Horizon Scan Report 0030 **10 June 2013**

Diagnostic Technology: Transcutaneous bilirubin measurement

Clinical Question: What is the accuracy and utility of transcutaneous bilirubin measurement compared to standard practice for the management of neonatal jaundice in primary care?

Background, Current Practice and Advantages over Existing Technology:

Neonatal jaundice is a common condition, affecting 60% of term and 80% of preterm infants in the 1st week of life. About 10% of breastfed infants are still jaundiced at 1 month of age. [1] The appearance of jaundice is caused by hyperbilirubinaemia, which is linked to neurological dysfunction and problems with psychomotor development later in life. [2-4] Increased levels of bilirubin that cross the blood brain barrier are toxic, resulting in icteric (yellow) staining within the brain termed kernicterus. Kernicterus is defined by the American Academy of Pediatrics as the "chronic permanent clinical sequelae of bilirubin toxicity characterized by severe athetoid cerebral palsy, paralysis of upward gaze, hearing loss and intellectual impairment." [5] This chronic bilirubin encephalopathy carries a morbidity rate of more than 70% and a mortality rate over 10%. [6, 7]

Although neonatal jaundice is common, there are approximately only 5 to 7 cases of kernicterus each year in the UK. [1] However, around 6% of visibly jaundiced infants have a high bilirubin level requiring treatment. [8] Some of these infants will have an underlying condition such as haemolysis and may present obviously unwell with rapid progression of jaundice. These infants with pathological jaundice may have identifiable risk factors such as ABO or rhesus incompatibility. However, healthy term newborns with no apparent risk factors and so-called 'physiological jaundice' can also develop kernicterus. [9] Therefore, it is difficult to predict which of the many jaundiced babies will develop serious clinical consequences.

The exact level of bilirubin that causes neurotoxicity is likely to depend on confounding factors such as concurrent illness, gestational age and postnatal age. [1] However, it is generally accepted that the higher the bilirubin level, the greater the risk of kernicterus. [10] Infants with clinically significant hyperbilirubinaemia, if successfully identified, can be effectively and safely treated with phototherapy. [11] However, in primary care, without a total serum bilirubin (TSB) value, how does a General Practitioner (GP) or a midwife ascertain which of the many jaundiced infants require admission and treatment?

Current practice in primary care is visual assessment of jaundice with subsequent TSB measurement if deemed necessary. However, visual estimation of bilirubin is inaccurate and NICE guidelines suggest all visibly jaundiced infants should have a bilirubin level measured within 6 hours. [1] This is usually done by referral to the local postnatal unit. [12] However, compliance with this recommendation is low - currently only around 10% of visibly jaundiced infants have a TSB measured. [1]

Handheld, point-of-care transcutaneous bilirubinometers (TcB) can provide rapid bilirubin measurements in the community. Indeed, TcB is included as an accepted method of measuring bilirubin in the latest NICE guidelines. Transcutaneous bilirubinometers provide an almost immediate (within 1 minute) measurement of bilirubin. [13] They require no laboratory support and therefore would be easier for a GP to use in the community. Using the point-of-care device saves time compared to measuring a serum bilirubin and may reduce costs. [14, 15] They also provide an opportunity to take multiple measurements of bilirubin over time to track trends without requiring multiple blood samples (although this has not been shown to be superior to a one-off measurement). [16]. Serum bilirubin tests are one of the most frequent reasons for blood sampling in newborns. [17] A non-invasive measurement would avoid the pain, inconvenience and complications associated with blood sampling for the majority of jaundiced neonates who are healthy. [8]

In order to justify routine use of transcutaneous bilirubinometers (TcB) in the community, the answers are needed to two specific questions:

- Are the current transcutaneous bilirubinometers accurate as point-of-care devices in the community?
- Would routine use of transcutaneous bilirubinometry in primary care improve management of neonatal jaundice?

Details of Technology:

Konica-Minolta Airshields JM 103, Drager Medical Inc, Telford, Pennsylvania (CE marked and FDA approved)
The JM 103 is a handheld, portable and re-chargeable jaundice meter that is held against the forehead or sternum of the infant after a calibration with a 'reflectance checker' (colour pad). It allows a quick, non-invasive estimate of TSB. It allows a single measurement of bilirubin or an average of up to 5 measurements. It takes 23.1 +/- 6.6 seconds for an average of 3 measurements. [13] The JM 103 measures the reflectance difference between two wavelengths. It measures the 'yellowness' of the subcutaneous tissue based on the difference between reflectance for light in the blue (450nm) and green (550nm) wavelength regions. There is a linear correlation between this difference in the reflectance and the TSB, allowing estimation of TSB. This keeps the influence of interfering factors including haemoglobin, melanin pigment and skin dermal maturity to a minimum. [18]

BiliChek Respironics Inc, Marietta, Georgia (CE marked and FDA approved)
BiliChek is also a handheld, portable and re-chargeable device that is pressed against the infant's forehead or sternum. It requires a new calibration tip for each use. Similarly to JM 103, users should avoid areas of bruises, birthmarks, subcutaneous haematoma or hair to ensure accuracy. It takes an average of 5 measurements over 55 +/- 31.5 seconds. [13] The BiliChek directs the full spectrum of white light onto the skin of the newborn and measures the intensity of the specific wavelengths returned. It mathematically isolates the skin components that impart spectral reflectance (haemoglobin, melanin pigment and dermal maturity). Therefore, by different methods, the BiliChek and JM 103 should be independent of gestational and postnatal age, race and weight. [19]

Patient Group and Use:

To estimate the serum bilirubin level in visibly jaundiced neonates, with the following restrictions:

- not suitable for infants with gestational age <35/40 weeks, postnatal age <24 hours [1]
- caution with suspected haemolytic jaundice as the bilirubin in subcutaneous tissue may rise slower than the TSB [18]
- caution with unwell infants who may have altered albumin carrying capacity, e.g. sepsis [19]
- exclusion/caution if used to monitor response to phototherapy as the bilirubin concentration in subcutaneous tissue is reduced before the serum bilirubin.
  - Despite development of light blocking patches to maintain reliability of measurements during concurrent phototherapy such as the 'BilEclipse Phototherapy Protective Patch', the NICE guidelines advise to use only TSB during and post-phototherapy. [1, 18, 19]

Importance:

In the late 1980's debate began over whether hyperbilirubinaemia has a direct toxic effect on the neurological system. A review found "no evidence of adverse effects of bilirubin on IQ, neurologic examination or hearing" and caused experts to question whether the relationship was by association rather than causation. [20, 21] As healthy, full-term infants are thought to be at very low risk of developing kernicterus, a "kinder, gentler" approach to hyperbilirubinaemia was suggested to avoid unnecessary blood tests and treatment. [22] The incorporation of this approach into accepted guidelines coincided with the trend for early discharge and increased prevalence of breastfeeding. [23] The subsequent multiple case-reports of kernicterus culminated in warnings from various safety and quality organisations of the threat of

kernicterus.[24-27] The widely reported re-emergence of kernicterus has since been challenged by US evidence demonstrating a 70% decline in neonatal hospitalisations with a diagnosis of kernicterus from 1988 to 2005. [6] However, recently the updated guidelines by both the American Academy of Pediatrics and NICE have recommended a more aggressive investigation and treatment strategy for neonatal jaundice. [1, 5]

However, the strategy to identify and treat hyperbilirubinaemia, usually with phototherapy, has failed to eradicate kernicterus. [28] Kernicterus continues to occur in otherwise healthy, full term infants in developed countries and may be increasing in incidence. [29, 30] One of the underlying concerns in the reported re-emergence of kernicterus is the lack of continuity in clinical care in the first week of life, often linked to early discharge. [9] The current UK practice of early postnatal discharge means that infants are commonly discharged when bilirubin levels are still rising. [31] Early discharge results in increased hospital re-admission rates for jaundice and has been linked to an increased risk of kernicterus. [32-37] Another important factor is the increase in prevalence of breastfeeding in the UK, given the association between breastfeeding and hyperbilirubinaemia. [38, 39] In a USA registry of kernicterus cases only 2 out of 125 infants were exclusively formula fed and in a UK surveillance study, 93% of the cases were exclusively breastfed. [9, 35] Early discharge also limits the opportunity to establish, support and monitor adequate breastfeeding. Suboptimal breastfeeding support is outlined in the root cause analysis in the report on the USA registry of kernicterus.

After discharge in the UK, GPs and midwives currently use visual estimation and clinical judgement to decide whether a jaundiced infant requires a serum bilirubin test or hospital admission. [1] Visual estimation can be good at excluding high levels of jaundice. However, it is not reliable or sensitive, is relatively poor at estimating risk levels, has a high false negative rate, a large amount of intra- and inter-observer variation, no predictable systematic variation and does not appear to improve with clinical experience. It also leads to a tendency to underestimate the severity of jaundice, which is likely to be particularly dangerous in the outpatient setting. [40, 41] Whilst nurses can interpret jaundice reasonably well, parents' assessment of jaundice may actually be more accurate. [42, 43] Therefore, in order to accurately identify all infants with severe hyperbilirubinaemia, a GP ought to arrange a serum bilirubin test if any infant is jaundiced. However serum bilirubin tests can be inconvenient to arrange in primary care and there may be significant delays in obtaining the result. An accurate point-of-care device would be useful to minimize blood sampling for a frequent and usually benign clinical condition. Ideally it would also enable a GP to identify infants with severe jaundice who would require further evaluation and management in hospital, thus reducing risk of kernicterus.

Previous Research:

Accuracy compared to existing technology

The NICE guidelines published in 2010 reviewed the literature on the accuracy of TcB up to June 2009. Due to the large number of studies, they included only prospective studies with evidence level II or above. A meta-analysis of 6 studies on the accuracy of JM 103 predominantly in hospital settings produced an area under the ROC curve of 0.87. [13, 44-48] Correlation with TSB was good, with R values ranging from 0.77-0.93, and a TcB cut-off of >200-204 μmol/L providing a sensitivity of 85% and a specificity of 80% in predicting a TSB >255 μmol/L. They also reviewed 7 studies in term and preterm infants on the accuracy of BiliChek. However, it was not possible to combine the data in a meta-analysis due to differences in study populations and threshold values for calculating diagnostic accuracy. [49-55] Evidence from good quality studies indicated that BiliChek correlates moderately well with TSB values, with R values ranging from 0.79-0.88. The results were comparable for use of either the forehead or the sternum for measurement and they could not recommend one particular TcB device over another. [1]

Evidence from outpatients

Almost all studies on the use of TcB to screen for neonatal hyperbilirubinaemia, including those in the NICE review, were performed in postnatal wards. [56] There are several reasons why the relationship of TcB to TSB may differ in the community and its accuracy and utility may be affected:

- The correlation between TcB and TSB is lower beyond 80 hours of postnatal age and at higher levels of TSB. [49, 51, 57] Given that bilirubin levels peak between 72-96 hours when the infant is in primary care, TcB results in primary care may be less accurate. [31]
- The correlation between TcB and TSB may be lower with exposure to sunlight, suggesting that discharge and subsequent exposure to daylight may adversely affect the utility of TcB. [58, 59] This may be "particularly true when the newborn has already been discharged home and is returning to a hospital, clinic or office facility for testing." [19] TcB measured from the sternum may correlate better with TSB than TcB measured from the forehead, as it is less likely to be affected by exposure to sunlight. [13, 52]

We identified six trials that have specifically evaluated the accuracy of TcB post-discharge. [44, 56, 60-63] These suggest that TcB has a different relationship to TSB in outpatients compared to inpatients. [61] The trials included between 31 and 327 otherwise healthy term infants having a TSB in the first postnatal week because of clinical jaundice or a high risk TSB pre-discharge. The settings included outpatients and a public health nurse program in the USA, a group of maternal and child health centres in Hong Kong and an emergency department in China. We did not identify any studies on the accuracy of TcB in outpatients in the UK.

The correlation between TcB and TSB post-discharge ranged widely from 0.39-0.93, correlation was lower as the postnatal age increased. [44, 60, 62] The lowest correlation was seen in a retrospective study in Hong Kong in which there was a significant time lag between TcB and TSB estimation (approximately 4 hours). Excluding this study, the correlation ranges were more similar, ranging from 0.77-0.93. Correlation was higher and fewer false negatives were found if the maximum of three TcB values was used rather than an average or a single measurement. [56, 62] The correlation is also improved by using sternum TcB measurements and this effect is exaggerated in outpatients, possibly due to the effects of natural phototherapy. [60]

In all of these studies, TcB is being compared to different methods of the 'gold standard' of laboratory TSB values. However, there are differences in the collection and transport of TSB samples between laboratories and up to 17% intra-laboratory variability in the measurement of TSB. [54, 64] There are inaccuracies in the measurement of bilirubin in clinical laboratories and the calibrators are often inaccurate. [65] Therefore, the imprecision in TcB may be comparable to the imprecision with laboratory tests. As TcB directly measures bilirubin deposition into the tissues it may actually be a more clinically relevant estimate of "brain bilirubin" than TSB. [52] However, it is likely that different processes regulate the movement of bilirubin into the brain than regulate bilirubin deposition into the skin. [53]

Actions based on level of bilirubin

In inpatients, TcB routinely underestimates TSB by between 5-34 μmol/L and this underestimation increases proportionally as TSB levels rise [44, 46, 48, 49, 52, 57, 66, 67] However, TcB may underestimate or overestimate TSB in the outpatient setting. [44, 61, 62] In outpatients, there appears to be decreased bias, but increased variability between TcB and TSB. Systematic bias in inpatient use of TcB has resulted in production of TcB specific nomograms for production of algorithms and protocols. However, in outpatients, the lack of predictability in the bias means that the variability cannot be overcome by manipulating the data. [61]

Table 1 describes the outpatient trials in more details including the TcB device used and the safe TcB thresholds for decision-making. The evidence seems to suggest that to ensure no infants with significant hyperbilirubinaemia (TSB >291 μmol/L [17 mg/dL]) or a 'high-risk' percentile TSB) are missed, infants with a TcB of over 222 μmol/L (13 mg/dL) require a TSB and further evaluation. However, a US group using TcB to make outpatient decisions, suggest that it may be safer to not just use set TcB thresholds for all infants, but to incorporate risk factors into the decision to obtain a confirmatory TSB. [56] The NICE review found good quality evidence that 4 factors are independently associated with an increased risk of hyperbilirubinaemia: gestational age <38 weeks, early jaundice, increased severity of clinically apparent jaundice and exclusive breast feeding. [1] Therefore, it may be that a GP could incorporate known clinical risk factors and their clinical assessment of the neonate with the TcB measurement to guide further management decisions; specifically the need for confirmatory TSB.

The evidence from primary care on TcB accuracy is from populations of otherwise healthy, jaundiced, term infants. Evidence from secondary care suggests that TcB accuracy may vary in populations including a wider range of infants.

Preterm/Unwell

The accuracy of TcB in preterm infants is particularly important as neonates less than 35 weeks gestation have a 3 times higher risk of hyperbilirubinaemia and an increased risk of developing kernicterus at lower bilirubin levels. [68, 69] Correlation between TcB and TSB is still moderate to high in preterm infants: JM 103 correlation ranges from 0.79-0.92 and this correlation is comparable across the full range tested of 24-34 weeks. [45, 47] BiliChek was tested on 340 white preterm infants between 30 and 36 weeks' gestation and had an R value of 0.79. There was a tendency for the TcB to overestimate in preterm infants, particularly at higher values. 'Sick' infants also have a higher TcB value for the same TSB value than well infants, which may be due to differences in albumin binding. [51]

Skin Pigmentation

Despite JM 103 and BiliChek accounting for skin pigmentation in their design, the relationship between TcB and TSB is different in black infants. The JM 103 can overestimate TSB in black infants and the imprecision of BiliChek increases as degree of skin pigment increases. [13, 53] The inaccuracies of both JM 103 and BiliChek associated with skin pigmentation are particularly important, as ethnic minorities are associated with a higher incidence of severe hyperbilirubinaemia and bilirubin encephalopathy. [35]

Phototherapy

Initial studies found no significant correlation between TcB and TSB after the onset of phototherapy. [70] If TcB values were used to guide withdrawal of phototherapy treatment, up to 45% of infants may have phototherapy stopped prematurely. [71] However, TcB can now be used in infants receiving phototherapy with the use of an opaque patch such as the BilEclipse. TcB with the use of a patch correlates with TSB without a statistically significant proportional bias. [72] However, TcB is still less reliable within 18 hours after cessation of phototherapy, even if patches are used, and the NICE guidelines do not recommend use of TcB during or post-phototherapy. [1, 73]

Impact compared to existing technology

Ideally, use of TcB would prevent cases of kernicterus. As kernicterus is such a rare outcome, no study has directly addressed whether the use of TcB can reduce the incidence of kernicterus. Available studies use surrogate markers, such as incidence and severity of hyperbilirubinaemia and readmissions for hyperbiliurbinaemia. The secondary outcome of numbers of TSB tests and associated costs are often included. Since early discharge has become commonplace, research has focused on use of predictive risk profiles pre-discharge to predict and minimise the risk of severe hyperbilirubinaemia in the community. TcB values are plotted in percentile zones on nomograms similar to the widely accepted Bhutani nomogram for TSB values. [74] This is combined with a risk factor assessment to guide follow-up plans and has been implemented in several health-care organisations across the USA. [75] The impact of TcB implementation in hospital may indicate the potential impact of TcB in primary care.

Impact in Secondary Care

Evidence from secondary care suggests that use of TcB can significantly reduce the number of required TSB tests with a number needed to prevent one TSB of 11. [15, 76-82] Any reduction in TSB tests is likely to have significant cost implications, as bilirubin tests are one of the most frequent reasons for blood sampling in newborns. [17] However, the reduction in TSB tests in hospital can be associated with an increase in outpatient TSB tests and outpatient phototherapy, seemingly 'switching' use of resources from inpatients to outpatients. [83]

A systematic review of TcB screening in 2009 found descriptive evidence that screening with risk factors and TcB is associated with increased diagnoses of hyperbilirubinaemia and fewer readmissions. The studies do not often have a concurrent control group and therefore it is almost impossible to causally associate the changes seen to the implementation of screening and account for confounding trends. For example, the AAP guidelines recommending a

more intensive, multi-faceted approach to jaundice were published in 2004. It is therefore difficult to attribute any benefits observed over this time period to one particular aspect of these guidelines or indeed to TcB screening. They also highlighted the fact that there are no data on the potential harm of screening and importantly, there is also no data on whether the infants identified by screening actually have a reduced risk of bilirubin encephalopathy due to treatment. [84]

Impact in the Community Setting

We only found one study that implemented, and assessed the impact of, TcB use in the community (as well as in hospital). A retrospective cohort study, including nearly 15,000 well infants from 3 hospitals in Calgary, investigated the impact of routine TcB daily in hospital and on all discharge visits. Babies were routinely seen by a public health nurse 1-2 days after discharge where a TcB was done, plotted on a locally validated nomogram, and a protocol used to guide further management. Routine TcB use in hospital reduced the incidence of hyperbilirubinaemia (>342 μmol/L [20 mg/dL]) on the initial TSB in the community by 55%. TcB use in the hospital and the community reduced the average age at re-admission for phototherapy by 15 % suggesting that significant hyperbilirubinaemia was being detected and treated earlier. There was also a reduced frequency in total number of TSBs by 23%. They concluded that "programmatic TcB implementation can significantly enhance patient safety with reduced demand on both laboratory and hospital resources but may lead to an increase in use of community health services." This may be because of earlier or more high-risk discharges because of increased clinician confidence in the reliability of the follow up. [85]

Use of TcB in the community may reduce the number of TSBs by a more modest reduction than that seen in inpatients as infants will be more likely to have TcB values over the safe cut-off thresholds. [85] As there are relatively higher levels of both TcB and TSB in the community, outpatient data suggests that only 20% of TSBs may be avoided by availability of TcB screening. [61] However, within the Emergency Department, it was estimated that 50% of infants could be discharged or admitted based on the TcB value. [62]

Evidence from secondary care suggests that adding TcB to visual assessment could reduce GP's overestimation and underestimation of jaundice and enable them to detect extra babies with clinically significant jaundice they may not have otherwise identified. [66, 86] Currently it is estimated that only 10% of visibly jaundiced infants in the community have a TSB test. Implementation of TcB in the community would enable easier measurement of bilirubin in all visibly jaundiced infants than TSB. Therefore, use of TcB may actually increase numbers of not only TSB tests but also readmissions and phototherapy, without a proven benefit in preventing kernicterus.

RCT Evidence

An abstract of a randomised controlled trial involving 14 community health centres and 13,225 newborns in Canada has recently been presented at the Pediatric Academic Societies Annual Meeting. It suggests that use of TcB in the community compared to visual assessment leads to decreased numbers of TSB tests without an increase in severe hyperbilirubinaemia and hospital re-admission. The intervention is routine TcB use by community nurses, with an algorithm to guide management, compared to usual care (TSB at the discretion of nurse/primary care physician). Fewer neonates in the intervention group received a TSB assessment (6.8% vs 14.3% $p<0.0001$). There was no statistically significant difference in incidence of severe hyperbilirubinaemia (TSB ≥ 350 μmol/l [20.6 mg/dL]) (1.1% vs 1.0%) and a slightly reduced incidence of significant hyperbilirubinaemia (TSB ≥ 300 μmol/l [17.6 mg/dL]) (2.8% vs 3.2% OR 0.77 CI: 0.6-0.94). There was no significantly significant difference in hospital readmissions (1.5% vs 1.7%).[87] Therefore, it seems that TcB thresholds can be used safely in the community to avoid TSB tests. The further results of this study will be an important step in evaluating the use of TcB in the community.

Guidelines and Recommendations

The NICE guidelines on neonatal jaundice were updated in 2010. [1] Relevant points include:

- examine baby for jaundice at every opportunity, especially in the first 72 hours
- ensure babies with risk factors associated with an increased likelihood of developing significant hyperbilirubinaemia receive an additional visual inspection by a healthcare professional during the first 48 hours of life
- do not measure bilirubin levels routinely in babies who are not visibly jaundiced

- do not rely on visual inspection alone to estimate the bilirubin level in a baby with jaundice
- if babies are visibly jaundiced, measure and record serum bilirubin within 6 hours
- use TcB if babies >35/40 and >24 hours of age, if TcB not available, use TSB
- during phototherapy, use only TSB
- if TcB > 250 μmol/L (14.7 mg/dL) measure serum bilirubin

A particularly important recommendation for GPs is that a visibly jaundiced baby should have a bilirubin level measured within 6 hours. They are instructed not to rely on visual inspection to guide management. If this guidance was followed, without the availability of TcB, a GP would have to order blood tests for 60% of the healthy neonates they see in the first postnatal week.

The NICE guidelines suggest that a TSB is required only if the TcB measurement is greater than 250 μmol/L. The limited evidence from outpatient studies suggests that a slightly lower cut-off of 13 mg/dL (222 μmol/L) is needed to ensure 100% sensitivity for high/high risk TSB values. [44, 61] Such a cut-off may result in many more jaundiced, but healthy infants being investigated and potentially over-treated. However, the suggested cut-off of 250 μmol/L may result in false negative results, risking infants with severe jaundice left at home without treatment.
Experts have recommended to measure a TSB in outpatients if: [88]

- TcB >222 μmol/L (13 mg/dL) [44]
- TcB >70% of the age-specific TSB phototherapy threshold [51]
- TcB >75th percentile on Bhutani nomogram or >95th percentile on TcB specific nomogram [74, 89]

The American Academy of Pediatrics and Canadian Paediatric Society guidelines also include the use of TcB as a screening tool for evaluation of jaundiced infants. [5, 90]

Cost-effectiveness and economic impact:

The NICE review performed an economic analysis, as it was "not possible to make recommendations based on published economic evidence." Current practice is 2-3 midwife visits within the 1st week in which visual assessment results in a subsequent TSB in around 10% of jaundiced babies. Given the known limitations of visual assessment, a more intensive strategy is suggested. The review therefore compared a TSB on all visibly jaundiced infants with a TcB on all visibly jaundiced infants (assuming 25% would need a confirmatory TSB). Based on an assumption that both strategies would be equally effective at preventing kernicterus, they performed a cost minimisation analysis. Total costs per year were calculated as £1.02 million for the current strategy, £10.22 million for the TSB strategy and £3.26 million for the TcB strategy (if JM 103 was used). If BiliChek was used, this would cost £6.26 million due to the cost of calibration tips. If less than 9200 JM 103 meters could deliver TcB to all visibly jaundiced infants, it would be more cost effective than TSB. This is based on the strategy successfully preventing 1.52 cases of kernicterus per year.

Implementation of routine TcB on all infants post-discharge in the Calgary hospital study required only 2.8 devices per 1000 births. [85] The NICE analysis accounted for 13.3 devices per 1000 births and therefore TcB is likely to be more cost effective than calculated. This also means that it would still be cost effective if it prevented fewer than 1.52 cases of kernicterus per year (based on a kernicterus case costing £5.5 million). [1] However, in the Calgary program, 25% of the devices did not perform to an acceptable level despite calibration and 60% of the devices have had to be re-calibrated or repaired over a 3-year period, leading to increased costs.

Research Questions:

1. What is the accuracy and precision of TcB compared to TSB in the primary care setting – both in the GP office and in the home by GPs or Midwifes?
2. What is the comparative accuracy of the two currently available devices, and how do these vary with different infants groups (e.g. dark skin infants)?

3. What impact would routine use of TcB in the community to assess visually jaundiced neonates have on management of neonatal jaundice?
4. Is routine use of TcB in the community to assess visually jaundiced neonates cost-effective?
5. If proved to be accurate and have a significant and cost-effective impact on management of neonatal jaundice in primary care, how would TcB best be incorporated into routine postnatal care? For example, would TcB be of use in the initial baby check, on midwife home visits or within GP consultations?

Suggested next step:

- A systematic review of the accuracy of TcB in the community.
  - -Assuming the devices are accurate in primary care settings, a nomogram and algorithm based on the measured level of bilirubin are needed in order to allow TcB measurement to guide management.
- A UK based RCT of the impact of TcB in the community on incidence of severe hyperbilirubinaemia

Expected outcomes:
TcB appears to correlate with TSB reasonably well in secondary care, and, to a lesser extent, primary care settings. The randomised controlled trial from Alberta will provide much needed information on the impact of implementation of TcB in primary care. Before implementation in the UK, an accepted nomogram with appropriate cut-off values needs to be developed. If currently adhered to, the NICE recommendations would appear to result in many more TSB tests being performed.

There is currently a paucity of evidence and therefore significant limitations on the use of TcB in primary care in the UK setting. There have been relatively few trials demonstrating the accuracy and utility of TcB in primary care. However, in the future, it seems likely that TcB will become a screening tool for use in the community to assist GPs as well as midwives and health visitors in their assessment of jaundiced neonates.

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Table 1. Overview of accuracy studies post-discharge

Study	Participants/Setting	Device	Correlation	To detect all TSB values mg/dL (μmol/L)	TcB threshold required mg/dL (μmol/L)	Sens	Spec	NPV PPV	Mean bias
Engle 2005	- 121 infants in USA - In-hospital outpatient centre - TSB due to clinical jaundice pre-discharge (d/c) or in outpatient follow-up (f/u) - 92% Hispanic - Gestational age (GA) median 40 (35-41/40) - Postnatal age (PA) median 91 hours (53-166) - Excluded – phototherapy - TSB median 14.8 (9.2-22.1)	JM 103	Diazo method within 30 minutes R = 0.77	>17 (291)	13 (230)	100%	58%	PPV 0.27 NPV 1	-1.6 (27.4)
Lam 2008	- 113 infants in China - Emergency Department - TSB due to clinical jaundice - Chinese - GA >35/40 - PA mean 5 days (3-7) - Excluded – pre-term, 'sick looking' or high risk - TSB range 4.3-22.4 (48%>14.6)	JM 103 x 3 forehead x 3 sternum (ave + max)	Direct spectrophoto-metric lab method within 5 minutes R = 0.83 (using max TcB)	>14.6 (250) >14.6 (250)	13 (230) 17.4 (298)	100%	 100%		+0.82 (14.4)
Maisels 2011	- 120 infants in USA - 2 hospital based outpatient clinics, 1 regional nurse program, 2 paediatric office practices - TSB due to clinical jaundice(except in PHN – routine TcB +/- TSB) - 35% Caucasian, 31% Hispanic, 16% Asian, 9% African American (Middle Eastern, Native Canadian) - GA >35/40 (76% > 38/40) - PA mean 90.4 hours (+/-32.9) - Exclusions – not specified - TSB mean 15.1 (5.7-23.2)	JM 103 x 3 sternum (ave + max)	Diazo method within 30 minutes R 0.78 (using max TcB)	≥17 (291)	14 (239)	100%	41%	PPV 0.44 NPV 1	Max TcB +0.3 (5.1) Ave TcB -0.5 (8.55)

Poland 2004	- 31 infants in New Mexico - Outpatients - TcB screening daily, TSB if TcB>12 or clinician ordered TSB - 21 Hispanic, 6 Native American, 4 Caucasian - GA - term - PA – range 13.5-196 hours - Excluded if special care >12 hrs, non-routine medications or signs/sx of illness - TSB mean 10.6 +/- 3.7	BiliChek	Vitros method R = 0.91 (using forehead) R = 0.93 (using sternum)						Fore-head -2.1 (36) Sternum -0.6 (10)
Wickrema singhe 2011	- 79 infants in USA - Outpatient clinic - TSB due to HIR/HR TSB pre-d/c or clinical jaundice at f/u - 73% Caucasian - GA 39+/- 2/7 (36+2/7 – 41+5/7) - PA mean 4.2 days (2.2-8.5) - Excluded – phototherapy - TSB mean 13.6 (7.6-19.5)	BiliChek	Diazo method within 90 minutes	>95th centile (Bhutani) >17 (291) >75th centile	13 (230) 13 (230) >75th centile	100% 100% 87%	58%		+1.5 (25.7)