation 10.16 missing	Please amend numbering of recommendations.	This has been rectified.
There are two 10.17 listed in recommendations	Please amend numbering of recommendations.	This has been changed.
Pg 66 – this paragraph is duplicated	Please amend typographical error.	This has been changed.
Pg 95 - The Royal College of Pathologist Australasia was not asked to endorse the Guidelines?	Please clarify RCPA position.	The RCPA will be approached for endorsement of the Guideline.
Pg 95 - The HGSA and several of its special interest groups are asked to endorse the guidelines. Should this be done under the single banner of the HGSA? It would be awkward for the HGSA if there were differing opinions?	Please consider suggestion and add text to clarify if you agree.	Suggestion taken on board and the HGSA as a single entity will be approached for endorsement of the finalised Guideline.
Pg 112 - Do NBS have high public confidence or low antagonistic views? Is awareness of NBS high?	Please consider adding text to into this section about public opinion.	Several studies from Australia show high public trust in this system and therefore the wording has not been changed.
Pg 117 - Should there be guidelines for the broader consenting process for NBS. I can understand it being out of scope for these guidelines.	Please consider comment and clarify.	This is considered outside the scope of the Guideline and has been added to the Scope section.

Pg 118 – typo a automated level required	Please amend typographical error.	Typographical error changed
Pg 119 – typo for f exon 7 variants	Please amend typographical error.	Typographical error changed