NICE National Institute for Health and Care Excellence

Appendix B: Stakeholder consultation comments table

2020 surveillance of Jaundice in newborn babies under 28 days (2010)

Consultation dates: 07 January to 20 January 2020

1. Do you agree with the proposal to not update the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Children's Liver Disease Foundation	Yes	In relation to the work Children's Liver Disease carry out and the impact of the guideline on the information, advice and guidance we provide to families and medical professionals as well as the evidence provided in the review proposal, we agree that the guideline on Jaundice in newborn babies under 28 days (NICE guideline CG98) does not need updating. However, the proposal may be better assessed by medical professionals who are able to provide greater specialist medical knowledge in this area.	Thank you for your comment.
Royal College of Paediatrics and Child Health	No	While some of our reviewers agreed that there is no new evidence to suggest need for updating the guideline, there	Thank you for your comment.

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees

		were a lot of comments on areas that are excluded from the guideline, please see below.	
Neonatal Critical Care Clinical Reference Group (CRG)	Yes	No comment	Thank you for your comment.

2. Do you have any comments on areas excluded from the scope of the guideline?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Children's Liver Disease Foundation	No	No comment	
Royal College of Paediatrics and Child Health	Yes	1) The guideline needs to state the management of preterm or term babies with jaundice persisting beyond 14 days and TSB remains above the treatment line viz-a-viz the need to continue Phototherapy in this age group or use a corrected gestational age chart especially the preterm babies in deciding if on-going need phototherapy or not. 2) A discussion at the Hot Topics in Neonatology in 2019 raised concerns about the possible risk of childhood cancer with Phototherapy (including leukaemia or renal cancer). Should these be discussed as possible long-term risks in counselling parents, and should this be included in	1) Thank you for your comment. The treatment threshold graph under tools and resources states "The graph that reflects the baby's actual gestational age should continue to be used until the baby is 14 days old. The baby's 'corrected' gestational age should not be taken into consideration, and you should not move up to the next graph when the baby is 7 days old. For example, for a baby of 35 weeks' gestation, the 35-week gestation graph should be used until the baby is aged 14 days. Please note that the NICE guideline does not cover treatment with phototherapy and exchange transfusion for babies older than 14 days. Trusts should therefore agree their own policy about when to treat babies over 14 days with phototherapy and exchange transfusion". It is recommended in section 1.7 of the guideline that in

		the guidelines so doctors are aware to counsel parents? 3) The reviewer suggested to see a consensus total bilirubin level for prolonged jaundice investigations. 4) The risk of a sensorineural hearing loss in babies has been found to be high in association with bilirubin levels in excess of the exchange transfusion thresholds (American Academy of paediatric exchange transfusion thresholds). Below these levels the risk of hearing loss was found to be low. Hearing therefore is only tested in those babies who have had an exchange transfusion. Reference: Risk of Sensorineural Hearing Loss and Bilirubin Exchange Transfusion Thresholds. Wickremasinghe, Andrea C; Risley, Robert J; Kuzniewicz, Michael W; Wu, Yvonne W; Walsh, Eileen M; Wi, Soora; McCulloch, Charles E; Newman, Thomas B. Pediatrics; Sep 2015; vol. 136 (no. 3); p. 505-512 Neurodevelopmental disability and auditory neuropathy spectrum disorder (ANSD) can be a result of high levels of unconjugated bilirubin. Reference: Auditory toxicity in late preterm and term neonates with severe jaundice. Amin, Sanjiv B; Saluja, Satish; Saili, Arvind; Laroia, Nirupama; Orlando, Mark; Wang, Hongyue; Agarwal, Asha Developmental medicine and child neurology; Mar 2017; vol. 59 (no. 3); p. 297-303	circumstances where there is prolonged jaundice a full clinical examination is conducted and expert specialist advice and care is followed as necessary. No further evidence was found regarding treatment thresholds for babies with jaundice persisting beyond 14 days. No evidence was found during the surveillance review regarding phototherapy specifically in preterm babies. 2) During the surveillance review no evidence was found regarding the long-term risks associated with phototherapy. However, recommendation 1.4.11 already advises that clinicians offer parents or carers verbal and written information on phototherapy including the possible adverse effects of phototherapy and the potential long-term adverse effects of phototherapy and this would include any possible risk of childhood cancer. 3) The treatment threshold graph under tools and resources states “Please note that the NICE guideline does not cover treatment with phototherapy and exchange transfusion for babies older than 14 days. Trusts should therefore agree their own policy about when to treat babies over 14 days with phototherapy and exchange transfusion. It is recommended in section 1.7 of the guideline that in circumstances where there is prolonged jaundice a full clinical examination is conducted and expert specialist advice is followed as necessary. Consensus total bilirubin levels for prolonged jaundice investigation would be outside of the scope. 4) Thank you for highlighting the risk associated with severely high levels of bilirubin. During the development of CG98 evidence was found that suggested that kernicterus caused

		Serum hyperbilirubinaemia is a risk factor for ANSD this leads to poor transmission of their sound signal beyond the cochlear to the brain leading to poor understanding of speech. Ref: Relationship research between auditory neuropathy spectrum disorder and exchange transfusion in neonates with severe hyperbilirubinemia. Xu, Jie; Weng, Meiling; Li, Nianqiong; Wu, Xiu'e; Gao, Li; Yao, Hongbing; Su, Shuping International journal of pediatric otorhinolaryngology; Aug 2019; vol. 123 ; p. 146-150 In section 1.9.4 'Following exchange transfusion', it was suggested that referral for hearing testing after exchange transfusion (and in those considered for exchange transfusion) could be included. References: 1. Guidelines for surveillance and audiological referral of infants & children following the newborn hearing screen Version 5.1 June 2012 Sited on 14/01/2020 2. Guidelines for aetiological investigation into severe to profound bilateral permanent childhood hearing impairment sited on 16/01/2020 3. Guidelines for aetiological investigation into mild to moderate bilateral permanent childhood hearing impairment sited on 16/01/2020	by very high bilirubin levels can be associated with hearing loss. The GDG then made a research recommendation for surveys of severe hyperbilirubinaemia and kernicterus which would lead to better understanding of the risk factors for kernicterus. Recommendation 1.5 advises checking for kernicterus in babies with hyperbilirubinaemia. Thank you for referencing the Wickremasinghe et al 2015 study. Although this was a cohort study and was not included as surveillance reviews generally only consider RCTs and systematic reviews, this study confirms that hearing loss is associated with very high bilirubin levels. Thank you for referencing the Amin et al 2016 study. Although this was a cohort study and was not included as surveillance reviews generally only consider RCTs and systematic reviews, this study confirms that unbound bilirubin is associated with certain dysfunctions such as auditory toxicity. Thank you for referencing the Xu et al 2019 study. Although this was a cohort study and was not included as surveillance reviews generally only consider RCTs and systematic reviews, this study confirms that severe hyperbilirubinaemia is a risk factor for auditory neuropathy spectrum disorder. This guideline is currently in line with guidance from Public Health England who updated their Newborn Hearing Screening Programme Operational Guidance recommendations in November 2019 and state that jaundice at exchange transfusion level does not require an immediate or targeted referral to audiology. Therefore NICE will not be updating its guideline at this time.

Neonatal Critical Care Clinical Reference Group (CRG)	No	No comment	

3. Do you have any comments on equalities issues?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Children's Liver Disease Foundation	No	No comment	
Royal College of Paediatrics and Child Health	Yes	The comments on smart phone use do not mention ethnicity which is relevant in the case of smart phone recognition of colour.	Thank you for your comments. The inclusion criteria for this study (Munkholm et al 2018) were for healthy Caucasians and the exclusion criteria were facial skins lesions. There is therefore an equality issue in that this study did not consider other ethnicities. This will be added to the description of the study in the evidence summary.
Neonatal Critical Care Clinical Reference Group (CRG)	No	No comment	

4. Do you agree with the proposed revised wording of recommendation 1.7.1 to raise awareness of the need for thyroid function tests in some babies with prolonged jaundice?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
Children's Liver Disease Foundation	N/A	This would need to be assessed by medical professionals who are able to provide greater insight into the link between prolonged jaundice and congenital hypothyroidism.	Thank you for your comment.
Royal College of Paediatrics and Child Health	Yes	1) Some cases with congenital hypothyroidism could be missed as the newborn spot only measures TSH and no T4. Hence routine TFTs should be included in the screening for prolonged jaundice. In one reviewer's unit, they have always undertaken Thyroid Function Test as a third line (extended) investigation for prolonged jaundice. The guidance needs to be consistent with the PHE document, but evidence needs to be offered by topic experts to support this. No - Is it worth mentioning that the risk of thyroid dysfunction is mainly in preterm babies? The reality is that the NICE guideline does not say much about prolonged jaundice and most paediatricians still do TFTs anyway. Hypothyroidism affects brain development every day that the baby has a low T4 so the argument	1) Thank you for your comment. Recommendation 1.7 already suggests that in babies with prolonged jaundice clinicians should ensure that routine metabolic screening (including screening for congenital hypothyroidism) has been performed. It is expected that clinicians will read the NICE guideline alongside official screening guidelines. Although we have identified no new evidence in this area, we agree that it would be useful for the guideline to recognise the need for thyroid function tests in babies with prolonged jaundice of unknown cause and we will amend the wording of the recommendation as follows: 'ensure that routine metabolic screening (including screening for congenital hypothyroidism) has been performed, and if no cause of prolonged jaundice has been identified, carry out diagnostic tests (TSH and FT4) for congenital hypothyroidism.' This guideline is for jaundice in both preterm babies as well as those born at term and no evidence was highlighted

		for doing TFTs if there is any doubt at all is fairly strong. 2) Any other comments - With regard to section 1.7: Care of babies with prolonged jaundice. It seems that the jaundice persisting is going to be diagnosed on clinical examination; but there could be clarification as to which chart to plot the bilirubin level on. The treatment graphs run in age bands up to day 14. After this, should a 34-week continue on a 34-week chart, or progress to an older chart? 3) At 38 weeks and above, the phototherapy threshold (see section 1.3.4) is 100micomol/L at time=0. At 37 weeks, it drops to 40micromol/L, which is the same level as any infant down to 23 weeks. This drop off could have the potential impact of a baby born at 37+6 with an initial level of 56micromol/L starting phototherapy, or even antibiotics (see NICE CG149 as early jaundice is a clinical indicator for Early Onset Sepsis), whereas they would not have any investigation if they had been born one day later. Given that Section 1.2.15 identified infants under 35 weeks as being at particular risk of jaundice, is there any evidence to support a gradation of acceptable levels at t=0 for 36- and 37-week infants? 4) Possible additions to wording: 1.5 Factors that influence the risk of isolated hearing loss OR kernicterus	during the surveillance review to suggest that these groups should be managed separately. 2) The treatment threshold graph under tools and resources states "The graph that reflects the baby's actual gestational age should continue to be used until the baby is 14 days old. The baby's 'corrected' gestational age should not be taken into consideration, and you should not move up to the next graph when the baby is 7 days old. For example, for a baby of 35 weeks' gestation, the 35-week gestation graph should be used until the baby is aged 14 days. Please note that the NICE guideline does not cover treatment with phototherapy and exchange transfusion for babies older than 14 days. Trusts should therefore agree their own policy about when to treat babies over 14 days with phototherapy and exchange transfusion'. It is recommended in section 1.7 of the guideline that in circumstances where there is prolonged jaundice a full clinical examination is conducted and expert specialist advice is followed as necessary. 3) The full guideline states that with regard to preterm babies, one longstanding and common approach has been to determine the threshold for phototherapy using the simple formula bilirubin in micromol/litre = (gestational age × 10) – 100. Based on informal consensus, the GDG agreed that this formula should be used for babies aged 72 hours or older. During the development of CG98 it was agreed for babies less than 38 weeks of gestation the threshold for phototherapy was best presented using a series of graphs (see treatment threshold graphs) of total bilirubin versus age in hours, with a separate graph for each gestational age

		1.5.1 Identify babies with hyperbilirubinaemia as being at increased risk of developing kernicterus or hearing loss if they have any of the following: Reference: https://www.ncbi.nlm.nih.gov/pubmed/30083525 Boskabadi H, Zakerihamidi M, Moradi A, Bakhshaee M. Risk Factors for Sensorineural Hearing Loss in Neonatal Hyperbilirubinemia Iran J Otorhinolaryngol. 2018 Jul; 30(99): 195–202.PMCID: PMC6064763. PMID: 30083525	(from 23 weeks to 37 weeks of gestation). The graphs were constructed using the formula for infants of 72 hours of age and older. The threshold levels during the first 72 hours were determined by drawing a straight line from a level of 40 micromol/litre (the upper limit of normal for the umbilical cord blood bilirubin) at birth to the formula-based level at 72 hours. In 2016 these threshold charts were considered during an evidence update. The committee proposed to make no changes to the actual treatment thresholds within the gestational age-based charts themselves as there seemed to be no issues implementing these. No further evidence was found to contradict these recommendations and therefore no amendment to the guideline will be made at this time. 4) During the development of CG98 evidence was found that suggested that hearing loss is a clinical manifestation of kernicterus, which can occur if the bilirubin levels become severely high. In response to this, recommendation 1.5 was created to ensure kernicterus was acknowledged and identified in babies with hyperbilirubinaemia. A research recommendation was also developed to ensure that national registries were created of cases of significant hyperbilirubinaemia, kernicterus and exchange transfusions. Thank you for referencing the Boskabadi et al 2018 study. Although this was a case control study and was not included as surveillance reviews generally only consider RCTs and systematic reviews, this study confirms that severe jaundice with high bilirubin levels is a risk factor for

			hearing impairments. Therefore there will be no impact to our guideline at this time. This guideline is currently in line with guidance from Public Health England who updated their Newborn Hearing Screening Programme Operational Guidance recommendations in November 2019 and state that jaundice at exchange transfusion level does not require an immediate or targeted referral to audiology. Therefore NICE will not be updating its guideline at this time.
Neonatal Critical Care Clinical Reference Group (CRG)	Yes	No comment	