Initial Clinical Referral Standards after Newborn Screening for Congenital Hypothyroidism

Final Report of the UK Newborn Screening Programme Centre (UKNSPC) Expert Working Group and Systematic Evidence Review 2010-2011

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1 Executive Summary

Introduction

In April 2010, the Initial Clinical Referral Standards (ICR) for Congenital Hypothyroidism (CHT) Expert Working Group was convened as a sub-group of the Joint Standing Committee for Congenital Hypothyroidism (CHT JSC) to review and revise the UK National Screening Programme Initial Clinical Referral Standards after Newborn Screening for Congenital Hypothyroidism.

The review commenced with a systematic review of the published evidence undertaken by Dr R Knowles and Ms F Olafsdottir.

Background to the Expert Working Group

The decision to form the ICR group was made at the last meeting of the CHT JSC in April 2010. The group report to the Joint Standing Committee for endorsement and recommendation. Recommendations are ratified by the Blood Spot Advisory Group (BSAG) and submitted to the Fetal Maternal and Child Health sub Group (FMCH) of the National Screening Committee (NSC) for approval of any changes to current policy.

At the meeting in April 2010, the JSC reviewed current policy and UK performance against national standards and with European standards and guidelines. The group agreed to review the existing (2005) UKNSPC standards and guidelines to support confirmatory diagnosis and initial management for babies in whom CHT is suspected.

Between July 2010 and September 2011 the Expert Working Group, chaired by Dr T Cheetham met on four occasions to review and revise the referral standards.

Scope of the review

- Screening result TSH cut-offs used to determine which infants are referred, not referred or for whom a repeat test might be indicated (borderline)
- Diagnostic schedule for confirmatory diagnosis of CHT
- Initial treatment including timing, starting dose, formulation and frequency of follow up to the point of diagnosis or definitive management.
- Communication flows
- Communication with parents
- To support the review process with evidence review and expert consensus where published evidence is lacking

Exclusions

- Definition for Congenital Hypothyroidism
- Timing of bloodspot sampling
- Screening test methods (TSH)
- Policy for repeating screening in preterm infants

Expected outputs

Revised 'Standards and guidelines for Initial Clinical Referral'
Evidence review (including tables where appropriate)
Possible recommendation for further research

Membership and meeting dates

Membership and meetings of the Expert Working Group (EWG) are detailed in Appendix 2. The EWG met on four occasions and five subgroups were convened to review topic-specific Standards:

The CHT Test Performance Group

The groups remit included review of:

- Screening result TSH cut-offs used to determine which infants are referred, not referred or for whom a repeat test might be indicated (borderline).
- Referral of babies with positive screening results
- Communication flows

Changes summarised

The group recommended that:

1. Standards and guidelines which were generic to all screening standards should be omitted from the revised standards, including the policy for screening preterm babies, guidelines on screening and blood transfusion, responsibility for taking the sample, and information and consent.
2. An additional section and algorithm that describes a standard pathway for blood spot testing should be developed (this approach is consistent with other conditions).
3. There should be no change in the TSH cut off levels used to define CHT suspected, borderline and not suspected.
4. Referral of all those with screening results indicating CHT is suspected should be to a paediatric endocrine team (regional specialist team) or to a clearly identified lead paediatrician with a special interest in CHT or experience of managing these patients.
5. Notification of presumptive positive children and results should be to the regional specialist team
6. A standardised diagnostic and initial treatment protocol should be used for those referred and treated for CHT respectively.
7. Communication of presumed positive screening results to parents should ideally be face-to-face be undertaken by an informed health care professional with good knowledge and experience of managing CHT.

The Referral Pathway Subgroup

The remit of the group included review of the referral pathway after a presumed positive screening result. In July 2011, a questionnaire was sent to all 16 screening laboratories in the UK to get a better understanding of the different models of care and to establish what works well.

Changes summarised

The group recommended that:

1. Babies with positive screening results for CHT should be referred by the laboratory the same or next working day.
2. Referral should be to a paediatric endocrine team (regional specialist team) or to a clearly identified lead paediatrician with a special interest in CHT or experience of managing these patients (who has a designated trained deputy).
3. Clinicians should work to a common protocol and back up should be provided by the regional specialist team.
4. Wherever possible parents should be offered an appointment with the paediatrician on the same day or the next day after being informed of their baby's positive screening result.

The Diagnostic Subgroup

The remit of the diagnostic subgroup included review of the investigations and imaging that might be appropriate for confirming the diagnosis of CHT after a positive screen result. A number of research articles on biochemical investigations were reviewed long with expert views on imaging. Dr

Tony Sirimanna, was invited to the ICR meeting in July 2011 to consider the need for hearing tests in addition to those offered in the newborn hearing screening programme

Changes summarised

Based on the available evidence, the group made specific recommendations about:

1. Confirmatory diagnostic tests to be undertaken in the baby
2. Investigations to be undertaken in the mother
3. Appropriate thyroid imaging
4. Confirmation of the diagnosis and exclusion of transient CHT at 2-3 years of age.

A diagnostic protocol has been developed to summarise the confirmation of diagnosis pathway.

The Treatment Group

The remit of the group included the standards relating to treatment initiation, including formulation, timing and dose.

Changes summarised

The group recommended that:

1. There should be an additional standard for age at start of treatment when a 'CHT is suspected 'result is preceded by borderline result. (Based on data from 2010/11, an acceptable standard of 24 days and achievable standard of 21 days were proposed).
2. The starting dose of levothyroxine should be raised, licensed solutions should be recommended and there should be increased monitoring in the first year of treatment.

Parent Communication Information Group

This group included two parents of children with CHT. The scope of the group was to review the following leaflets and documents:

- *CHT and Your Child* leaflet
- *CHT is Suspected* leaflet
- Pre-Screening leaflet
- Communicating a request for a borderline repeat
- Communicating a screen positive result

Changes summarised

Suggested changes were presented to the ICR CHT on 16th September 2011. At a final meeting with additional input from Ms S Langham and Dr R Knowles, amendments to 'CHT and Your Child Leaflet' and the 'CHT is Suspected' leaflet including images, text and web links were reviewed and agreed. Combining both leaflets was considered, however it was decided that separate leaflets were more appropriate.

Public Consultation

A public consultation on the proposed new standards was carried out in 2012. Any changes made to the standards on the basis of the responses received are noted in this final version of the report.

Summary and Recommendations

This final report presents the revised standards, screening protocol and diagnostic protocol developed by the Expert Working Group (Section 2) and finalised after public consultation, as well as the evidence basis for the revised standards and guidelines (Sections 3 -12).

2 Revised CHT ICR Standards, Screening and Diagnostic Protocols

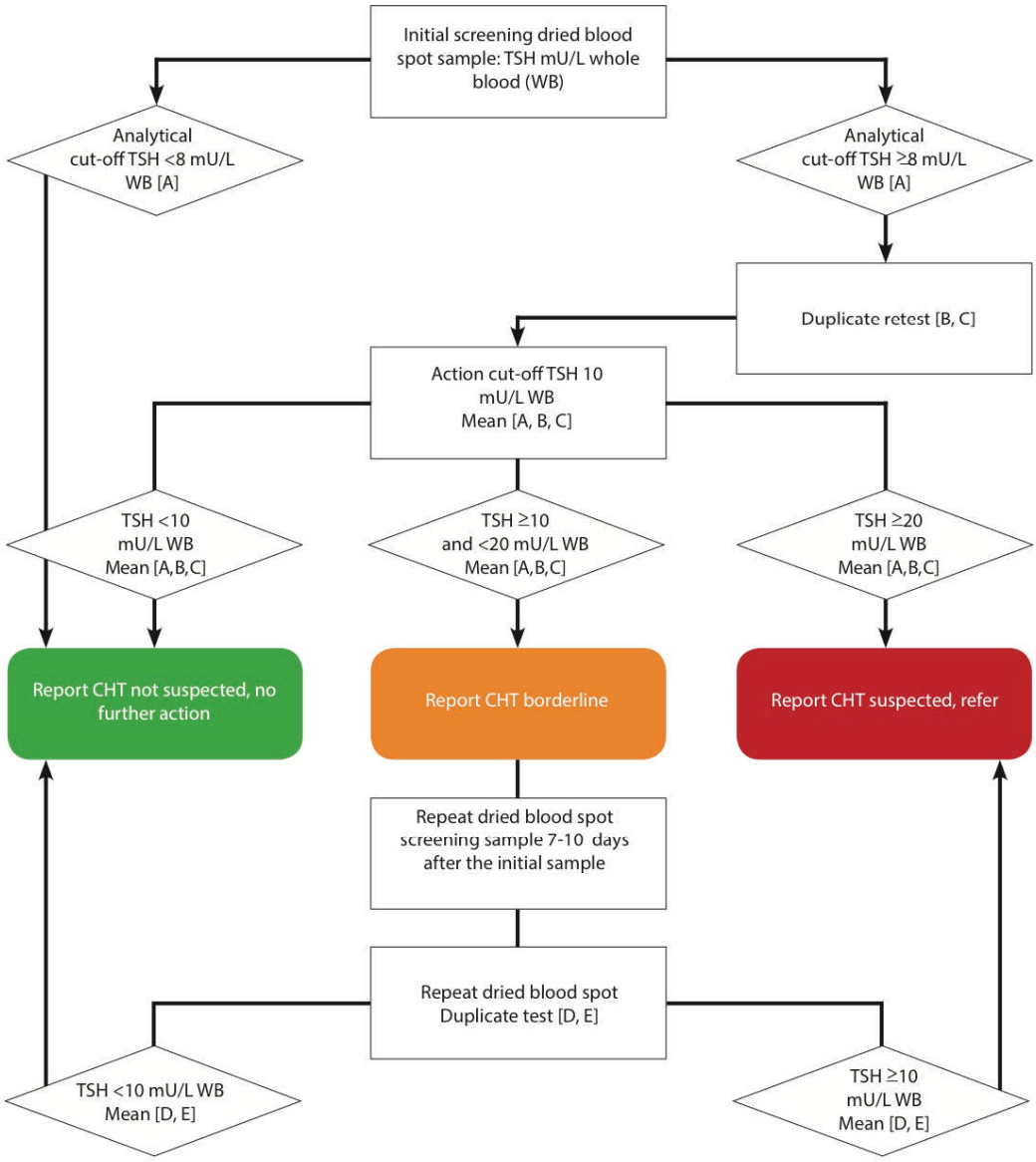
Stage of process	No.	Standards
The screening protocol	1	<u>The initial screening sample</u> Thyroid stimulating hormone (TSH) analysis is performed on a single spot from the initial dried blood sample. Samples with TSH ≥ a preliminary threshold (analytical cut off*) of 8mU/L whole blood (WB) are re-tested in duplicate from the same card but on a different spot(s). Action is taken on the triplicate mean result. Second sample – TSH is analysed in duplicate and action taken on duplicate result. (See Screening Protocol flow diagram) Timeliness of analysis – analysis is timed to permit referral of screen positive results within 2-4 working days of sample receipt. *The analytical cut off is set at 20% below the screen action cut off of 10mU/L WB to allow for the natural variation in the TSH assay (i.e. the coefficient of variation, CV=10%) and to minimise the effect of volumetric variability that occurs in dried blood spots. Re-testing also acts as confirmation of correct sample identification.
Categorisation of initial screen result	2	Babies in whom the TSH concentration is <10mU/L WB in the initial screening sample should be considered to have a negative screening result for congenital hypothyroidism (CHT). Report CHT not suspected.
	3	Babies in whom the TSH concentration is ≥ 20mU/L WB on the initial screening sample should be considered to have a positive screening result for CHT. Report and refer as CHT suspected.
	4	Babies in whom the TSH concentration is ≥ 10 and <20mU/L WB on the initial screening sample should be considered to have a borderline result for CHT.
Borderline screen result	5	On detecting a borderline result a second blood spot sample is to be taken 7-10 days after the initial sample.
	6	If the TSH concentration is <10mU/L WB in this second sample, the baby should be considered to have a negative screening result for CHT. Report CHT not suspected.
	7	If the TSH concentration is ≥ 10mU/L WB in this second sample: Report and refer as CHT suspected.

Stage of process	No	Standards
Referral of babies with positive screening results	8	The laboratory shall refer babies with positive screening results for CHT the same or next working day. Referral is to a paediatric endocrine team (regional specialist team) or to a clearly identified lead paediatrician with a special interest in CHT or experience of managing these patients. Appropriate failsafe mechanisms must be in place to ensure CHT suspected babies have entered into the diagnostic pathway. Clinicians should work to a common protocol and have access to the full range of diagnostic investigations recommended. Where referral is out-with a regional endocrine centre, the regional specialist team should be able to provide support and facilitate access to diagnostic investigations where required.
	9	The first clinical appointment with the paediatrician must take place on the same day or the next day after parents are informed of their baby's positive screening result.
Communication flows	10	Laboratories shall notify a positive screening test (blood spot results expressed as a whole number), verbally and in writing by secure fax or email, to the lead paediatrician or deputy and the health professional responsible for communicating results. This notification should include a link to the standardised diagnostic and initial treatment protocol. This initiates the clinical referral of screen positive cases.
	11	The result should be communicated by an informed health professional. The health professional making initial contact should provide the following information to the family: a) UKNSPC standardised parent information 'When CHT is suspected' (via hard copy or web link). b) Details of the time and date of the appointment with the paediatrician and appropriate contact telephone numbers.
	12	The outcome of the first appointment should be reported to the newborn screening laboratory. The regional endocrine centre should also be informed about diagnostic outcome to facilitate regional and national audit.

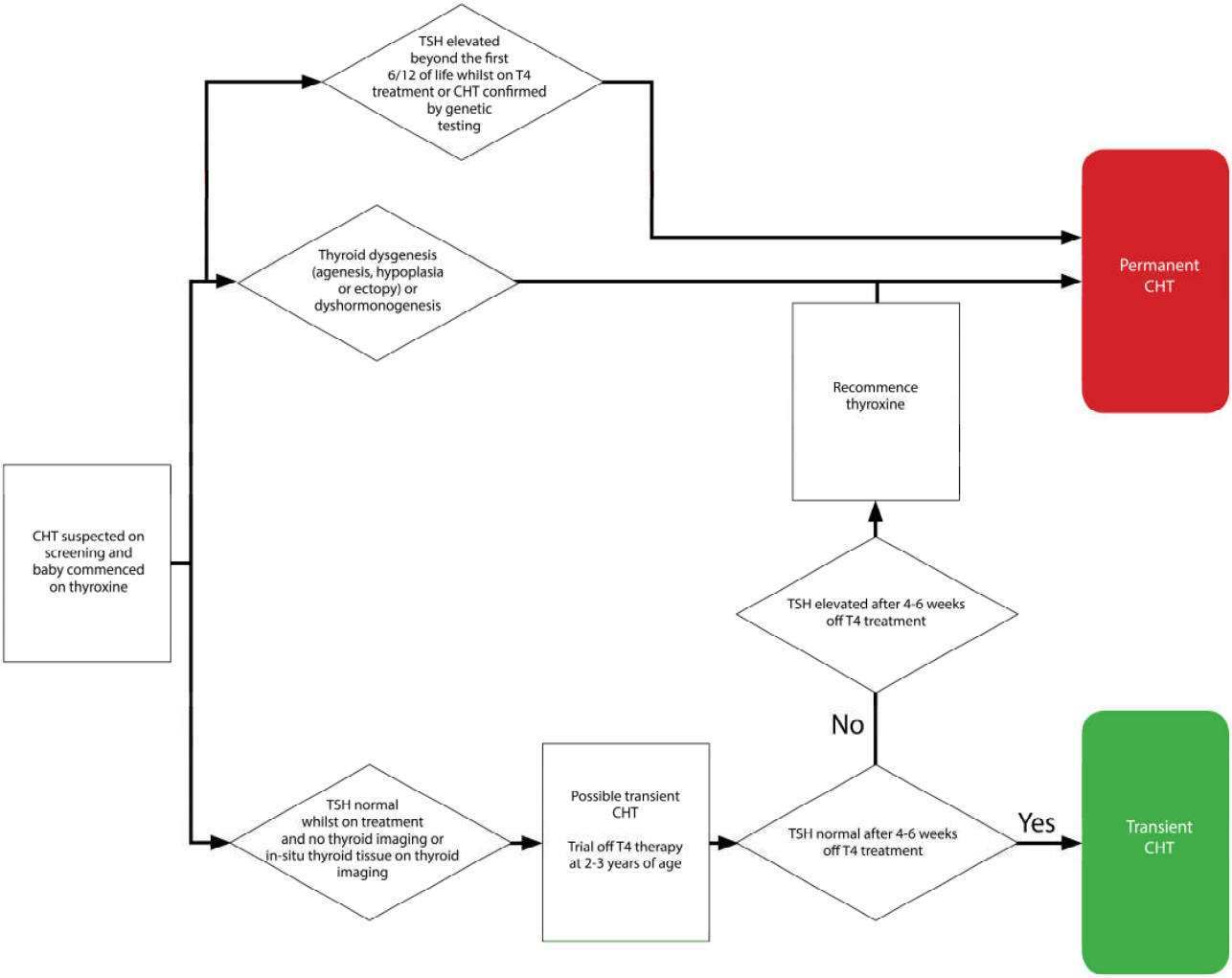
Stage of process	No	Standards
Clinical evaluation and confirmatory diagnostic tests	13	The clinician responsible for assessing the baby with a positive screening result shall take a clinical history and perform a clinical exam (See Note 1)
	Note 1: Babies with CHT are more likely to have associated anomalies, particularly congenital heart defects and mild hearing loss and require careful neonatal examination. A complete history, including maternal thyroid status (previous history of thyroid dysfunction, maternal anti-thyroid medications), maternal diet (e.g. vegan or other low iodine diet) and family history should be obtained.	
	14	Diagnostic tests considered essential in the baby are: a) freeT4 (plasma or serum) b) TSH (plasma or serum) (See Note 2)
	Note 2: Diagnosis using freeT4 and TSH should be performed on a plasma or serum sample using the appropriate age-related reference range as defined by the laboratory in relation to the equipment used.	
Desirable additional diagnostic tests	15	Appropriate imaging techniques (radio-isotope and/or ultrasound scans), may help to establish whether the thyroid gland is a) normally situated and normal in size and shape b) normally situated but abnormal in size and shape c) ectopic d) absent (See Note 3)
	Note 3: A radioisotope scan and an ultrasound examination may establish the cause of the child's CHT and indicate whether the condition is likely to be permanent. Initiation of treatment should not be delayed whilst waiting for an isotope scan, which can be performed up to 5 days after starting therapy. An ultrasound scan can be performed at any stage and investigation need not be confined to the neonatal period. These investigations may increase awareness of potentially related problems such as deafness and can provide information about recurrence risk. Recurrence is unusual in the case of thyroid dysgenesis but there is likely to be autosomal recessive inheritance with a 1:4 recurrence risk for families of babies with thyroid dyshormonogenesis. Both isotope scanning and thyroid ultrasound in neonates require specialist skills and can generate misleading results.	
	16	In addition, the following test may be helpful: a) Thyroglobulin (See Note 4)
	Note 4: Plasma thyroglobulin needs to be measured on a sample taken prior to the start of treatment; this must not delay initiation of treatment. If plasma thyroglobulin is detectable then there must be some thyroid tissue present. Concentrations will be undetectable in thyroid agenesis.	
Advisable tests in the mother	17	Diagnostic tests considered advisable in the mother to exclude interference in the infant's TSH measurement and to exclude thyroid dysfunction in the mother include: a) freeT4 (plasma or serum) b) TSH (plasma or serum) These investigations should be extended to include an assessment of TSH antibody receptor status in mothers with a current or previous history of autoimmune thyroid disease.

Stage of process	No	Standards
Treatment	18	A baby in whom a diagnosis of CHT has been made, should commence treatment with oral levothyroxine by: a) CHT positive on initial screening sample Acceptable standard: 17 days of age (≥99% of infants) Achievable standard: 14 days of age (≥99% of infants) b) CHT positive on a repeat blood spot sample Acceptable standard:24 days of age (≥99% of infants) Achievable standard: 21 days of age (≥99% of infants)
	19	The starting dose of oral levothyroxine should be 10-15mcg/kg/day, with a maximum dose of 50mcg/day. The objective of treatment is to normalise TSH within the first month. The dose of levothyroxine may need to be reduced if TSH is suppressed or if the baby is showing signs of overtreatment. Babies with significant endogenous thyroid hormone production may need smaller initial doses. (See Note 5)
		Note 5: Treatment with levothyroxine should lead to normalisation of free T4 and a 50% reduction in TSH within days. However, TSH normalisation can take weeks and timing does not correlate well with the administered levothyroxine dosage or the severity of the underlying diagnosis. The aim of treatment is therefore to increase free T4 close to the upper reference range within the first 2 weeks of treatment and to normalise the TSH within the first month. Free T4 concentrations may exceed the normal reference range at the time of TSH normalisation but significant elevation should be avoided. Regular dose adjustments may be required.
	20	Only licensed solutions and tablets of levothyroxine should be used. Suspensions may be unreliable. Parents should be shown how to administer preparations and accompanying written information should be provided.
	21	Once levothyroxine treatment has been started, TSH and thyroid hormone concentration should be checked at an appointment with a paediatrician at approximately 2 weeks, 4 weeks, 8 weeks, 3 months, 6 months, 9 months and 12 months after treatment is started, and thereafter as indicated. More intensive biochemical monitoring may be required. (See Note 5)
	22	Assessment of Permanence of Hypothyroidism. In cases where the cause or persistence/permanence of hypothyroidism has not been confirmed (see Diagnostic Protocol flow diagram), confirmatory testing should be undertaken at 2-3 years of age with thyroid function tests checked 4-6 weeks later.. The outcome should be fed back to the regional endocrine centre to facilitate regional and national audit.

Screening Protocol Flow Diagram



Diagnostic Protocol Flow Diagram



3 Introduction to Newborn Screening for Congenital Hypothyroidism

3.1 Congenital hypothyroidism

Congenital hypothyroidism (CHT) is a disorder of the thyroid gland, which is normally situated at the front of the neck. The thyroid gland produces a hormone called thyroxine, which is needed for normal growth and development. If the thyroid gland does not produce enough thyroxine, it causes hypothyroidism and, when this disorder is present from birth, it is called congenital hypothyroidism (CHT). In babies with CHT, the thyroid gland either fails to develop normally (dysgenesis) or does not work properly to produce adequate hormone (dyshormonogenesis). The production of thyroxine by the thyroid gland is regulated by thyroid-stimulating hormone which is released by the pituitary gland in the brain.

Most babies with CHT in the UK are detected by the newborn screening bloodspot programme before they have any symptoms. However, if signs and symptoms are present, these may include feeding difficulties, sleepiness, constipation and jaundice. If CHT is not diagnosed and treated soon after birth, it can cause problems with mental development, clumsiness and abnormal growth. CHT is treated by lifelong replacement of thyroid hormone, usually as levothyroxine sodium given daily by mouth.

In the UK, around one in every 3,500 newborn babies has CHT and the disorder is more common in girls than boys.

3.2 Newborn screening for CHT

Newborn screening for CHT was introduced in the UK in the 1970s.The aim of screening in the UK is to prevent adverse neurodevelopmental outcomes by identifying infants with primary CHT due to an abnormal or absent thyroid gland and to initiate treatment by 14-17 days of age.[1 2] UK babies are screened for CHT by looking for raised levels of thyroid-stimulating hormone (TSH) in the newborn bloodspot (in whole blood) at 5-8 days of age. The sensitivity of this screening test is generally considered to be very good but, as the TSH assay has become more refined, there has been a tendency to set lower thresholds at which diagnostic investigation is indicated.[3] A raised TSH concentration at birth may also be a transient phenomenon, particularly in preterm infants and in babies who are unwell or exposed to certain drugs. In the UK, a repeat screening test is conducted in babies born at less than 32 weeks gestation as these preterm infants are more likely to have an inappropriately low TSH level.[4] The diagnosis of CHT is confirmed by measuring serum TSH and serum thyroxine (T4) levels in a venous blood sample. Investigations such as ultrasound and radio-isotope scanning of the neck can be used to determine the specific underlying thyroid abnormality (dysgenesis or dyshormonogenesis).

Internationally, different methods are used for newborn screening. In most European countries a whole blood TSH assay is initially performed on the newborn bloodspot although the threshold chosen for a positive result may vary.[5] In contrast, North American screening programmes often measure whole blood T4 levels in the bloodspot initially and then undertake whole blood TSH measurements as required for confirmation.

4 Initial Clinical Referral Standards Review Expert Working Group

An Expert Working Group (EWG) was established in July 2010 by the UK Newborn Screening Programme Centre (UKNSPC) with the aim of reviewing the existing Initial Clinical Referral Standards (ICR) for Congenital Hypothyroidism (2005). Terms of reference are provided in Appendix 1. These standards provide the standards and guidelines for best practice in investigating and confirming the diagnosis of CHT after newborn screening, as well as communicating with parents and initiating management for babies in whom CHT is suspected.

The EWG was chaired by Dr Tim Cheetham, Paediatric Endocrinologist, and members are listed in Appendix 2.The Expert Working Group met on four occasions. Five subgroups (Appendix 2) focusing on specific standards were constituted from the Working Group members; each subgroup met on average on two occasions and then presented recommendations to the Expert Working Group for approval. In 14th December 2011, the Expert Working Group recommendations for revised ICR standards were presented to the UKNSPC Joint Standing Committee for CHT.

An evidence review (Olafsdottir and Knowles, 2010) to inform the development of revised ICR standards was commissioned by the UKNSPC and presented to the first meeting of the EWG.

The review excluded screening of preterm infants as review of this policy was the responsibility of another working group.

5 Systematic Literature Review and Evidence Synthesis

The methodology for the systematic literature review and evidence synthesis is described here and the findings are presented in Sections 7-11. The report is divided into sections corresponding to the standards reviewed by each topic subgroup.

5.1 Aim of the systematic review

Test performance

With regard to the screening test performance,

- To clarify the appropriate screening test TSH value at which infants should be referred for diagnostic investigation (positive result), a repeat screening test might be indicated (borderline result) or a negative screening result should be reported.

Screening result

After a positive test result, to define the

- Referral pathway and timeliness of referral by laboratory to designated clinician
- Referral pathway and timeliness of first visit to a designated clinician when a 'CHT is suspected' result is given after the first test result.

After a borderline test result, to define the

- Referral pathway and timeliness of repeat test for an initial borderline result
- Referral pathway and timeliness of referral to a designated clinician when a 'CHT is suspected 'result is preceded by borderline result.

After a positive or borderline test result, to define the

- Diagnostic schedule for confirmatory diagnosis of CHT
- Initial treatment including starting dose, formulation
- Frequency of follow up and repeat blood tests, including review to exclude transient CHT
- Standards for communication about the condition, investigations and treatment to parents.

A secondary aim was to consider the evidence for the economic effectiveness of the recommended pathways for screening, diagnostic referral and investigation, and on-going management.

5.2 Methodology for the systematic review

Literature Search Strategy

Embase, Medline, PsychInfo and Cochrane Trials Register were searched for the period up to June 2010, without imposing any language restrictions, to identify all abstracts of papers relevant to newborn screening for congenital hypothyroidism. Seven search concepts were developed through the combination of various search terms, including 'Congenital Hypothyroidism', 'Newborn', 'Screening', 'Diagnosis', 'Outcome', 'Treatment' and 'Economics'. Finally, to facilitate the exclusion of papers that were not relevant to UK screening practice, a 'Countries' concept was developed to include only European countries, Canada, the USA, Australia, New Zealand and Japan. The search terms included within each concept are detailed in Box 1.

Box 1: Search terms included within each search concept

Search Concept	Search terms within each concept
Congenital Hypothyroidism (CHT)	congenital adj2 hypothyroid* primary adj2 hypothyroid* cretin* myxodem* myxoedem*
Newborn	Newborn Infant neonat*
Screening	screen*
Diagnosis	diagnos* manage*
Outcome	biomark* development* IQ Growth behaviour* social* psycho*
Treatment	treatm* therap* drug* manage*
Economics	econom* cost* financ*

Initially, a general search was carried out combining the *CHT, Newborn, Screening* and *Countries* concepts. Following this, searches were carried out that excluded the *Screening* concept, in order to identify any additional relevant papers that did not contain the search term screen*. Reviews were excluded during abstract selection (see Box 2 for exclusion criteria); however reference lists of all review papers retrieved by the searches were searched in order to identify additional papers.

Abstract Selection

All retrieved abstracts were reviewed against the inclusion and exclusion criteria in Box 2.

Box 2: Inclusion and Exclusion Criteria for Abstract and Study Selection

Inclusion criteria	Exclusion criteria
Studies of newborn screening for CHT involving ≥ 20 participants	Studies of CHT focusing on incidence rate, aetiology, iodine deficiency and/or associated anomalies
Papers published before July 2010	Screening practices not relevant to the UK (e.g. screening using T4 or a combined T4/TSH test on the newborn bloodspot, using cord blood, or selecting infants)*
Studies from countries with newborn screening and management practices relevant to the UK	Papers reporting experience with 'pilot' screening programmes (established for <3 years)
Screening for CHT undertaken within the newborn period (first 6 months of life)	Studies involving less than 20 participants[§]
Screening test using TSH assay on the newborn bloodspot (relevant to UK testing at 5-8 days of age)	Review papers

*The exclusion criterion involving the screening assay (i.e. whether TSH alone or TSH and T4 were measured) was not applied to studies that *only* reported *longer-term outcomes* for children living with CHT. Such studies were included if (1) the method of detection was through newborn bloodspot screening and (2) treatment was offered early in life.

[§]One study retrieved through Embase addressed parent responses to false positive screening results[6] – this paper was exceptionally included as (1) the qualitative methodology did not necessitate a larger sample size for validity and (2) no other studies focused on this research question for parents of children with CHT were identified.

Papers which concerned reviews of previously published studies, were searched for relevant references and useful background information but were not included in the systematic review. All papers (n=498) retrieved from the first search, undertaken through Embase, were reviewed against the inclusion and exclusion criteria by two reviewers (FO and RK), and inter-rater agreement was evaluated. As the agreement was high for this initial search (82%), one reviewer (FO) searched through the remaining abstracts.

Table 1: Agreement between reviewers on abstract selection (including kappa statistic)

		Reviewer 2		
Reviewer 1		*Exclude*	*Include*	*Total*
	Exclude	**201**	59	260
	Include	31	**207**	238
	Total	232	266	**498**

Statistical analysis	
Actual agreement	82%
Expected agreement	50%
Kappa statistic	0.64

Data Extraction

A hard copy of every paper that met the abstract selection criteria was retrieved, and data extracted from each paper by one reviewer (FO). The data extraction sheet was developed through an iterative process involving pre-specifying data required to address the research questions, testing on a small sample of papers and further refinement of the data extraction sheet based on the results. The final data extraction sheet recorded details of screening, re-screening and diagnostic methods used by each study, such as type of test, timing, cut-off values, sensitivity, specificity, positive predictive value and false positive rate. Moreover, details relating to management were also recorded, such as timing, dosage, formulation, type and frequency of clinical review. Finally, details of outcomes were noted, including the tests of outcomes used, length of follow-up, key results and conclusions.

Box 3: The GRADE approach to quality rating

*Systematic reviews were also rated as high if these conformed to Cochrane-type methodology.

Levels of quality for evidence using the GRADE approach	
Underlying methodology	***Quality rating***
Randomized trials; or double-upgraded observational studies.*	High
Downgraded randomized trials; or upgraded observational studies.	Moderate
Double-downgraded randomized trials; or observational studies.	Low
Triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports.	Very low

Factors that may decrease the quality level of a body of evidence
1. Limitations in the design and implementation of available studies suggesting high likelihood of bias.
2. Indirectness of evidence (indirect population, intervention, control, outcomes).
3. Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).
4. Imprecision of results (wide confidence intervals).
5. High probability of publication bias.
Factors that may increase the quality level of a body of evidence
1. Large magnitude of effect.
2. All plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect.
3. Dose-response gradient.

Quality assessment

Each paper included in the review was assigned a quality rating by the reviewer (FO) at the time of data extraction. Ratings were based on the GRADE approach developed by the Cochrane Collaboration (see Box 3 above).

Initial ratings were based on the study design alone but these were then increased or decreased if a study had additional features influencing quality. Papers were given one of the following ratings for quality: Low, (L), Medium (M), and High (H). Due to the large number of papers receiving M quality rating, these papers were quality rated a second time, and assigned either a – or + rating.

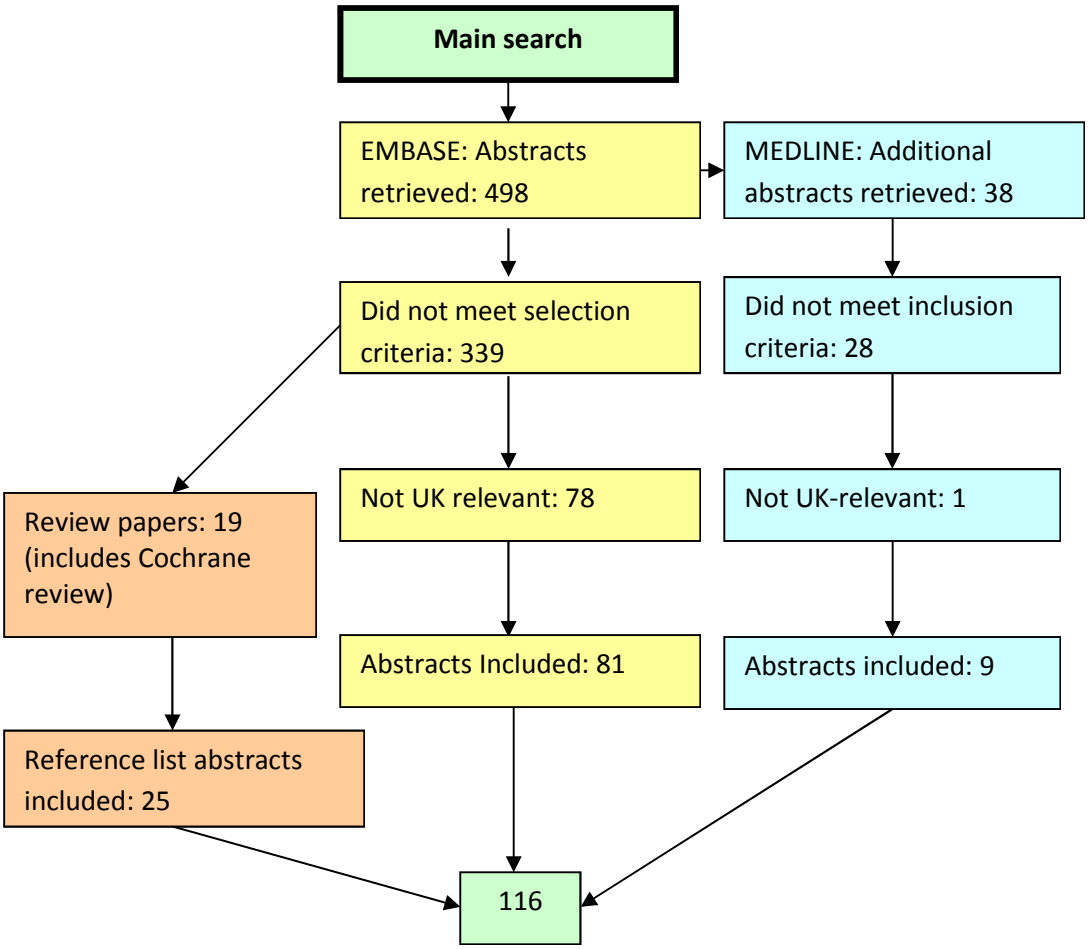
5.3 Papers retrieved for review

A total of 116 papers were included in the review (Figure 1). Initial searches through Embase retrieved the majority of papers and, of 498 abstracts retrieved, 81 papers were included. Further searches retrieved a total of six papers from the Medline database. No papers were found through PsychInfo. One systematic review of levothyroxine dosage was identified through the Cochrane Trials Register.

Sixteen review papers were retrieved by the general search through the Embase database. Three additional review papers were identified through searching through reference lists of these review papers. Reference lists of these review papers were searched in order to identify any additional papers that had been missed by the electronic searches. This search yielded 25 more papers to be included in the literature review.

Evidence from the retrieved papers, relevant to each of the specific research objectives, are reviewed and discussed under each section of the report below.

Figure 1: Flowchart of search strategy and abstract selection process



6 Results of the EWG and Literature Review

Published evidence from the literature review, additional unpublished evidence and expert views were considered by topic-specific subgroups and an interpretation of the evidence presented to the EWG. The EWG considered this evidence then made recommendations for revisions to the ICR Standards.

In this section of the report, the evidence considered by each subgroup, and the final interpretation of the evidence and recommendations of the EWG are presented by topic.

EWG Topic Subgroups

Each subgroup was allocated a range of topic-related standards to consider. The evidence report was discussed by EWG subgroup members who then also sought additional evidence from published and unpublished sources, as well as from invited experts, before revising the standards. Each set of revised standards agreed by a subgroup was then brought to the full EWG as a set of recommended revisions for approval. In a final meeting, the full EWG agreed the final revisions to be recommended.

The evidence review and interpretation of this by the EWG is presented below, subdivided into five sections corresponding to the topic subgroups of the EWG.

7 Performance of the TSH assay as a screening test

7.1 Original (2005) ICR standards relevant to screening test performance

The test performance subgroup considered the need for revisions to standards 1-10 from the 2005 document (Box 4).

EWG members drew on four sources of evidence:

- Evidence from the literature review of test performance by Ms F Olafsdottir & Dr R Knowles
- Minutes of the Initial Clinical Referral Standards Working Group of 2004 at which evidence was discussed and current standards were established.
- Evidence from the Great Ormond St study of borderline screen test results from Dr C Peters & Ms S Langham
- Evidence relating to the costs of 'missed' cases.

Box 4: Standards 1 to 10 (2005)

1. Babies in whom the TSH concentration is greater than 20mU/L whole blood on the initial screening sample should be considered to have a positive screening test result for CHT.
2. Babies in whom the TSH concentration lies between 10 and 20mU/L whole blood on the initial screening sample should be considered to have a borderline result for CHT.
3. Babies in whom the thyroid stimulating hormone (TSH) concentration is less than 10mU/L whole blood in the initial screening sample should be considered to have a negative screening result for congenital hypothyroidism (CHT). Collection and assay of the blood spot sample should not be delayed in premature infants for whom it should be repeated when the baby attains the equivalent of 36 weeks gestation. Similarly it should not be delayed in babies who have received a blood transfusion for whom the sample should be repeated 72 hours later.
4. On detecting a borderline screening result, a repeat assay should be performed on the original blood spot card before a second blood spot sample is requested.
5. If the TSH concentration is less than 10mU/L whole blood in this second assay, the baby should be considered to have a negative screening result for CHT.
6. If the TSH concentration is greater than or equal to 10mU/L whole blood in this second assay, a second blood spot sample should be requested.
7. This second blood spot sample should be, taken by a midwife or if the baby is still in hospital, by the clinician responsible for their clinical care.
8. Parents of babies with borderline results, irrespective of whether the baby is at home or in hospital, should be informed of the reason for a second blood spot sample and given appropriate information about how and when they will hear the result of repeat tests.
9. After being informed of the need for a second blood spot by the screening laboratory, the designated maternity screening lead for that area is responsible for notifying the appropriate health professional and ensuring that the second blood spot sample is taken as a matter of urgency. In the case of second blood samples for initially borderline results (as defined above) this should be no sooner than one week from the date of the original blood spot sample.
10. The result of the second blood spot sample should be available within 2-4 working days of receipt by the screening laboratory and, if the TSH concentration is greater than or equal to 10mU/l whole blood, the screening result should be considered positive.

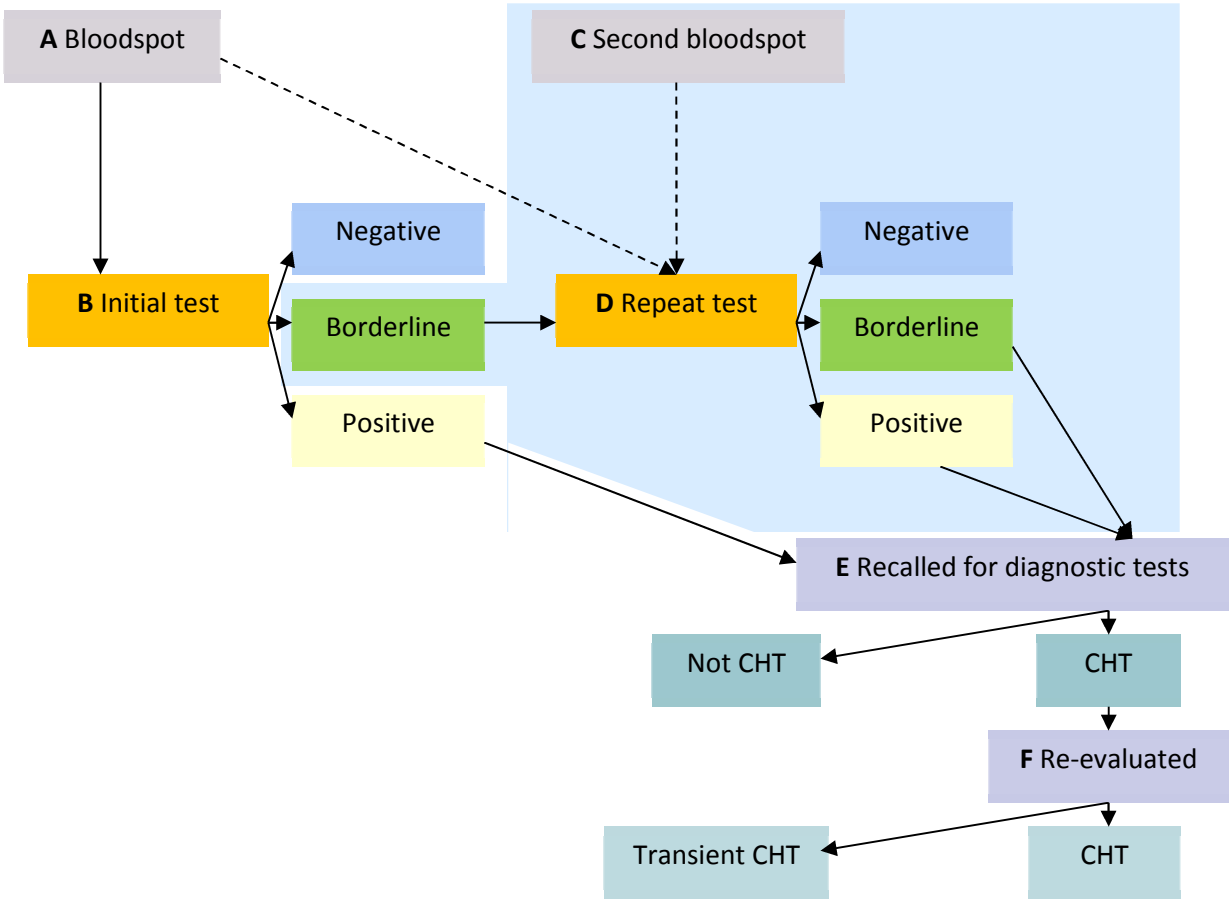
7.3 Results from the evidence review

Sixteen papers described aspects of test performance using, as the screening test, a TSH assay on the newborn bloodspot taken at 3-8 days of age. These papers described a range of practice in different countries and during different periods.

It was common practice to use both a borderline cut-off and a positive cut-off value for the TSH assay results. Children whose first bloodspot TSH was above the positive cut-off were recalled for diagnostic confirmatory testing. For children whose bloodspot TSH was higher than the borderline cut-off but below the positive cut-off, a repeat test was usually undertaken on the same bloodspot sample before requesting a new blood test or alerting the family, however sometimes a new sample was requested at the same time as repeating the test on the original sample. Children were usually only recalled for diagnostic testing if they had a borderline or positive value on the repeat test.

Many studies described results of screening at stage E, without clarifying the proportion of children who reached this stage after an initial positive or borderline result at B. The methods for the repeat screening test procedure (blue shaded area of Figure 2) varied by programme, with some repeating the screening test on the original bloodspot sample and others requesting a new sample for testing. Some children who were defined as having CHT (true positives) at stage D underwent further evaluation at a later time point and were subsequently defined as transient CHT (stage E). The heterogeneity between screening protocols was marked between countries and over time, thus presenting considerable difficulty in estimating test performance at different cut-off levels.

Figure 2: Overview of screening procedures most commonly described



In Table 2, papers which provided information about test performance are grouped by cut-off values used to define a positive screening result on TSH assay (whole blood). For papers that defined a borderline screening result after the initial test, the borderline cut-off values are also presented. Four of the papers included in Table 2[7-10] either did not fully report screening test performance or contained insufficient information for sensitivity, specificity and positive predictive values to be calculated. Further discussion of the findings of these papers is therefore limited to the 13 papers with adequate data for these estimations.

Table 2: Screen positive cut-off values in papers describing test performance

POSITIVE cut-off value	Author	Country	Year of publication	Age at bloodspot	Test method	BORDERLINE cut-off value
≥8mU/l						
	Nakamizo[9]*	Japan	2007	4-6 days	Enzyme-linked immunoabsorbent assay	-
≥15mU/l						
	Gjurkova[8]*	Macedonia	2008	2-5 days	DELFIA	-
≥17mU/l						
	Hopfner[11]	Germany	2005	≥3 days	Corning radiolabelled	-
≥20mU/l						
	Pharoah[12]	UK	1992	5-8 days	Not stated	**≥5mU/l**
	Law[13]	Wales	1998	7 days	Immunoradiometric assay	-
	Korada[7]*	UK	2008	6 days	DELFIA	**≥6mU/l**
	Korada[14]	UK	2010	6 days	DELFIA	**≥6mU/l**
≥25mU/l						
	Hummer[15]	Denmark	1982	5 days	Double antibody RIA	-
	Foo[16]	N. Ireland	2002	6-8 days	1983-86 Pharmacia 1986 DELFIA	**≥10mU/l**
	Jones[17]	Scotland	2006	6-7 days	1994 IRMA (IDS) 2002 DELFIA	**≥8mU/l**
≥40mU/l						
	Dockeray[18]	Ireland	1980	4-5 days	Pharmacia, Uppsala RIA	**≥20mU/l**
	Ray[19]	Scotland	1997	7 days	1979-82Corning radiolab. 1982-89 polyclonal Ab 1989-93 IRMA (IDS)	**≥25mU/l**
	Corbetta[20]	Italy	2009	3-4 days	AutoDELFIA	**≥10mU/l**
≥50mU/l						
	Gruters[21]	Germany	1983	5 days	Lab-specific RIA	**≥20mU/l**
	Ilicki[22]	Sweden	1988	5 days	Not stated	-
	Pettersen[10]*	Norway	1995	newborn	Before 1988 Radiolabel. 1988 DELFIA	**≥15mU/l**

*Insufficient data to calculate (or verify reported) test performance.

Using information from 12 papers which provided sufficient data, the sensitivity, specificity, positive predictive value (PPV) and false positive rate (FPR) for the screening test were calculated. Within the group of children who had false positive (FP)screening results were (1) those who were found on diagnostic tests not to have CHT despite a positive screening results, and (2) those who were recognised after a period of treatment to have transient CHT. Test performance was calculated after assuming only those who were negative at diagnostic testing to be FP. If transient CHT was evaluated, this is noted in Table 3B. Where possible, the proportion of all those screened who had (i) a repeat screening test on the same bloodspot (Figure 1, A and D), (ii) a repeat screening test on a new bloodspot (Figure 1, C and D), or (iii) were recalled for diagnostic confirmation (Figure 1, E) is provided in Table 3B.

Box 4: Calculating screening test performance

		Disease			Test performance:
Screening test results		yes	no	total	Sensitivity = TP/(TP+FN) Specificity = TN/(FP+TN) Positive predictive value (PPV) = TP/(TP+FP) False positive ratio = FP/total screened
	positive	True positive (TP)	False positive (FP)	TP+FP	
	negative	False negative (FN)	True negative (TN)	FN+TN	
	total	**TP+FN**	**FP+TN**	**Total screened**	

The information provided by each of the 12 studies is presented in Tables 3A and 3B below. Only three studies used a single cut-off without a borderline (Table 3A). Hummer[15] tested T4 levels on bloodspots with TSH>25mU/l before repeating the TSH assay and findings from this complex testing process cannot be directly compared with other studies. Despite a higher cut-off, the sensitivity and specificity of Ilicki's[22] screening test was similar to Law[13], whilst the PPV (proportion of children with a positive screen who have CHT) described by Ilicki was lower. As Law's study is based on a larger population, provides greater detail of test performance and is higher quality, results are likely to be more reliable.

Test performance within the remaining nine papers is presented in Table 3B; these studies used a borderline and a positive cut-off level. After a borderline result, the TSH assay was repeated on the same bloodspot sample (except two studies[12 20] which used a second bloodspot sample). A positive screening test was either two results above the borderline or one result above the positive cut-off level.

Population coverage (percentage of newborns screened), reported in three papers was 97% or over in the most recent years studied. Only two studies[12 19] described actively identifying 'missed cases' or late diagnoses (false negative [FN]) using multiple sources; these suggest that there may be one FN screening result for every 200,000 to 300,000 babies screened. FN results are likely to be underestimated by most investigators as there were no procedures for following up negative screening results. Consequently, studies are likely to overestimate sensitivity. The lowest sensitivity at any cut-off level was 95%, suggesting the TSH newborn bloodspot assay is sensitive whether a borderline or single positive cut-off is used. The specificity of the TSH assay across all cut-off levels was above 99%.

Most variation between studies was in the proportion of children whose bloodspot was re-tested or who were recalled for diagnostic tests, and PPV. Studies in Table 3B are arranged in order of ascending cut-off level, thus Korada[14] and Pharoah[12] have low cut-off levels but only around 30% of children who have a positive screen are diagnosed with CHT. At higher cut-off levels, the PPV rises to 60-70%, similar to that estimated by Law using a single positive cut-off of 20mU/l. Exceptions to this, e.g. Dockeray[18] and Corbetta[20], may be related to differences in screening procedures.

Table 3A: Screen positive cut-off values in papers describing test performance

Author	Total screened	Coverage	Sampling process	TSH cut-off	TP	FP	FN	TN	Sensitivity	Specificity	PPV	FPR
Results from a single assay												
Law[13]	445,902	99.8%	Used cut-off of >20mU/l for referral for diagnostic tests. Test performance results provided for positive screen (defined as single result **>20mU/l**).	>20	136	49	*0*	445,717	100.00%	99.99%	73.51%	0.01%
Ilicki[22]	188,340	99.8%	Used cut-off of >50mU/l for referral for diagnostic tests. Test performance results provided for positive screen (defined as single result **>50mU/l**).	>50	68	50	0	188,222	100.00%	99.97%	57.63%	0.03%
Hummer[15]	127,111 (126,966)*	-	Used cut-off of >25mU/l and tested T4 on same sample; if T4 normal (>45nmo/l), then repeated TSH on same sample. Test performance results calculated for initial TSH assay.	-	32	785	1	126,294	96.97%	99.38%	3.92%	0.62%

Table 3B: Screen positive cut-off values in papers describing test performance

Author	Total screened	Coverage	Sampling process		TP	FP	FN	TN	Sensitivity	Specificity	PPV	FPR
Results from combined assays (e.g. repeated screening tests for borderline samples)				**Double screen**								
Korada[14]	63,208	-	Used cut-off of ≥6mU/l and repeated screen on same sample. If two results ≥6mU/l or first result >20mU/l, then referred for diagnostic confirmation. Test performance estimated for positive screen (defined as two results ≥6mU/l or one result >20mU/l).	n=98	33	87	0	63,088	100.00%	99.86%	27.50%	0.14%
Pharoah[12]	193,226	85%-97%[§]	Used cut-off of >5mU/l and repeated screen on same sample, then requested new sample and tested again. Test performance results provided for positive screen (defined as three results >5mU/l or one result >20mU/l).		60	162	2[‡]	193,002	96.77%	99.92%	27.03%	0.08%
Jones[17]	561,833	-	Used cut-off of ≥8-24mU/l for repeating screen on same sample, or ≥25mU/l for referral for diagnostic testing. Test performance results provided for positive screen (defined as two results ≥8mU/l or one result ≥25mU/l).		158	92	0	561,864	100.00%	99.98%	63.20%	0.02%
Foo[16]	(295,670)[†]	-	Used cut-off of ≥10-25mU/l for repeating screen on same sample, or >25mU/l for referral for diagnostic testing. Test performance results provided for positive screen (defined as two results ≥10mU/l or one result >25mU/l).		85	46	0	295,539	100.00%	99.98%	64.89%	0.02%
Hopfner[11]	298,175	99.1%	Used cut-off of ≥17mU/l and repeated screen on same sample. Test performance results provided for 129 positive screens (defined as two results ≥17mU/l).	All ≥17	90	39	0	298,046	100.00%	99.99%	69.77%	0.01%

Table 3B (continued): Screen positive cut-off values in papers describing test performance

Author	Total screened	Coverage	Sampling process		TP	FP	FN	TN	Sensitivity	Specificity	PPV	FPR
Ray [11]	992,709	-	Used cut-off of ≥15-40mU/l for repeating screen on same sample, or >40mU/l for referral for diagnostic testing. Test performance results provided for positive screen (defined as two results **≥15mU/l** or one result **>40mU/l**).	0.01%	234	108	3‡	992,864	98.7n3%	99.99%	68.42%	0.01%
Dockeray [18]	76,224	-	Used cut-off of >20-40mU/l for repeating screen on same sample, or >40mU/l for referral for diagnostic testing. Test performance results provided for positive screen (defined as two results **>20mU/l** or one result **>40mU/l**).		19	31	1	76,174	95.00%	99.96%	38.00%	0.04%
Gruters [21]	63,200	98.0%	Used cut-off of ≥20-50mU/l for repeating screen on same sample, or >50mU/l for referral for diagnostic testing. Test performance results provided for positive screen (defined as two results **≥20mU/l** or one result **>50mU/l**).	0.37%	25	7	1	63,167	96.15%	99.99%	78.13%	0.01%
Corbetta [20]	629,042	-	All bloodspots >97.5% centile were repeated on same sample. If second test was: (1)<99% centile (<10-12mU/l), no further testing; (2)10-20mU/l – new bloodspot, ≥5mU/l referred; (3)20-40mU/l – new bloodspot/serum test, referred if ≥5 (bloodspot) or ≥10 (serum); (4)>50mU/l referred for diagnostic testing; Test performance results provided for positive screen (defined as three results **>10mU/l** or one result **>40mU/l**).	1.71%	435#	578	0	627,989	100.00%	99.91%	42.95%	0.09%

* Total screened after removal of invalid screens due to technical problem; † Total newborns during period – coverage not provided; § Variability over period of study; ‡ Reliable false negative count as traced through multiple sources; # includes 53 cases considered true CHT after diagnostic testing but later re-evaluated and found to be transient; if transient cases are considered false positive, then sensitivity=100.00%, specificity=99.90%, PPV=37.72% and FPR=0.10%.

Using the information provided within most papers, it is difficult to estimate the impact of having a borderline cut-off level on the frequency of repeat testing. However results from the studies by Ray[19] and Jones[17] are presented in Table 4 and demonstrate that, with the decrease in cut-off levels, there was an increase in the total number of screening test samples processed as a percentage of the total number of children screened. This suggests that there was an increase in the number of children who had a repeat test. If the repeat test was undertaken on the original sample, this would have implications for the volume of work in the laboratory and for the timeliness of screening test results, but would not result in an additional contact with the family.

Table 4: Increase in numbers of additional TSH assays required (repeated on same bloodspot) as borderline cut-off decreases (taken from Ray[19] and Jones[17])

Time period	Initial test	Repeat test	
	Borderline cut-off (mU/L)	*extra (repeat tests)*	*as % all children tested*
1980-82	>25-50	1,180	0.58%
1983-89	>15-40	4,135	0.90%
1990-01	>10-40	14,725	2.04%
2002-03	>8-25	18,330	17.68%

False negative results

Leger[23] assessed 'missed' cases or false negative screen results in the first nine years of the French newborn screening programme, during which over 6,000,000 infants were screened and 1,742 infants diagnosed with CHT. Of 50 cases not detected by screening and diagnosed clinically between ages 7 days and 5 years 2 months, 27 were missed due to samples not being taken, being lost en-route to the laboratory or being mis-read in the laboratory, whilst 23 were re-evaluated and found to be negative on the original bloodspot also. Leger noted that less false negatives occurred in more recent years of the programme, however it is unclear if follow-up was sufficiently long to verify this.

Psychological impact of false positive results

Two studies considered the impact on parents of a false positive screening result.[6 24] the majority of families had strong emotional reactions at the time of finding out that the screening result was a false positive, but insecurity about their child's health persisted only in a minority beyond one year of age.[24] In the longer-term, the child-parent relationship was affected in some families up to 4 years of age.[6] It is likely that additional family and coping factors may influence the persistence of problems.

7.4 Interpretation of the published evidence

Evidence from the literature review suggested that the sensitivity and specificity of the TSH assay is high and that these do not differ markedly if either a single screening cut-off level of around 20mU/l or borderline cut-offs from 5-20mU/l are combined with positive cut-off levels of 20-50mU/l. As most screening programmes did not actively seek 'missed cases', false negative rates presented by most studies are likely to be underestimated and Leger suggests up to five cases per year could be missed. The PPV varies with TSH cut-off level and is best with either a single positive cut-off of around 20mU/l or borderline cut-off levels over 10mU/l. When borderline cut-off levels are below 10mU/l, the number of repeat tests increases markedly with implications for laboratory workload and timeliness.

Members of the test performance subgroup considered that all published evidence, except for Corbetta's study, was based on laboratory methods no longer in use, and therefore the cut-off values used could not be applied to current UK laboratories which universally employ AutoDELFIA methods. The published evidence was not considered adequate to support a specific cut-off threshold.

7.5 Additional evidence relating to development of the 2005 standards

A review of laboratory TSH test thresholds was undertaken in 2004 to inform the 2005 standards. Written reports indicated that, in 2004:

- 11 laboratories were using Autodelfia and one manual Delfia methods
- Presumptive negative cut-offs were <6 to <13 (4 used <8 and 4 used <10) mU/L in whole blood
- Borderline cut-offs were >6 to <30 (2 used <19; 2 used <20; 2 used <25) mU/L in whole blood
- Presumptive positive cut-off was >20 mU/L in whole blood
- It was recognised that regional variance in thresholds may be due to genetics or iodine deficiency and that these should be mapped
- A consensus was reached that national cut-offs should be: <10mU/L=negative, ≥11-20mU/L=borderline, >20mU/L=positive. This consensus was based on the fact that these values were in keeping with the majority of contemporary reference ranges and would establish uniformity across the UK.

- *EWG members concluded that the cut-off values in the 2005 standards were established by a consensus of expert opinion.*

7.6 Great Ormond St Hospital 'Borderline Study' 2011

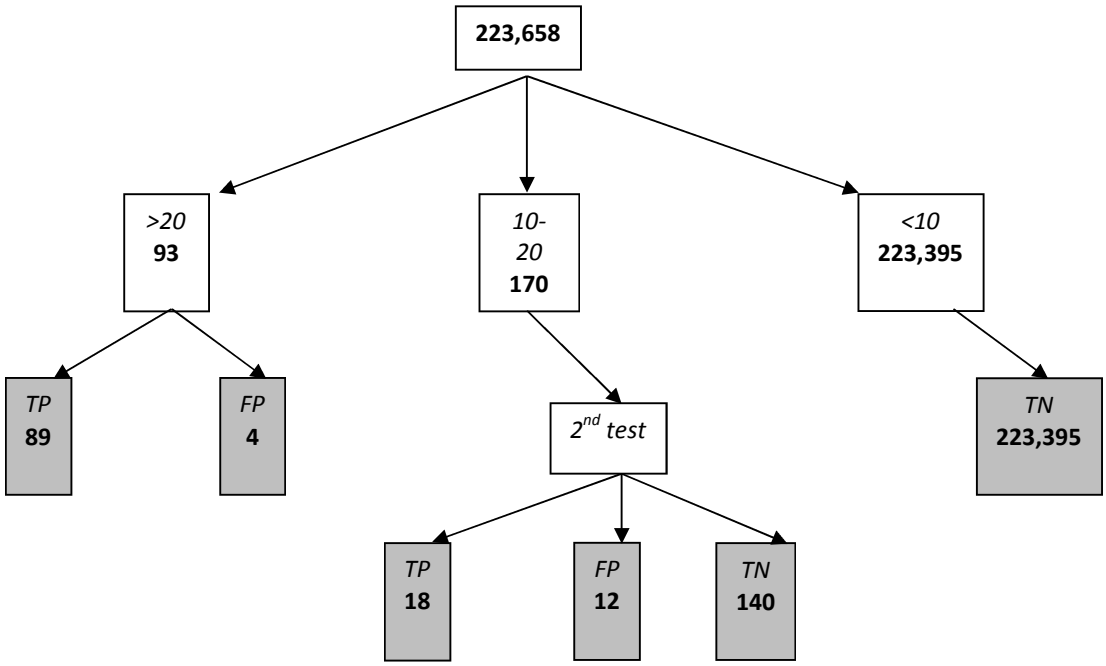
Dr Catherine Peters and Ms Shirley Langham provided original data from a study at Great Ormond St (GOS) Hospital, which aimed to follow-up outcomes in children who had been diagnosed with CHT after two borderline (TSH ≥6mU/L and <10mU/L on bloodspot) screening test results. Using this dataset, which included the bloodspot TSH values of 223,658 newborns

screened at GOS, the number of children who would require a repeat bloodspot and further investigation were compared for borderline cut-off thresholds of 6mU/L and 10mU/L (Figure 3).

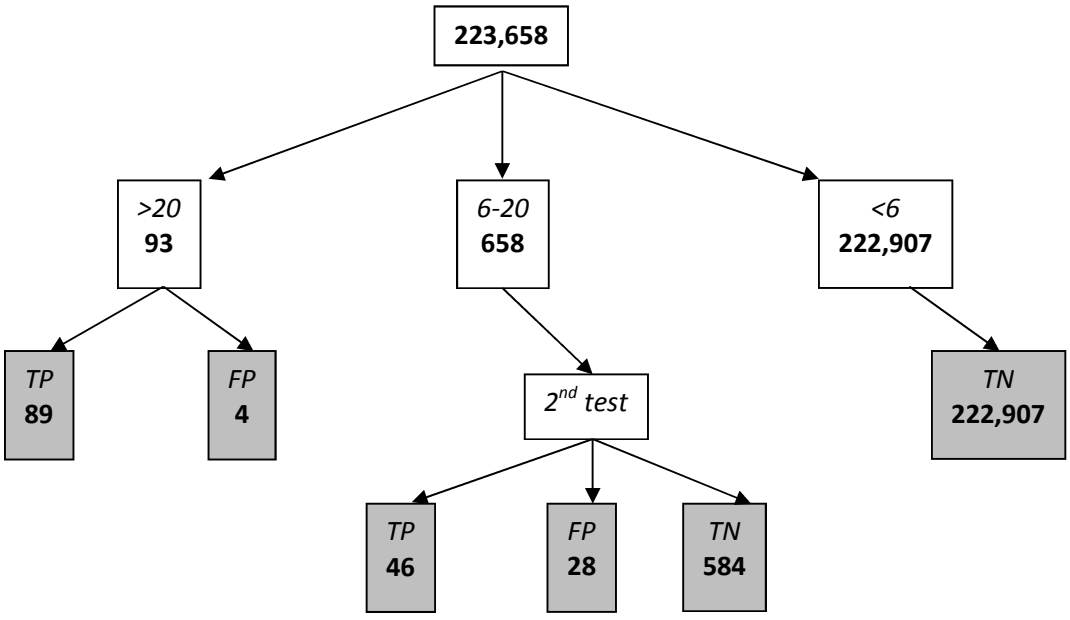
Figure 3: GOS borderline study data – comparison of cut-off thresholds

Key: ***bold text***=number of children*; italics*=TSH cut-off level*; Screen results - true positive (TP), false positive (FP), true negative (TN), false negative (FN)*

Cut-off: ≥10mU/L to <20mU/L



Cut-off: ≥6mU/L to <20mU/L



Box 5: Assumptions made in estimating test performance using the GOS study data

True Positive (TP) – starting treatment after a positive result on diagnostic investigation indicates that the child has a confirmed diagnosis of CHT. It is possible that some of these children do not continue treatment lifelong.
False Positive (FP) – children who have repeated positive screening results but do not start treatment after diagnostic investigations. It is possible that starting treatment is also dependent on clinician variation, or that some children start treatment later in life.
True Negatives (TN) – children who have a negative initial bloodspot, or who have an initial positive screening bloodspot then a second negative bloodspot. If children are not followed up to determine if there are any 'missed' cases (or **False Negatives [FN]**), all will be assumed to be true negatives.

Using the GOS study data, Figure 3 compares the number of children who would be referred for investigation with presumed positive screening test results when the cut-off is TSH>6mU/L with >10mU/L. Children who are treated with levothyroxine after diagnostic testing are deemed to be true cases (either true positive or false negative results of screening). As children with negative screening test results were not followed up, they are all assumed to be 'true negatives', however there may be missed cases of CHT within this group. Of the 223,658 children screened between January 2006 and December 2007 by the GOS laboratory, 170 had a TSH result on or above 10mU/L and were referred for further testing. Of these, 30 were referred for diagnostic investigation and 18 were given treatment. Using the cut-off of ≥6mU/L, 658 children would have required re-testing, of which 74 were referred for diagnostic investigation and 46 given treatment.

Table 5: Test performance estimates using data from GOS borderline study

Cut-off TSH	TP	FP	TN	FN	sensitivity	specificity	PPV	FP rate
≥10 mU/L	107	16	223,535	0	100.00%	99.99%	86.99%	0.01%
≥6 mU/L	135	32	223,491	0	100.00%	99.99%	80.84%	0.01%

Key: True positive (TP), false positive (FP), true negative (TN), false negative (FN), positive predictive value (PPV)

Test performance estimated using GOS study data was compared with three published studies using Delfia laboratory screening methods (see Table 6 below):

- *The GOS study dataset, using the Autodelfia method, provided the best direct comparison of cut-off levels and demonstrated that, whilst sensitivity and specificity did not alter, the PPV was higher for a cut-off of 10mU/L than 6mU/L. However, outcomes were based on commencement of treatment immediately after diagnostic testing therefore permanence or severity of CHT diagnoses could not be assessed.*
- *The EWG concluded that sensitivity and specificity was similar when the upper cut-off is 20-25mU/L and lower cut-off is 5-10mU/L using either testing method.*
- *EWG members considered that this would support an upper cut-off value of 20mU/L.*

- *Some studies suggested that the false positive rate was 4-7 times higher and PPV was halved when lower cut-offs of 5-6mU/L - 20mU/L were used compared with cut-off of 8-10mU/L - 25mU/L, however EWG members felt that lower and upper limits should not be viewed separately using these data as laboratories often adjusted the range as a whole.*

Table 6: Comparing screening test performance for three studies using Delfia methods with the Great Ormond St study dataset:

			Number	Sensitivity	Specificity	PPV	FP rate
6mU/L – 20mU/L							
Korada	2010	Delfia	63,000	100.0%	99.9%	27.5%	**0.14%**
8mU/L – 25mU/L							
Jones	2006	Delfia	562,000	100.0%	99.9%	63.2%	**0.02%**
10mU/L – 25mU/L							
Foo	2002	Delfia	296,000	100.0%	99.9%	64.9%	**0.02%**
10mU/L – 20mU/L							
GOSH study	2007	Autodelfia	223,658	100.0%	99.9%	87.0%	**0.01%**
6mU/L – 20mU/L							
GOSH study	2007	Autodelfia	223,658	100.0%	99.9%	80.8%	**0.01%**

7.7 Additional evidence relating to long-term outcomes and late diagnoses

Cognitive outcomes in unscreened populations

Grosse and Van Vliet's paper (2011) reviewed population-based studies which measured cognitive test scores in children with clinically diagnosed CHT born prior to the introduction of newborn screening.[25] The authors found that the prevalence of CHT increased from 1 in 6,500 before the introduction of screening to 1 in 3,000 after, suggesting that screening might have led to increased detection of milder CHT cases that were not previously recognised clinically (i.e. subclinical cases). In four studies of children with clinically diagnosed CHT, 8-28% had intellectual disability (IQ <70) and the mean IQ was 85 (minus 1 SD). Among children with subclinical CHT, the risk of overt intellectual disability was lower than previously estimated but IQ appeared to be reduced by on average seven points and increased behavioural abnormalities were documented.

- *As a screening threshold for TSH of 10mU/L may already detect around twice as many cases as would become apparent clinically in an unscreened population, the EWG did not consider this sufficient evidence to support lowering the cut-off.*

Economic effects of late diagnosis

The economic effects of seven points loss of IQ for an individual child was reviewed in the literature relating to environmental lead exposure and effects on IQ. Two sources estimated the lifetime economic effect, in earnings lost, of a reduction in childhood IQ of seven points:

- £23,800 across the lifetime

Source: Dr Gul IZMIR, 1993 NSW EPA, reference: "Interdepartmental Lead Taskforce: New South Wales Lead Management Action Plan. Background Papers" Publ. NSW EPA 1994. Accessed at http://www.lead.org.au/lanv5n3/lan5n3-4.html on 17-06-2011. (1 point = £3,400; at exchange rate £1 = AU$ 1.53)

- £9,527- £41,580 across the lifetime

Source: President's Task Force on Environmental Health Risks and Safety Risks to Children, Eliminating Childhood Lead Poisoning: A Federal Strategy Targeting Lead Paint Hazards, February 2000, pA-26. Accessed on 17-06-2011 at http://yosemite.epa.gov/ochp/ochpweb.nsf/content/leadhaz.htm/$file/leadhaz.pdf (1 point = £1,360-£5,940; at exchange rate £1 = US$ 1.62)

Long-term outcomes and permanence of CHT

Published evidence about later cognitive outcomes related to different screening cut-off levels was noted by the EWG to be limited, highlighting the need for longer-term outcome studies with a particular focus on transient or mild hypothyroidism.[26 27]

- *EWG members concluded that test cut-off levels could only be considered in relation to the outcomes of confirmatory diagnostic test results and investigations of transience of CHT at 2-3 years of age.*

Studies of longer-term outcomes did not always describe a 'withdrawal' or 'trial off-therapy' to confirm permanence of CHT at 2-3 years of age.[28] Outcomes after newborn screening were often described only up to diagnostic confirmation or the initiation of treatment.

- *EWG members noted that, as a 'trial off-therapy' to confirm permanent CHT often did not occur within the first three years of life, ICR standards should provide guidance as to when a 'trial off-therapy' is warranted.*

7.8 EWG Final Recommendations and Revised Standards relating to Screening Test Performance

Generic standards:

The expert working group (EWG) considered that some standards should be regarded as generic, i.e. applying across all screening programmes and need not be repeated within the standards specific to CHT. Standards which on this basis could be removed included:

Standard 3 (2005): Collection and assay of the bloodspot sample should not be delayed in premature infants for whom it should be repeated when the baby attains the equivalent of 36 weeks gestation. Similarly it should not be delayed in babies who receive a blood transfusion for whom the sample should be repeated 72 hours later.

- *The EWG considered that standards for preterm babies and blood transfusion were covered elsewhere in the standards and should not be repeated in the congenital hypothyroidism (CHT)-specific screening standards.*

Standard 7 (2005): 'This second blood spot sample should be taken by a midwife or, if the baby is still in hospital, by the clinician responsible for their clinical care.

- *The EWG considered that this standard should be covered in generic standards about responsibility for taking second blood spots. They recommended deletion from CHT-specific screening standards.*

Standard 8 (2005): Parents of babies with borderline results, irrespective of whether the baby is at home or in hospital, should be informed of the reason for a second blood spot sample and given appropriate information about how and when they will hear the result of repeat tests.

- *The EWG considered that this standard should be covered in generic standards about responsibility for taking second blood spots. They recommended deletion from CHT-specific screening standards.*

Standard 9 (2005): After being informed of the need for a second blood spot by the screening laboratory, the designated maternity screening lead for that area is responsible for notifying the appropriate health professional and ensuring that the second blood spot sample is taken as a matter of urgency. In the case of the second blood spot samples for initially borderline results (as defined above) this should be no sooner than one week from the date of the original blood spot sample.

- *The EWG considered that the first statement in this standard should be covered in generic standards about responsibility for taking repeat blood spots. The second statement is now covered by the revised standard 4. Members recommended deletion of this standard from the CHT-specific screening standards.*

Standard 10 (2005): The result of the second blood spot sample should be available within 2-4 working days of receipt by the screening laboratory and, if the TSH concentration is greater than or equal to 10mU/L whole blood, the screening result should be considered positive.

- *The EWG considered that this standard should be covered by new standard 3 which defines the positive cut-off for a presumed positive screening test and the need for referral. The time period for laboratories to report tests should be covered by new standard 1. Members therefore recommended deletion of this standard.*

Newborn blood spot testing pathway

EWG members acknowledged that previous guidelines were unclear about the procedure to be followed for testing blood spots. A standard pathway for blood spot testing as agreed and a flow diagram developed for guidance (see Section 2 for the Screening Protocol flow diagram).

New headings were proposed for each section of the standards relating to testing:

- Section 1 heading: 'The screening protocol'
- Section 2 heading: 'Categorisation of initial screen result'
- Section 3 heading: 'Borderline screen result'

Standards relating to the testing pathway were amended to comply with the standard testing pathway:

Section 1: The screening protocol

- *To maintain consistency with standards for other conditions, a new additional standard was proposed (new Standard 1). Details of the analytical cut-off and laboratory test process were included in this standard:*

New Standard 1 <u>The initial screening sample</u> (not included in 2005 standards):
TSH analysis is performed on a single spot from the initial dried blood sample.
Samples with TSH ≥ a preliminary threshold (analytical cut-off*) of 8 mU/l whole blood (WB) are retested in duplicate from the same card but a different spot(s). Action is taken on the triplicate mean result.
Second sample – TSH is analysed in duplicate and action taken on duplicate result.
Timeliness of analysis – analysis is timed to permit referral of screen positive results within 2-4 working days of sample receipt.

*The analytical cut-off is set at 20% below the screen action cut-off of 10mU/L WB to allow for natural variation in the TSH assay (i.e. the coefficient of variation, CV=10%) and to minimise the effect of volumetric variability that occurs in dried blood spots. Re-testing also acts as confirmation of correct sample identification.

Section 2: Categorisation of initial screen result

- *The EWG recommended that Standards 1-3 (2005) became standards 2-4 in the new version and are re-ordered so that negative, then positive, then borderline test results are defined.*
- *EWG members reviewed the evidence for changing the cut-off level and concluded that there was insufficient evidence, in particular using the Autodelfia process, to support defining a new cut-off level. The cut-off level defined in the new standards was therefore not altered from previous standards.*

New Standard 2. Babies in whom the TSH concentration is <10mU/L whole blood in the initial screening sample should be considered to have a negative screening result for CHT
Report CHT not suspected.

New Standard 3. Babies in whom the TSH concentration is ≥20mU/L whole blood on the initial screening sample should be considered to have a positive screening result for CHT
Report and refer CHT suspected.

New Standard 4. Babies in whom the TSH concentration is ≥10mU/L and <20mU/L whole blood on the initial screening sample should be considered to have a borderline result for CHT.

Section 3: Borderline screen result

- *Standards 4-6 (2005): These should become standards 5-7 in the new version and they define the actions to be taken after a borderline test result.*

New Standard 5. On detecting a borderline result a second blood spot sample is to be taken 7-10 days after the initial sample.[1]

- *EWG members considered it important to recommend a period of at least 7 days delay to allow normal stabilisation of TSH levels in newborns before taking a second blood spot sample.*

New Standard 6. If the TSH concentration is less than <10mU/L whole blood in this second sample, the baby should be considered to have a negative screening result for CHT.
Report CHT not suspected

New Standard 7. If the TSH concentration is ≥10mU/L whole blood in this second assay, the baby should be referred.
Report and refer as CHT suspected.

7.9 Recommendations for further research

Across the UK, screening laboratories use varying TSH assay thresholds as the cut-off to define positive and borderline screening results. EWG members also noted the lack of studies with long-term population follow-up to determine false negative (missed) and transient CHT cases, necessary to evaluate screening test performance with Autodelfia. EWG members highlighted the need for further research to define optimum cut-off thresholds for the TSH assay that could be applied nationally.

[1] The working group proposed the wording of the standard as 'to be taken (as close to) but no sooner than 7 days after the initial sample', however this was changed 'to be taken 7-10 days after the initial sample' after the public consultation as it was considered that delay beyond 10 days would not be optimal.

8 Confirmatory Diagnostic Tests: Type, Timing and Association with Outcome

8.1 Original (2005) ICR standards relevant to diagnostic tests

Children who have a positive screening result are referred for further testing to confirm or exclude a diagnosis of CHT. The diagnostic test subgroup considered standards 16-21 and 25 from 2005 (Box 6).

EWG members drew on four sources of evidence:

- Evidence from the literature review of test performance (Olafsdottir & Knowles)
- Additional published evidence highlighted by the diagnostic test subgroup
- Data from an audit of diagnostic laboratories in Wales
- Expert evidence was considered by a subgroup consisting of a diagnostic laboratory director, consultant radiologist, thyroid research assistant and consultant paediatric audiologist.

Box 6: Standards 16 to 21, 25 (2005)

16. He designated clinician responsible for assessing the baby with a positive screening result should take a clinical history and perform a clinical examination.
17. Diagnostic tests considered essential are:
    a. Free T4 (plasma or serum)
    b. TSH (plasma or serum)
18. Diagnosis using Free T4 should be performed on a plasma or serum sample using the appropriate age-related reference range as defined by the laboratory in relation to the equipment used.
19. Clinicians may, using appropriate imaging techniques, investigate whether the thyroid gland is:
    a. Normally situated
    b. Of a normal size
    c. Of a normal shape
    d. Present at all
20. In addition, the following tests may be helpful:
    a. Thyroid antibodies
    b. Thyroglobulin (if the radiological imaging indicated that there is no thyroid present, thyroglobulin analysis should be requested)
21. The following tests may be performed on the mother to aid diagnosis:
    a. Thyroid antibodies
    b. TSH
    c. Free T4

25. Once treatment has been started, a baby should be reviewed, with a blood test at each visit. The timing of such visits may vary according to local circumstances but it is suggested should occur at 2 weeks, 6 weeks, 3 months, 6 months, 12 months after treatment is started, and thereafter as indicated, with management complying with BSPED recommendations for interpretation of tests and dosage. Visits may occur more frequently as necessary.

8.2 Results from the evidence review

Within the literature review, published studies describing the process of diagnostic confirmation were examined to assess the:

- timing of the diagnostic confirmatory testing
- range of tests undertaken at the time of establishing diagnosis
- purpose of undertaking each test.

Particular issues which were addressed were whether repeat screening after a borderline result might delay diagnostic testing, the timing of treatment onset after diagnostic testing, and discriminating between permanent and transient CHT.

Eighty-nine papers were reviewed which described some or all of the tests used for diagnostic confirmation of CHT in infants with a positive screening result. The screening test in 56 studies was a TSH assay on the newborn bloodspot, however the cut-off levels for a borderline or positive test varied or were not defined. The remaining studies used bloodspot T4 assay instead of, or in addition to TSH assay (n=8; Netherlands, Italy and US), or did not specify the screening test. Due to the heterogeneity of newborn screening procedures, no attempt was made to relate confirmatory diagnostic tests to the screening test used.

Timing of tests for diagnostic confirmation

The age at which diagnostic tests were undertaken varied between studies, however the mean (and/or median) age ranged from 10 to 27 days in most studies, thus most diagnostic testing took place during the second to fourth weeks of life. Diagnostic tests were normally undertaken prior to treatment, but some authors noted that thyroid scans might also be undertaken at a later age, in particular during a trial withdrawal of treatment to confirm permanence of CHT at 2-3 years of age.

In most studies, confirmatory tests were performed between birth and 60 days of age and most frequently included serum TSH, T4 and triiodothyronine (T3) levels and thyroid radioisotope scans (scintigraphy).

Clinical examination (CE) was performed at a mean 10-15 days, whilst neck ultrasound (US), serum thyroid binding globulin (TBG) and serum thyroglobulin (Tg) levels were assessed between 10 and 23 days of life. Evaluation of skeletal maturity (bone age) was more likely to occur after two weeks of age (in studies where the timing was specified).

In one study by Mathai[29], diagnostic testing varied by screening test result; diagnostic testing took place at a mean of 2-3 days of age if the first screening result was positive but was delayed until day 14 for children whose first screen was borderline as repeat screening tests were performed. No other studies directly compared the timing of diagnostic testing after positive and borderline screen results. Although Law[13] and Hummer[15] employed a single cut-off result, without repeat screens, diagnostic testing took place at a mean of 15 and 26 days respectively.

Table 7: Timing of diagnostic testing

Timing of diagnostic tests	Studies reporting testing at this age
1st week of life (0-7 days)	Alvarez[30] (Day [D.] 1), Mathai[29] (D. 2-3 if positive screen), Dubuis[31] (D. 3-14)
2nd week (8-14 days)	Dimitropoulos[32]/Glorieux[33] (D. 9), Corbetta[20]/Jones[17]/Ray[19]/ Bakker[34]/Dockeray[18]/Korada[7] [14]/Connelly[35] (D. 10-13), Campos[36]/Kohler[37] (D. 14), Mathai[29] (D. 14 if borderline screen result)
3rd week (15-21 days)	Law[13] (D. 15), Gunn[38]/Heyerdahl[39]/Tillotson[40]/Oerbeck[41 42] (D. 17), Toublanc[43] (D. 17-20), Gjurkova[8] (D. 19), Newland[44] (D. 21)
4th week (22-28 days)	Salerno[45-49] (D. 21-26), Niu[50] (D. 22-23), Hummer[15] (D. 26), Delvecchio[51] (D. 27), Fisher[52] (D. 24-50)

Whilst some authors listed all tests undertaken, others only highlighted the tests that were relevant to their study findings. In Table 8, the number of papers describing each test and the purpose of each test is summarised. The tests mentioned most often were serum TSH and T4 estimations, measurement of bone age and thyroid scintigraphy.

Table 8: Diagnostic tests described by different studies

Diagnostic test		Number of studies using test	Purpose of the test
TSH	Serum	66	*Confirm the diagnosis*
T4	Serum	66	
Triiodothyronine [T3]	Serum	21	*Assess severity*
Thyroglobulin [Tg]	Serum	5	
Thyroid binding globulin [TBG]	Serum	2	
Low molecular weight iodopeptides	*Not stated*	1	
Urinary iodides	Urine	2	
Clinical examination	Signs of CHT	8	*Assess severity*
Length, weight & head circumference		2	
Clinical photo		1	
Thyroid scintigraphy/radioisotope scan	^{123}Iodine	18	*Identify aetiology*
	^{99}Technetium	27	*Assess severity*
Neck ultrasound		7	
Bone age	Knee X-ray	34	*Assess severity*
	Knee & foot X-ray	1	

Purpose of tests performed at the time of diagnosis

The purposes for which tests were undertaken at the time of diagnosis were:

- To confirm/exclude the diagnosis of CHT in children with a positive newborn screening result

And in children in whom the diagnosis was confirmed, to:

- Define the presence or absence of thyroid tissue (and thus the aetiology)
- Assess the severity of CHT
- Guide initiation of treatment with replacement therapy
- Predict later outcomes.

Serum and urinary hormone tests were described as **confirming the diagnosis**, including serum TSH, T4, T3, TBG, Tg and urine iodide excretion.

Thyroid scans, either using radio-isotopes (scintigraphy) or neck ultrasound, were described as determining '**aetiology**', through determining the absence of thyroid tissue or presence of a partial thyroid or ectopic thyroid tissue.

Serum and urinary hormone estimations, thyroid scans, bone age estimation and clinical examination (for symptoms and signs of CHT) were all described as defining the **severity** of the CHT. In the majority of studies 'severity' was defined by aetiology, thus absence of a thyroid gland was deemed most severe. However, some authors defined severity by a low level of serum T4 or a greater delay in bone maturity at the time of diagnosis.

Variation in test methods described

There was heterogeneity across studies in the test methods used, in particular for evaluating skeletal maturity (bone age) or the presence of thyroid tissue.

Most bone age assessments appeared to measure femoral epiphyseal development in a knee joint X-ray (Table 9).

Table 9: Methods for skeletal maturity (bone age) assessment:

Bone maturity test method	Reference
Greulich & Pyle (knee or knee/foot comparison)	Salerno et al (1999)[46] Salerno et al (2001)[47] Salerno et al (2002)[45] Heyerdahl et al (1996)[53] Hulse et al (1982)[54]
Kuhns and Finnstrom (knee)	Germak (1990)[55] Salerno et al (2002)[45]
Senecal (knee)	Moschini et al (1986)[56] Newland et al (1991)[44]
Von Harnack (knee)	Newland et al (1991)[44]

Table 10: Type of thyroid scan used

Type of Thyroid Scan	Study references
Technetium scans (^{99m}Tc) scans	Alvarez (2010)[57]
(27 studies)	Battisti (1996)[58]
	Connelly (2001)[35]
	Costa (1998)[59]
	Delvecchio (2007)[51]
	Dockeray (1980)[18]
	Dubuis (1996)[31]
	Gruters (1983)[21]
	Gunn (1996)[38]
	Heyerdahl (1991)[60]
	Jones (2006)[17]
	Leger (2001)[61]
	Mathai (2008)[29]
	Moschini (1986)[56]
	Niu (2004)[50]
	Oerbeck (2003)[42]; Oerbeck (2005)[41]
	Rovet (1992)[62]; Rovet (1996b)[63]; Rovet (1999)[64]; Rovet (2000a)[65]; Rovet (2005)[66];
	Salerno (1999)[46]; Salerno (1999)[46]; Salerno (2002)[45]; Salerno (2004)[48]
	Winkler (1993)[67]
Iodide-123 (^{123}I) scan	Bakker (2002)[34]
(18 studies)	Corbetta (2009)
	Germak (1990)
	Glorieux (1992)
	Heyerdahl (1991)
	Hopfner (2005)
	Hulse (1982)
	Jones (2006)
	Kooistra (2004)
	Leger (2001)
	Murphy (1986)
	Oerbeck (2003); Oerbeck (2005)
	Salerno (2001); Salerno (2002); Salerno (2004)
	Toublanc (1997); Toublanc (2005)
Neck ultrasound	Bakker (2002)
(7 studies)	Corbetta (2009)
	Heyerdahl (1991)
	Jones (2006)
	Kooistra (2004)
	Niu (2004)
	Winkler (1993)

In Table 10, studies are divided by the type of thyroid scan that was used. Some studies used more than one type, usually because multiple centres or time periods were involved.

8.2.1 Tests which were most frequently used after a positive screening result to confirm the diagnosis and aetiology

Serum hormone levels

All studies reported measuring serum TSH and T4 levels to enable diagnostic confirmation after a screening result suggestive of CHT.

Thyroid scan

Sixty-two studies (of medium quality rating, M+ or M-) described a thyroid scan using either radio-isotope scintigraphy (n=54) and/or neck ultrasound (n=10) at the time of diagnosis. Scans were used to define three groups for comparison: children with complete absence of the thyroid (also called *agenesis*, *aplasia or athyreosis*), those with *ectopic* thyroid tissue (present but in an abnormal position) and those with *dyshormonogenetic* thyroid tissue (present but with abnormal hormonal production). Perry reported that whilst thyroid scintigraphy was better overall at defining thyroid abnormalities, ultrasound detected additional detail of gland structure that was of importance.

Thyroid scans were not the primary method for confirming the diagnosis of CHT but evidence from these studies suggested that children with complete absence of thyroid tissue might have a more severe form of CHT, demonstrated through higher serum TSH or lower serum T4 levels[68] and/or greater delay in bone maturation at initial diagnosis. In particular, Delvecchio and colleagues[51] found that children with an absent thyroid gland were more likely to demonstrate delayed bone age at diagnosis than those with an ectopic thyroid or thyroid dyshormonogenesis.

8.2.2 Association of diagnostic test results with replacement therapy

Serum hormone levels

Pre-treatment serum T4 levels at diagnosis were strongly associated with serumT4 values measured after the onset of therapy, thus low serum T4 levels (<21nmol/L) at diagnosis were predictive of suboptimal T4 levels one month after start of treatment.[38] Delvecchio et al also reported that serum T4 <30nmol/L at diagnosis predicted a higher dose requirement for levothyroxine (LT4) replacement therapy to maintain normal serum hormone levels throughout childhood and adolescence, although this difference only became statistically significant after 15 years of age.

Thyroid scan results

Evaluation of the underlying aetiology of the CHT was often used to guide the starting dose of replacement therapy. Absence of the thyroid was associated with the need for a higher initial dosage of LT4.[29 51 55] and more frequent dose adjustments in the first year[68], compared with children who had dyshormonogenesis. Germak[55] reported that patients with dyshormonogenesis achieved normal TSH levels more rapidly than patients with thyroid agenesis.

Gunn and colleagues[38] found that pre-treatment serum T4 values were significantly lower in children with agenesis or dyshormonogenesis (12.9 ± 10.3nmol/l) than in those with thyroid ectopia (51.1 ±32.9nmol/l). Moreover, Gunn reported that a T4 >26nmol/l positively predicted ectopic thyroid tissue in 100% children. Germak[55] found that serum T4 and T3 concentrations were lower in infants with thyroid agenesis than ectopic thyroid, however this difference was not statistically significant.

Children with thyroid dyshormonogenesis appeared to have the most favourable response to replacement therapy. In a 12 year follow up study, Delvecchio[51], found that these patients were more likely to have their replacement therapy dose reduced during follow-up and were least likely to require increased therapy to maintain thyroid hormone levels in the normal range. Similarly, Mathai[29] found that dyshormonogenetic patients had significantly fewer dose changes relative to other aetiological groups. Germak[55] reported that in the first months of treatment, dyshormonogenetic patients required lower LT4 doses relative to patients with absent or ectopic thyroid glands and normalised TSH levels quicker and Song[68] noted that children with absent thyroids were not as frequently found within their group of children who most rapidly normalised TSH levels on treatment.

Only Mathai[29] described varying the initial dose of replacement therapy based on aetiological diagnosis. He gave children with thyroid agenesis a dose of 15µg/kg/day LT4, while patients with ectopic thyroid received 12 µg/kg/day and dyshormonogenetic patients 10 µg/kg/day. This was found to normalise serumT4 levels more rapidly within each group and had a lower risk of overtreatment.

Bone age

Children with greater delay in bone age at the time of diagnosis have been reported to need higher initial doses of LT4 supplementation[45 51] and an increased frequency of changes in dosage after initiation of therapy[51], suggesting that they may represent a more severely affected group. Only Dubuis[31] has reported adjusting the initial dose of replacement therapy based on bone maturity.

8.2.3 Association of diagnostic tests with late outcomes

Eighteen studies reported outcomes in relation to serum T4 levels (described as T4, total T4 or free T4) and one in relation to T3 levels at diagnosis. Of these, 12 received a quality rating of M+. Only two studies reported outcomes in relation to TSH and one with regard to clinical examination. The findings of studies associating late outcomes with diagnostic testing are summarised in Table 11.

Serum hormone levels

Most studies investigating the relationship between confirmatory test results and prognosis focused on the relationship between initial serum T4 levels and later developmental and cognitive outcomes. Verbal and performance IQ[36 46], perception, attention[69], reading[69], memory[69], motor[42], language[69] abilities and global development[62] were assessed using a variety of measures, including standardised psychometric instruments, such as the WISC-R (assessment of IQ), McCarthy Scales of Children's Abilities[2] and Bayley Scales of Infant Development.[42 46 62 70]

A low initial serum T4 concentration at diagnosis was associated with poorer intellectual and motor development scores.[32 40 69 70] Whilst most studies investigated a linear relationship, three authors described threshold values of serum T4 predictive of later outcome. Murphy and colleagues[70] found that children who had an initial T4 <20nmol/l tended to achieve lower scores on the McCarthy Scales than those with higher initial concentrations. Tillotson and colleagues[40] reported differential outcomes at a slightly higher threshold of 42.8nmol/l and initial T4 values below this were associated with 11-12 points deficit in IQ. Rovet[62] found that patients with T4 <4 µg/dl had impairment of global intellectual functioning at one year of age. A further six studies defined severity as a specific T4 cut-off level at the time of diagnosis and explored outcomes relative to this. Heyerdahl[71] and Salerno[45] both reported using T4 <40nmol/l as the cut-off for a severe CHT diagnosis, whilst Leger[61] used a cut-off value of T4<53nmol/l for a severe case of CHT. Rovet[69] defined a T4 level <4µg/dl as severe CHT. Finally, Oerbeck and colleagues[42] used T4 as an index of severity, but did not report any cut-off. In each of these studies, children defined as having 'severe' CHT experienced worse developmental and cognitive outcomes.

Murphy[70] found that an initial serum T3 value lower than 2nmol/L was associated with poorer scores on the McCarthy Scales.

[2] The McCarthy Scales of Children's Abilities measures the abilities of preschool children aged 2.5-8.5 years on six scales: verbal, perceptual-performance, quantitative, composite (general cognitive), memory and motor.

Thyroid scan results

Studies discussing outcomes in relation to thyroid scans at diagnosis generally indicated less favourable intellectual outcomes for children with absence of the thyroid, relative to those with ectopic thyroid tissue or dyshormonogenetic thyroid tissue.[32 46 60 62 68-70] Some studies indicated a global neurological impact for patients with thyroid agenesis[32 46 62], while others indicated a more narrow impairment, specifically related to IQ scores.[60] This variability in findings may partly have been due to differences in the instruments used for assessment and the age at which assessments were made. Finally, children with absent thyroid were found to be at an increased risk of late entry into the first grade of secondary school.[61]

The differences in cognitive outcomes were only noted between children with absent thyroids compared with other groups, and no authors reported a difference in IQ between children with dyshormonogenetic and ectopic thyroid glands.

Bone age

Twenty-one studies discussed outcome in relation to bone age, 15 of which received a quality rating of M+. Bone age was measured in weeks and expected to be approximately 37 weeks at birth or at the time of diagnosis in most studies. Leger[61] defined absence of the knee epiphyseal ossification centres as severe CHT, while Dubuis[31] associated a knee epiphyses $<0.05cm^2$ with severe CHT.

Various studies reported worse developmental outcomes for patients with more marked delay in bone age at diagnosis.[36 60 62 69 70] This association was noted using different measures of developmental outcomes, including the McCarthy scales[70], delayed entry into the first grade of secondary school (Leger et al, 2001), verbal IQ [VIQ] scores[36], performance IQ [PIQ] scores and visuo-spatial ability.[69] Moreover, this negative relationship was evident from preschool tests up to the age of 13 years.[69]

Rovet et al[62] found that CHT patients with bone age ≤36weeks at birth were outperformed, on measures of language ability at two years of age, visuomotor skills at 3 years, motor skills at three years and Bayley's mental development index score at 18 months, by patients whose bone age was >37 weeks at birth. Similarly, Campos[36] found that a bone age >32 weeks gestation at birth was associated with higher verbal IQ, and Murphy[70] found that a bone age <30 weeks gestation at birth was associated with poorer scores on the McCarthy Scales.

Table 11: Relationship between Diagnostic Confirmatory Tests and Later Outcomes

Type of test	Relation to outcomes
T4	**Preschool ability scales:** Predicts performance on the McCarthy scales at 3yrs (Murphy 1986)[70] Correlated with Developmental Quotient (DQ) of the Griffiths test at age 1 and 2 (Law 1998[13]; Nakamizo 2007[9]) Predicts development at 2 and 6 yrs (Heyerdahl 1991[60]). **Intelligence Quotient (IQ):** Predicts Full-Scale Intelligence Quotient (FSIQ), Performance IQ (PIQ), 3rd grade reading & arithmetic ability (Rovet 2000[65]) Predicts global intellectual functioning (Rovet 1992[62]) Predicts IQ (Salerno 1999[46]) Predicts IQ values below 42.8nmol/l were associated with an average deficit of 11-12 IQ points (Tillotson 1994[40]) Verbal IQ (VIQ) significantly higher in patients with T4 >2ng/dL (Campos 1995[36]) Associated with WISC-R FS score (Connelly 2001[35]) Predicts FSIQ, VIQ, and PIQ scores at 10yrs (Kempers 2007[72]) **Wider cognitive skills:** Correlated with increased risk of late entry into first grade of secondary schooling (Leger 2001[61]) Correlates with attention, language, motor and memory skills (Rovet 1999[69]) **Motor performance:** Predicts motor performance (Oerbeck 2003[42]) **Behaviour:** Predicts behavioural problems in 3rd grade of schooling (Rovet 2000[65])
TSH	**Preschool ability scales:** Association with Developmental Quotient (DQ) scores (Nakamizo 2007[9]) **Wider cognitive skills:** Predicts language performance at 18 months (Alvarez 2004[30])
T3	**Preschool ability scales:** Predicts performance on the McCarthy scales at 3yrs (Murphy 1986[70])
Clinical evaluation	**Preschool ability scales:** Major clinical symptoms associated with lower DQ scores (Nakamizo 2007[9])

Table 11: Relationship between Diagnostic Confirmatory Tests and Later Outcomes (continued)

Type of test	Relation to outcomes
Thyroid scan	**Preschool ability scales:** Children with absent thyroid did worse than those with ectopic/normally situated glands on the McCarthy scales (Murphy 1986[70]) **Intelligence Quotient (IQ):** PIQ higher in ectopic thyroid patients, V IQ higher in the agenesis patients. A more homogenous development of intellectual ability for children with ectopic thyroids (Battisti 1996[58]) Poorer VIQ, PIQ and FSIQ for thyroid agenesis patients, relative to dyshormonogenetic or ectopic patients (Salerno 1999[46]) Absent thyroid predictive of poorer PIQ at 6yrs (Heyerdahl 1991[60]) Absent thyroid associated with worse WISC-III (IQ) scores (Song 2001[68]) Absent thyroid associated with poorer IQ scores (Dimitropoulos 2009[32]) **Wider cognitive skills:** Children with absent thyroid glands performed worse than those with dyshormonogenetic and ectopic glands on various developmental scales (Rovet 1992[62]) Outcome based on school reports were marginally more favourable for ectopic patients (Connelly 2001[35]) Absent thyroid associated with poorer intellectual performance at age 5 (Rovet 1999[69]) **Behaviour:** Inhibition control was better for children with absent thyroid glands (Alvarez 2010[57])
Bone age	**Preschool ability scales:** Predicts performance on the McCarthy scales at 3yrs (Murphy 1986[70]) Predicts development at 2 and 6yrs (Heyerdahl 1991[60]) **Intelligence Quotient (IQ):** Associated with WISC-R scores at 8yrs (Connelly 2001[35]) VIQ significantly higher in patients with bone age >32 weeks (Campos 1995[36]) Predicts PIQ at 13yrs, and visuo-spatial ability (Rovet 1999[69]) **Wider cognitive skills:** Correlated with 6th grade phonological processing skill, reading & grammatical sensitivity (Rovet 2000[65]) On various developmental indices, patients with intrauterine CH were significantly outperformed by patients with postnatal CH (Rovet 1992[62]) Correlated with increased risk of late entry into 6th grade (Leger 2001[61])

8.2.4 Withdrawal of treatment to assess transience or permanence of CHT

Four studies examined the proportion of CHT diagnoses which were later found to be transient; all described withdrawal of treatment at three years of age and assessment of serum hormone levels without treatment as the method for assessing transience (Table 12).

Table 12: Studies describing withdrawal of treatment at 3 years of age

Hulse 1982[54]: One out of 32 (3%) patients remained euthyroid after treatment withdrawal.
Costa 1998[59]: 11 (4 preterm) of 23 cases remained euthyroid after withdrawal. Replacement thyroxine dose was lower in those found to have transient CHT, and TSH normalised more quickly after commencing treatment.
Corbetta 2009[20]: Permanent CHT was confirmed in 34% of 59 cases.
Hopfner 2005[11]: 39/150 (26%) CHT cases were euthyroid after withdrawal. Screening TSH values were lower in these transient cases.

Corbetta[20] described the results of a treatment withdrawal at three years of age for 59 CHT children with a thyroid gland visible on scan. After one month of therapy withdrawal, 34% of children were diagnosed as having permanent CHT. Interestingly, transient CHT was not found more frequently in children identified through the newborn screening programme using a TSH >10mU/l cut-off versus a programme using a TSH >20mU/l cut-off.

Other studies, with lower quality ratings, reported widely varying proportions of transient CHT cases after withdrawal. Hulse[54] found that only one patient out of 32 had normal thyroid function after withdrawal, while Costa[59] found that almost 50% of CHT cases were transient.

8.3 Interpretation of the published evidence

Evidence from the literature review suggested that diagnostic investigation after a presumed positive screening result focused on three tests: serum T4 and TSH levels, thyroid scan and bone age assessment. Serum T4 and TSH levels were primarily undertaken to confirm newborn bloodspot findings and rapidly establish the diagnosis. They might also provide information about the severity of CHT and thus guide initial treatment. Thyroid scans investigated the aetiology of CHT through defining the absence/presence and location of functioning thyroid tissue. This might also provide an indication of the severity of thyroid hormone deficiency and guide initial treatment if undertaken at the time of diagnosis. Finally, bone age assessment at the time of diagnosis could provide a further guide to severity and requirement for replacement therapy, although it appeared a less essential test for confirming diagnosis. Diagnostic tests were usually performed between 10 and 23 days of age, and rarely within the first week or after the first month of life. Nevertheless, one study provided evidence of a delay in diagnosis of 11-12 days for children who had initial borderline screening tests results and required repeat screening, compared with children whose initial screening result was clearly positive.

Diagnostic test results which indicated the severity of CHT guided the initial dose of replacement therapy in some studies. Research into late outcomes explored development, cognitive and psychosocial parameters at two to 16 years of age and findings from these studies strongly suggested that children with 'severe' CHT, defined by absence of a thyroid, markedly low T4 levels or delayed bone age, had lower IQ, poorer developmental scores and worse school performance than children without or less severely affected by CHT.

Transience of CHT was only formally assessed in four studies which described the effect of withdrawal of therapy at three years of age. The proportion of children with transient CHT in these studies varied very widely from 3% to 50%, making the findings difficult to generalise to other populations, but this may be due to differences in the severity of CHT affecting participants in different studies.

Members of the diagnostic test subgroup considered additional relevant published and unpublished evidence, audit and expert advice as described below.

8.4 Additional evidence relating to different diagnostic tests

Clinical examination

The original standard 16 (2005) recommended a clinical history and clinical examination for every infant referred for diagnostic investigation. The EWG noted specifically evidence that CHT is associated with other congenital anomalies in around 5% of affected infants[73-76], including congenital heart defects, hip instability in 3-5% of infants with CHT[74] and sensorineural hearing loss.[77 78] Additional expert evidence regarding hearing testing for children with CHT who have had a negative result on newborn hearing screening was sought from Dr Tony Sirimanna who presented data from an audit of CHT patients at GOS between 2006 and 2008. Three cases of 85 assessed were found to have sensorineural hearing loss (SNHL), which appears higher than in the general population and raised the concern that not all might be detected through newborn hearing screening.

- *EWG members considered it important to emphasise that all children referred for diagnostic testing after a presumed positive screening test for CHT should be carefully examined. In particular, clinicians should look to exclude associated anomalies, such as heart defects, hip dislocation and hearing loss.*
- *Whilst the EWG did not feel that there was sufficient evidence to support referral for audiological assessment in every child, parental concerns about hearing or speech should lead to further investigations even if newborn hearing screening was presumed normal.*
- *EWG members considered that investigation after a presumed positive screening test for CHT should be undertaken early so that parents can be advised on recurrence risk in future children.*

Family history

The EWG considered evidence relating to collecting information about maternal health, anti-thyroid medications and iodine status, as well as family history.[28] Four recent reports have highlighted insufficiencies in the dietary intake of iodine in up to 60% of UK girls and pregnant women[79-82], although it is not yet clear if this is having an impact on neonatal screening results. Further evidence has suggested that maternal veganism during pregnancy might also lead to transient neonatal hypothyroidism in some newborn infants.[83]

- *EWG members did not consider that there was sufficient evidence to suggest testing for iodine status in all mothers of children referred for diagnostic investigation, however they concluded that the clinical history and examination should include enquiry about maternal iodine status and factors that might affect this.*

Serum T4 and TSH levels for diagnosis of CHT

The EWG reviewed additional published evidence supporting the use of laboratory reference ranges for serum free T4 and TSH in neonates that were appropriate for age and the type of equipment used.[84 85] They were provided by Dr C Evans with unpublished audit data from the All Wales Laboratory Survey, which highlighted the variation in test methods and reference ranges used across 11 different Welsh laboratories. Age-related reference ranges were derived from different manufacturers, historical data or in-house standards.

- *EWG members determined that there was an important requirement for robust age- and method-dependent reference ranges to be developed for free T4 and TSH.*

Expert advice relating to thyroid imaging

Details were provided of the different imaging available for diagnostic investigation in infants with presumed CHT. Radio-isotope scans can identify ectopic thyroids or thyroid agenesis[28 86-88] and may be supplement by an ultrasound scan.[89] Ultrasound and radio-isotope scans were compared:

Table 13: Comparison of different types of thyroid scan

	Ultrasound	Radio-isotope Technetium 99m	Radio-isotope Iodine 123
Availability	Readily available	Readily available	Less available
Radioactivity absorption	None	6 hour half-life Low absorbed radiation dose	13 hour half-life Taken up into hormone
Timing	Any time	Before or within 5 days of initiating treatment	Before or within 5 days of initiating treatment
Results	Position of thyroid	Position of thyroid Thyroid tissue activity	Position of thyroid Thyroid tissue activity

It was also noted that ultrasound scans may be more accessible in some hospitals and need not be done within 5 days of initiating treatment as with a radio-isotope scan. However thyroid ultrasound in neonates requires specialist skills, training and experience and may give misleading results[90], for example an ultrasound scan might identify tissue in the correct location but this might be non-functioning thyroid. Expert recommendation was that ultrasound scans should not be routinely done in isolation and must be interpreted with caution.

The EWG were advised that a radio-isotope scan was preferable as it

- provides diagnostic information
- allows the family to be given an explanation of the cause of the CHT
- identifies babies with possible dyshormonogenesis.

An ultrasound scan may also supplement a radio-isotope scan, particularly in infants with apparent thyroid agenesis on the radio-isotope scan, as this will identify infants with 'trapping defects, i.e. thyroid tissue that is present but not functioning normally.

Additional evidence relating to testing maternal thyroid status

EWG members also considered published evidence relating to the potential for maternal thyroid status[91-100] to lead to transient abnormalities in thyroid hormones in neonates, and in particular to the effect of anti-TSH receptor antibodies (TRAb). Pregnant women might have a history of previous thyroid dysfunction, thus taking a maternal history to explore thyroid problems is important. However testing of the mother may also be required in other cases as mother's may not manifest symptoms and signs of hypothyroidism, yet still have abnormal thyroid function that interferes with their baby's screening test results.

- *EWG members agreed that further research was required in this area.*

Additional evidence relating to thyroglobulin tests

Thyroglobulin (Tg) is a sensitive biochemical marker for the presence of thyroid tissue and may also provide additional information about aetiology and underlying genetic mutations.[101] Production of Tg is regulated by TSH so testing for Tg must be undertaken within five days of commencing replacement therapy (as for radio-isotope scans). Tg levels may also be affected by anti-thyroglobulin antibodies so antibody testing should be performed. Published evidence relating to the measurement of thyroglobulin as a diagnostic test was considered.[85 101 102 103] Authors of two papers suggested that thyroglobulin could complement ultrasound scanning and avoid the need for radio-isotope scans.

- *EWG members considered that there was no evidence to suggest that thyroglobulin should be removed from the list of desirable tests but emphasised that Tg measurement should be undertaken prior to or within 5 days of initiating treatment and should be accompanied by testing for Tg antibodies.*

Confirmation that CHT is permanent: withdrawal of therapy

Clinical guidelines and published evidence were considered by the EWG with regard to defining the cause of CHT and the establishment of an early CHT diagnosis as permanent.[28 40 70 73 104-106] It was proposed that CHT should be considered permanent if:

- Thyroid scan reveals an ectopic or absent thyroid gland
- Serum TSH>10mU/L after the first year of life (presumably because of insufficient T4 replacement).

If a permanent cause of CHT has not been established, then further tests should be undertaken to confirm this at a later date. Testing for permanence through a 'withdrawal of therapy' testing would usually be performed after the child is 3 years of age and would typically involve:

- Discontinuation of levothyroxine (LT4) for 30 days
- Measurement of free T4 and TSH.

As severely affected children may become clinically hypothyroid by 30 days, reducing the dose by half might be considered as an alternative. If after 30 days, the TSH is >20mU/L, then CHT is confirmed to be permanent and therapy should be resumed. If the serum TSH has not increased, then therapy should be discontinued for a further 30 days and serum free T4 and TSH testing repeated.

- *EWG members noted that if therapy was withdrawn for such testing, great care must be taken that the child is not lost to follow-up and that therapy is re-started if there is any suspicion of hypothyroid symptoms. If such testing is inconclusive, it may be repeated at a later date but the child should remain on therapy in the meantime.*

- *EWG agreed that a new standard should make recommendations for confirming the permanence of CHT in all children. A Diagnostic Protocol was drawn up to define the steps in the diagnostic testing pathway leading to definition of a CHT diagnosis as permanent.*

8.5 EWG Final Recommendations and Revised Standards relating to Diagnostic Investigation

Clinical evaluation and confirmatory diagnostic tests

The clinical history and examination of the baby, mother and wider family was addressed in the former 2005 Standards 16 (2005). Members considered this should now become Standard 13 with additional notes for clarification.

New Standard 13. The clinician responsible for assessing the baby with a positive screening result shall take a clinical history and perform a clinical exam.
(See Note 1)

Note 1: Babies with CHT are more likely to have associated anomalies, particularly congenital heart defects and mild hearing loss and require careful neonatal examination. A complete history, including maternal thyroid status (previous history of thyroid dysfunction, maternal anti-thyroid medications), maternal diet (e.g. vegan or other low iodine diet) and family history should be obtained.

- *EWG members did not consider that there was sufficient evidence to support audiological referral in all children, however they highlighted that a hearing test should be considered if there were concerns about hearing or language development even if the newborn hearing screening test result appeared normal.*

Standards 17 and 18 (2005) became new Standard 14 with an accompanying note regarding the need to use appropriate reference ranges.

New Standard 14. Diagnostic tests considered essential in the baby are:
a) Free T4 (plasma or serum)
b) TSH (plasma or serum)
(See Note 2)

Note 2: Diagnosis using free T4 and TSH should be performed on a plasma or serum sample using the appropriate age-related reference range as defined by the laboratory in relation to the equipment used.

- *EWG members considered that the previous Standards 19-20 (2005) concerning tests in the baby should remain as 'Desirable additional diagnostic tests'.*

Desirable additional diagnostic tests

New Standard 15. Appropriate imaging techniques (radio-isotope and/or ultrasound scans), may help to establish whether the thyroid gland is
a) normally situated and normal in size and shape
b) normally situated but abnormal in size and shape
c) ectopic
d) absent.
(See Note 3)

Note 3: A radioisotope scan and an ultrasound examination may establish the cause of the child's CHT and indicate whether the condition is likely to be permanent. Initiation of treatment should not be delayed whilst waiting for an isotope scan, which can be performed up to 5 days after starting therapy. An ultrasound scan can be performed at any stage and investigation need not be confined to the neonatal period. These investigations may increase awareness of potentially related problems such as deafness and can provide information about recurrence risk. Recurrence is unusual in the case of thyroid dysgenesis but there is likely to be autosomal recessive inheritance with a 1:4 recurrence risk for families of babies with thyroid dyshormonogenesis. Both isotope scanning and thyroid ultrasound in neonates require specialist skills and can generate misleading results.

- *EWG members considered that the thyroid imaging at the time of diagnosis was desirable to confirm aetiology and, if absence of the thyroid was confirmed, this might avoid the need for a future 'withdrawal of therapy' or 'trial off-therapy' to test for transient CHT.*

New Standard 16. In addition, the following test may be helpful:
a) Thyroglobulin
(See Note 4)

Note 4: Plasma thyroglobulin ideally needs to be measured on a sample taken prior to the start of treatment; this must not delay initiation of treatment. If plasma thyroglobulin is detectable then there must be some thyroid tissue present. Concentrations will be undetectable in thyroid agenesis.

- *EWG members considered that it was important to clarify aspects of the methods and interpretation of the thyroglobulin test in the notes.*

Advisable tests in the mother

The EWG recommended rewording Standard 21 (2005) as below:

New Standard 17. Diagnostic tests considered advisable in the mother to exclude interference in the infant's TSH measurement and to exclude thyroid dysfunction in the mother include:
a) Free T4 (plasma or serum)
b) TSH (plasma or serum)
These investigations should be extended to include an assessment of TSH antibody receptor status in mothers with a current or previous history of autoimmune thyroid disease.

- *The EWG considered it important to highlight the importance of always considering investigations in the mother by creating a new subheading 'Advisable tests in the mother'.*

Assessment of Permanence of Hypothyroidism

A new Standard 22 was proposed:

New Standard 22. In cases where the cause or persistence/permanence of hypothyroidism has not been confirmed (see Diagnostic Protocol), confirmatory testing should be undertaken at 2-3 years of age, with thyroid function tests checked 4-6 weeks later.

- *The EWG determined that a clear protocol for diagnostic confirmation of CHT, up to the point of clarifying if withdrawal of therapy was required to define whether CHT was transient or permanent, should be specified as part of the new standards.*[3]

[3] After the public consultation on the revised standards, New Standard 22 was amended to include a recommendation for regional and national audit of outcomes: 'The outcome should be fed back to the regional endocrine centre to facilitate regional and national audit.' This amendment has been included in the final list of revised standards in the Executive Summary of this report.

8.6 Recommendations for further research

The EWG recommended that further research would be merited to define age- and method-related reference ranges for serum levels of free T4 and TSH, as well as to investigate TSH interference in thyroid-receptor antibody assays.

9 Referral Pathway and Clinical Responsibilities

9.1 Original (2005) ICR standards relevant to the referral pathway

Children who have a positive screening result are referred for diagnostic testing and further care. A subgroup considered evidence relating to the referral pathway and clinical responsibilities for further care as described in standards 11-15 and 25 from 2005 (Box 7).

EWG members drew on the following sources:

- Specifically designed questionnaire to newborn screening laboratories
- British Society for Paediatric Endocrinology & Diabetes (BSPED) Clinical Standards 2010
- UK Newborn Screening Programme Centre information leaflets
- Expert clinical opinion.

Box 7: Standards 11-15, 25 (2005)

11. Babies with positive screening results for CHT should be referred to a designated clinician as defined by the BSPED who has access to the full range of diagnostic investigations recommended.
12. Parents should be offered an appointment with a designated clinician within at least 3 days of being informed about their baby's positive screening result.
13. Laboratories should notify a positive screening result verbally (by telephone) as well as in writing (by fax/email) to a designated clinician and either the GP and health visitor, or the health professional responsible for communicating results. This initiates the clinical referral as measured within standard 6 of the process standards.
14. The GP, health visitor, midwife or other health professional responsible for making initial contact with the family to explain the positive screening result should be provided with:
    a. Standardised information – for parents and health professionals
    b. The contact numbers of the designated clinician, local health professionals as appropriate and details of parent support groups
    c. Details of the time and date of an appointment with the designated clinician.
15. Parents should be offered an appointment with the designated clinician on the next working day of hearing about a positive screening result. They therefore should not normally be notified of a positive screening result of Fridays, Saturdays, or Sundays preceding Bank Holidays.

25. Once treatment has been started, a baby should be reviewed, with a blood test at each visit. The timing of such visits may vary according to local circumstances but it is suggested should occur at 2 weeks, 6 weeks, 3 months, 6 months, 12 months after treatment is started, and thereafter as indicated, with management complying with BSPED recommendations for interpretation of tests and dosage. Visits may occur more frequently as necessary.

9.2 Results from the laboratory survey

All 16 newborn screening laboratories responded to a questionnaire based on the above standards.

Laboratory staff members were asked to describe what systems for referral work well and which do not work, what they would change, who they consider should manage local CHT referrals, whether any local areas lack a designated paediatrician for CHT and what happened when the designated paediatrician or deputy was not available to take a referral.

Laboratory staff responses to who should manage CHT cases in their region were:

- Paediatrician (n=6)
- Paediatric endocrinologist (n=3)
- Paediatrician with an interest in CHT/endocrinology (n=2)
- Paediatrician and clinical nurse specialist (n=1)
- Other/no view (n=4)

However, laboratory staff also suggested that care immediately after referral might differ from long-term follow-up care, for example that immediate diagnosis and early management should be concentrated in specialist centres but long-term care provided in local centres. There was an emphasis on the need for consistency in early management. Drawbacks to locally provided care were highlighted as the lack of a specialist or named responsible consultant leading to variation in care provision. No formal shared care protocols were identified and few examples of shared care were elicited and some centres are moving towards tertiary centre follow-up long-term. Nevertheless, laboratory staff stated that a designated clinician to receive all referrals and six monthly multidisciplinary meetings worked well to improve consistency and quality of treatment.

Difficulties were highlighted in the use of the term 'designated clinician' as few areas are able to refer to a specialist during periods of out-of-hours care.

Laboratories stated that they used a wide variety of routes for referring or communicating presumed positive screening results to a responsible clinician, however all initiated this with a telephone call and the majority followed this with a written communication by letter or fax. Some laboratories preferred to notify GPs also.

Of the 16 laboratories surveyed, three provided the UKNSPC leaflet with the referral, one was aware that the clinician already has the leaflet, one was unsure and 11 did not provide the leaflet. In some areas a locally developed leaflet was provided.

- *EWG proposed that 'designated clinician' might be more appropriately described as a 'named paediatrician with a designated deputy' as they key issue was for the initial referral and on-going care to be provided by a paediatrician who was trained and experienced in CHT and had a sufficiently high volume of referrals per annum to maintain this expertise.*
- *EWG members proposed that a statement highlighting the need for specialist support networks be included in the standards.*

- *EWG members considered that standards 12 and 15 were contradictory regarding the timing of referral and proposed that these be combined into a single standard.*

9.3 BSPED Clinical Standards 2010

No clinical training standards or requirements currently exist to define 'expertise' in managing CHT. CHT is defined as a Level 2 endocrine disorder, i.e. a 'relatively common endocrine disorder'. These are defined by BSPED as *"conditions with a need for input from a paediatrician with an interest in endocrinology usually managed at local … clinics with occasional input by a paediatric endocrinologist on a shared care basis with local teams."*

- *EWG members proposed that a statement highlighting the need for specialist support networks be included in the standards.*

9.4 UKNSPC leaflets

The UKNSPC produces a leaflet aimed at parents and developed with parents, to communicate information about CHT screening and about a suspected diagnosis of CHT. This leaflet is intended for clinicians to share with parents when a child is referred for further investigation. However the UKNSPC reported that many clinicians are unaware of the leaflet and produce a local leaflet or use information downloaded from the BSPED website, 'Nick's Notes' and the Child Growth Foundation some of which require updating.

- *EWG members agreed that the UKNSPC leaflet required updating and wider dissemination. This might be supported by including distribution of the leaflet within the new standards.*

9.5 EWG Final Recommendations and Revised Standards relating to Referral Pathways and Clinical Responsibility

Referral of babies with positive screening results

Standards 11, 12 and 15 (2005) were revised by the EWG and became new Standards 8 and 9. These defined the need for a designated named paediatrician and deputy, support from a regional specialist clinical network and provision of a timely appointment to parents.

New Standard 8. The laboratory shall refer babies with positive screening results for CHT the same or next working day.

Referral is to a paediatric endocrine team (regional specialist team) or to a clearly identified lead paediatrician with a special interest in CHT or experience of managing these patients.

Appropriate failsafe mechanisms must be in place to ensure CHT suspected babies have entered into the diagnostic pathway.

Clinicians should work to a common protocol and have access to the full range of diagnostic investigations recommended.

Where referral is out-with a regional endocrine centre, the regional specialist team should be able to provide support and facilitate access to diagnostic investigations where required.

New Standard 9. The first clinical appointment with the paediatrician must take place on the same day or the next day after parents are informed of their baby's positive screening result.

Communication flows

Standards 13 and 14 (2005) were extended by the EWG and became new Standards 10-12. These standards clarified the methods for communicating results between the laboratory and clinicians, and between clinicians and parents, and also the information to be provided.

New Standard 10. Laboratories shall notify a positive screening test (blood spot results expressed as a whole number), verbally and in writing by secure fax or email, to the lead paediatrician or deputy and the health professional responsible for communicating results.

This notification should include a link to the standardised diagnostic and initial treatment protocol.

This initiates the clinical referral of screen positive cases.

New Standard 11. The result should be communicated by an informed health professional. The health professional making initial contact should provide the following information to the family:

a. UKNSPC standardised parent information 'When CHT is suspected' (via hard copy or web link).
b. Details of the time and date of the appointment with the paediatrician and appropriate contact telephone numbers.

New Standard 12. The laboratory should provide a link to a standardised diagnostic and initial treatment protocol.[4]

[4] Following responses to the public consultation and identification of the need for national outcomes audit, New Standard 12 was amended to: 'The outcome of the first appointment should be reported to the newborn screening laboratory. The regional endocrine centre should also be informed about diagnostic outcome to facilitate regional and national audit.'

10 Initiation of treatment and clinical follow-up

10.1 Original (2005) ICR standards relevant to treatment and follow-up

Children with CHT should be commenced on treatment as soon as possible as laid out in standards 22-24 in 2005 (Box 8). Standard 25 (Box 8) defines follow-up and has also been addressed under the previous sections relating to diagnostic investigations and clinical responsibilities.

EWG members drew on the following sources:

- Evidence from the literature review
- UKNSPC data relating to the timeliness of treatment.

Box 8: Standards 22-25 (2005)

22. A baby in whom the essential confirmatory diagnostic tests are positive on the initial screening sample should commence treatment by:
    Developmental standard: 18 days of age (100% of infants)
    Core standard: 21 days of age (100% of infants)
23. Starting dose of levothyroxine sodium should be 10 microg per kilogram per day.
24. Suspensions should not be used as the dosage may be unreliable. Parents should be given verbal and written information about how to give tablets to their baby.
25. Once treatment has been started, a baby should be reviewed, with a blood test at each visit. The timing of such visits may vary according to local circumstances but it is suggested should occur at 2 weeks, 6 weeks, 3 months, 6 months, 12 months after treatment is started, and thereafter as indicated, with management complying with BSPED recommendations for interpretation of tests and dosage. Visits may occur more frequently as necessary.

10.2 Results from the evidence review: initiation of therapy

A total of 82 papers discussed initial treatment variables, of these only one received a high quality rating, while 42 received a medium plus (M+) quality rating, 26 a medium minus (M-) quality rating, another 14 a low rating. The focus of this discussion will be on the M+ rated papers. Of the M+ papers, 18 discussed treatment variables in relation to outcome.

Age at commencement of therapy

The mean age at commencement of thyroxine replacement therapy ranged from seven to 33 days of age (Table 13). In most studies, replacement therapy was commenced within the first month of life, however Mathai[29] noted that a borderline screening result was associated with a mean delay in therapy of approximately 11 days. Kooistra[72] reported earlier commencement of therapy for children with more severe CHT, defined as a lower serum T4 or absence of the thyroid at initial diagnosis, however also found no improvement in outcomes from advancing the start of replacement therapy from 28 to 20 days of age.

A few studies described the timing of treatment onset and later outcomes, usually in respect of intellectual outcome. For example, Rovet found that poorer performance IQ scores, visuol-motor

ability and poorer language ability were associated with a later onset of treatment.[62 69] Salerno and colleagues[45] found a correlation between higher full scale IQ scores and earlier age at start of treatment. Finally, Battisti[58] found that a group of children with delayed onset of therapy demonstrated poorer performance on various measures of mental capacity, such as the WISC-R test for IQ, the Bender test, and Toulouse-Pieron test of attention. Importantly, Rovet[107] noted that children who commenced replacement therapy within the first two weeks of life were less likely to be hearing impaired than those who commenced treatment later. She suggested that there might be a critical period within the first two weeks of life, during which thyroxine is crucial for normal development of hearing. Heyerdahl[71] found that children with delayed growth in childhood had started treatment at an older age than those with normal growth.

Table 13: Age at which treatment was commenced in different studies

Age at initiation of treatment	References
1st week of life (0-7 days of age):	Mathai[29] (Day [D.] 2-3 if positive screen) Arenz[108] (D. 7)
2nd week (8-14 days):	Alvarez[57] (D. 8) Hopfner[11]/Dimitropoulos[32]/Gruters[21] (D. 9) Jones[17]/Selva[109 110] (D. 11) Rovet[69 107] (D. 12-33) Gjurkova[8]/Connelly[35] (D. 13) Bongers-Schokking[111 112]/Winkler[67]/Simoneau-Roy[113] (D. 13-14) Dubuis[31]/Brown[114] (D. 14) Mathai[29] (D. 14 if borderline screen result)
3rd week (15-21 days):	Rovet[69 107] (D. 12-33) Ilicki[115] (D. 15) Law[13] (D.17) Glorieux[33] (D. 18) Toublanc[43] (D. 18-21) Heyerdahl[53] (D. 19) Kempers[72] (d. 20) Pharaoh[12] (D. 21)
4th week (22-28 days):	Niu[50] (D. 22-23) Fuggle (D. 23) Kooistra[116 117] (D. 23-24 if agenesis) Oerbeck[41 42]/New England Collaborative[118]/Adachi[119] (D. 24) Moreno[120]/Weber[121] (D. 25) Salerno[45 47 48] (D. 25-28) Murphy[70] (D. 27) Bargagna[122] (D. 28-30) Delvecchio[51] (D. 28)
Within the first month:	Illig[123] Germuk[124]
After the first month or 28 days:	Hulse[54] (D. 31) Moschino[56] (D. 33) van der Sluijs[125] (D. 28-39) Nakazimo[9] (D. 31) Battisti [58](D. 33) Kooistra[116 117] (D. 52 if dysgenesis)

Initial dose of thyroxine replacement therapy

There were 64 papers that reported dose at initiation of treatment (Tables in Appendix 3). In addition, Hrytsiuk presented a systematic review of dose at initiation of therapy. Marked variation in initial dose levels existed across papers. The lowest reported dose was around 2µg/kg/day[38] and the highest 15 µg/kg/day. Doses varied within a study either to adjust for severity, by time period or because of a randomised control trial design. The majority of studies reported doses in micrograms per kg per day (µg/kg/day), however some only reported the total amount per day (i.e. µg/day) and occasionally other units were employed.

All except two studies[40 126] reported a positive relationship between dose level and intellectual outcome.[45 53 61 117 127] Rovet and Ehrlich[127] found that at seven years of age, CHT patients receiving a high initial dose of levothyroxine (>7.8 µg/kg) had a higher full scale IQ and verbal IQ compared with those patients receiving a low initial dose (<7.8 µg/kg). Children started on a dose >7.8 µg/kg had significantly higher scores on the verbal comprehension, similarities and arithmetic subtests of the WISC-R and, at age 8 years, scored higher on the McCarthy memory subtests and the Passage comprehension subtest of the Woodcock Reading Mastery scale. Finally, Leger and colleagues[61] reported that a dose of less than 7µg/kg/day was associated with an almost twofold increase in the risk of late entry into the first grade of secondary school.

Salerno[45] reported findings from a study where participants were split into three dosage groups: Group 1: 6.3 µg/kg/day; Group 2: 9.1 µg/kg/day; Group 3: 13.4 µg/kg/day. At four years of age, the full scale IQ of patients in group 3 was significantly higher relative to patients in Groups 1 and 2 and a significantly lower performance IQ was observed in patients from Group 1 compared to both Group 2 and 3 patients. The subtests most affected were comprehension, mazes, geometric design and block design.

The impact of initial dose of thyroxine on outcomes varied by study: Kooistra[128] reported that initial dose accounted for 21% of the variance in verbal IQ at age 20, whilst Heyerdahl[53] found that it only accounted for 12% of the variance in mental development scores of the Bayley's Scales of Infant Development. The reason for this discrepancy is unclear, but differences in test measures and times of testing between these studies may have influenced the results.

There was less consensus about the relationship between initial dosage and attention and behavioural outcomes. Rovet & Hepworth[129] reported better attention scores for patients who had a lower initial dose of thyroxine replacement. In an earlier study, Rovet noted a higher incidence of internalising behaviour problems (social withdrawal, anxiety/depression, social problems, delinquency and aggression subscales of the Child Behaviour Checklist; conduct and hyperactivity problems on the Conners Scales) for children commenced on high dose replacement therapy.[127] Of three children with behaviour problems in the psychopathic range, all had a starting dose > 18 µg/kg. In contrast, Oerbeck[42] found that children started on a higher initial dose of thyroxine achieved better scores on the Freedom from Distractibility test.

In terms of growth variables, only one study discussed this in relation to initial dose level. Salerno's study[45] evaluated bone maturation under three treatment regimes, described above, and reported delayed maturation in Group 1 children receiving the lowest does of replacement therapy relative to Groups 2 and 3 for the first two years of life. However, bone maturation for this group of children 'caught up' by the third year of study suggesting only temporary impairment.

Initial dose and normalisation of hormone levels

Most studies found that a higher initial dose led to more rapid normalisation of both T4 and TSH levels. However, some studies reported a period of 'overtreatment', usually demonstrated by abnormally high serum T4 levels, with high initial doses. Selva[110], in a randomised controlled trial, assessed hormone levels up to 12 weeks after treatment onset in infants receiving one of three treatment regimes: Group1: 37.5 µg/d; Group 2: 62.5 µg/d for three days then followed by 37.5 µg/d; Group 3: 50 µg/d). She found that children in Groups 2 and 3 normalised serum T4 by day three of treatment whereas children within Group 1 took one week to achieve normal T4 levels. TSH levels were normal by week 2 for Group 3, receiving the highest dose, while infants in Group 1 only achieved normal TSH levels by week 12. Interestingly the group commencing on a high dose then dropping to a lower does never achieved TSH values in the normal range during the follow-up period. All groups showed periods of overtreatment, when T4 values were above the normal range; for Groups 1 and 2, this was between weeks 2 and 4, whereas the highest dose group experienced overtreatment from week 3 to 12. Similar findings have been reported by other studies.[29 38 45 130] Nevertheless, in Rovet & Ehrlich's study[127], children who commenced on a lower starting dose had higher T4 levels at 7 and 8 years of age, and higher TSH levels at 7 years, suggesting that they had been given higher therapeutic doses subsequent to their initial therapy with the aim of 'correcting' serum T4 and TSH levels.

In conclusion, the optimal starting dose of thyroxine remains to be established. Most studies appear to suggest that a dose of ≥10 µg/kg/day is needed to achieve normalisation of thyroid hormones quickly, and that this dose is associated with improved long-term outcomes. However, some studies also suggest that using high doses of thyroxine to rapidly normalise T4 levels might result in periods of overtreatment.

Timing of Treatment and Initial Dose

One study analysed outcomes in relation to a combined time of treatment/initial dose variable and children were divided into early/high, early/low, late/high and late/low groups depending on when they started treatment and their initial dose. Bongers-Schokking's group[131] analysed mental development and psychomotor development scores of infants with severe and moderate CHT (based on initial T4 levels). They found that for children with severe CHT, only those treated early and with high dose therapy had mental development scores comparable with those of patients with mild CHT and a reference control population. Within the mild CHT group, children treated early with low or high doses, and those treated late but with high doses had mental and psychomotor development scores comparable with the reference control population. Children

with mild CHT who commenced treatment late and at low doses had lower scores. Moreover, the early treatment/high dose group achieved normal serum T4 concentrations by day 16, while those of the other three groups were only normal by day 24. As this is the only study to discuss this combined variable in relation to outcomes, no firm conclusions can be drawn.

Formulation of levothyroxine

Two studies described the formulation of treatment; Jones[130] and Selva[110] both described the administration of crushed tablets as the preferred formulation although liquid suspensions were used by up to one third of clinicians.

Summary

Findings from most studies supported an effect of initial dose of therapy on later outcomes, with worse intellectual outcome associated with lower initiating doses. However, it is unclear whether this relationship is linear or if there is a cut-off dose above which intellectual outcomes should be optimal. Few studies attempted to relate current levels of treatment to the initiating dose and to outcomes. Higher initiating doses of replacement therapy were associated with better outcomes in terms of development and cognitive abilities, however, Rovet noted that high initiating doses were associated with increased attention and behaviour problems, in particular where doses were >18 µg/kg/day. Whilst high initial doses led to more rapid normalisation of serum hormone levels, they were also associated with periods of over-treatment.

Several studies suggested that earlier onset of treatment was associated with improved cognitive and developmental outcomes. In particular, Rovet found that children who commenced treatment within the first two weeks of life were less likely to be hearing impaired, and proposed that a critical period for commencing treatment may exist.

Based on the evidence presented here, the relationship between outcomes of CHT and the age and dose at initiation of replacement therapy is complex, and may be influenced by the severity of the underlying CHT and/or hypothyroidism during prenatal development. Worse outcomes may be observed both with low and very high initiating doses; the influence of subsequent changes in therapy during follow-up has not been fully explored. Nevertheless, early initiation of therapy is of benefit and initiation of therapy within the first two weeks of life may avert hearing impairment associated with CHT.

10.3 Evidence from the literature review relating to follow-up

There were 28 papers which discussed frequency, purpose and place of clinical follow-up after initiation of replacement therapy. Twenty-three were of moderate quality (18 M+, 5 M-) and a further five were of low quality. Clinical follow-up regimes described in these papers are summarised in Table 14 below. The timing of the first follow-up appointment was often not specified, and clinical practice regarding frequency of monitoring varied widely in the first few months after commencing therapy. Where information about the managing clinician was

provided, this was most often a paediatrician or paediatric endocrinologist who supervised therapy in the first few years of therapy. The aim of follow-up within most studies was focused on monitoring and adjusting the dose of levothyroxine in response to achieve optimal levels of serum T4 and TSH.

No studies appraising follow-up and monitoring from the perspectives of children or families, or evaluating outcomes using different methods of follow-up, were identified. Thus, while the heterogeneity of different monitoring and follow-up regimes can be presented here, the relative effectiveness of these cannot be assessed from current evidence.

Table 14: Studies reporting clinical follow-up

Reference	1st follow-up	Frequency	Who	Tests	Purpose of tests	Influence
Delvecchio et al (2007)[51]	Not stated	Every month in first trimester, then every three months till 3 years of age, then every 6 months.	Not stated	Physical and audiological exam; hormone assay, length/ height (H) performed monthly	Measure height, and monitor thyroid hormone value (maintain in normal range)	LT4 dose adjusted to keep TSH within normal limits, and T4 in the upper half of the normal range
Mathai et al (2008)[29]	Not stated	Weekly for 4 weeks, then at 6 weeks, then monthly until 24 months of age and then 3 monthly.	Paediatric endocrinologists	Thyroid hormone test	Monitor hormonal levels	Maintain T4 in the upper half of the normal range.
Alvarez (2010)[57]	Not stated	Every month during the first 6 months after initiating treatment	Not stated	TSH and T4	Monitor hormonal level	Not stated
Song et al (2001)[68]	Not stated	1, 3, 6, 9, 12, 18, 24, and 36 months of age.	Paediatric endocrinologist	TSH and T4	Monitor hormonal levels	Not stated
Dimitropoulos (2009)[32]	Not stated	Initially every 2–4 wk, then every 3–6 mo,	Paediatrician	TSH and T4	Monitor therapy	Dose adjustments
Ilicki & Larsson (1988)[22]	Not stated	1, 3, 6, 9, 12 and 18 months of life and on each birthday thereafter.	Paediatrician	Physical examination; T4, TSH in serum.	Not stated	Not stated
Dubuis et al (1996)[31]	4 weeks after therapy onset	3.6.9.12 and 18 months	Not stated	Plasma TSH, FT4 and TT4. X-ray12 months	Compliance bone age.	Not stated
Salerno et al (1999)[46]	Not stated	At 3, 6, 9 and 12 months during the first year, then every 3 or 6 months until 3rd year of age, and annually thereafter.	Not stated	Not stated	Dosage adjusted to keep serum T4/TSH levels in normal range.	Not stated
Leger et al (2001)[61]	Not stated	Two to three times a year from the age of 6 months	Not stated	TSH, FT4	Control TSH and FT4	Not stated

Table 14: Studies reporting clinical follow-up (continued)

Reference	1st follow-up	Frequency	Who	Tests	Purpose of tests	Influence
Rovet et al (1992)[62]	Not stated	Monthly until 4 months, then at 6, 9, 12 and 18 months; then yearly	Not stated	Growth and thyroid functioning	Maintain thyroid hormone levels in the upper end of the normal range	Not stated
Salerno et al (2002)[45]	After 4 weeks of treatment	Every 3 months until age of 2 years, every 6 months thereafter	Not stated	T4, T4 and TSH	Keep serum T4 levels in the upper normal range and serum TSH within the normal range.	Dose adjustments
Battisti et al (1996)[58]	1 month after starts therapy	Every 3 months during the first year of therapy, and annually thereafter	Not stated	Serum TSH,TT4, FT4 and T3	Assess adequacy of therapy	Not stated
Adachi et al (2003)[119]	Not stated	1–3 month intervals, at least twice a year	Endocrine specialist	Height, TSH	Monitor growth and adequacy of treatment	Thyroxine doses adjusted to keep TSH below 10 mU/L.
Bargagna et al (2000)[132]	Not stated	2, 3, 6, 9, and 12 months in first year then every 3 months up to 3 years old, then every 6 months	Not stated	T4 and TSH	Maintain TSH in 0.5-5mU/L range	Dose adjustment
Bongers-Schokking et al (2000)[111]	1, 2 and 3 weeks after treatment onset.	1.0, 1.7, 2.8, 4.0, 5.9, 8.5 and 11.5 months.	Not stated	FT4, TSH	Not stated	Dose adjustments
Jones et al (2009)[130]	7-21 days after start of treatment	3, 6, 12, 18, 24 and 36 months of age.	Not stated	Weight, length, bone age, thyroid function, dose	To monitor growth and adequacy of treatment	Dose adjustments
Germak & Foley (1990)[55]	Twice during first weeks of treatment	Monthly for the first 6 months of therapy, then every 3 to 6 months.	Not stated	T4, FT4, TSH	Maintaining serum T4 in upper normal range; serum TSH within the normal range	Dose adjustments

Table 14: Studies reporting clinical follow-up (continued)

Reference	1st follow-up	Frequency	Who	Tests	Purpose of tests	Influence
Campos et al (1995)[36]	Not stated	3-6 weeks for 6 months, then 2-4 month intervals	Not stated	T4 and TSH	Keep T4 in mid-normal range	Dose adjustments
Bargagna et al (1994)[133]	Not stated	3, 6, 9, 12, 18 and 24 months	Not stated	Not stated	Not stated	Not stated
Nakamizo et al (2007)[9]	Not stated	Every 2 months up to 12 months of age then every 3 months.	Not stated	Biochemical and clinical	Not stated	Not stated
Arenz et al (2008)[108]	Not stated	2-3 times per year	Not stated	Not stated	Not stated	Not stated
Kooistra et al (1996)[117]	Not stated	Weekly, increasing to every 3 months during the first 2 years, then every 6 months.	Not stated	Plasma T4 and TSH	Monitor treatment compliance	Dose adjustments
Simoneau-Roy (2004)[113]	Not stated	1.5, 3, 6, 9 and 12 months, then 6 monthly until 3 years, then yearly	Not stated	Plasma TSH, T4, T3, x-rays (at 1 & 3 years)	Maintain plasma TSH 0.5 to 5.0mU/L. Bone age.	Dose adjustments
Moschini (1986)[56]	1 month after onset of therapy	Every 3 months in first year, then 6 monthly	Not stated	Serum T3/T4/ TSH, physical exam, length, weight, head size, annual x-ray	Monitor thyroid function, growth, bone maturation	Not stated
NECHC (1984)[134]	2 & 6 weeks after starts treatment		Not stated	Hormone concentrations	Not stated	Not stated
Vogiatzi & Kirkland (1997)[135]	Not stated	2 month intervals during the first year then 3-month intervals.	Not stated	T4 and TSH	Maintain T4 levels in the normal range	Dose adjustments
Bargagna (1999)[122]	Not stated	Every 3 months in the first year of life, then every 3–6 months.	Not stated	FT4, TSH and T3	Maintaining serum TSH in normal range.	Dose adjustments

Summary

Across most studies, follow-up within the first year of life was every three months, and this frequency was often decreased to every six months during the second year of life. A few authors reported more frequent assessment within the first month of life. Follow-up provided an opportunity for assessing T4 and TSH levels and for adjustment of replacement therapy dose regimes on the basis of these and was therefore undertaken by a paediatrician although this was not always a specialist endocrinologist.

10.4 Additional evidence from the UKNSPC

The UKNSPC defines acceptable and achievable standards for commencing treatment after positive newborn bloodspot screening results. Standards are set by considering the clinical urgency and the need to commence therapy in a timely manner to prevent unwanted sequelae. To determine whether the standards were consistent with current practice, the median and interquartile ranges (IQR) currently achieved against these standards were estimated by UKNSPC staff. Currently the median age at commencing therapy for a child with a positive screen on the first sample is 10 days (IQR 8-13 days) and for a child who has positive screen on a repeat sample, it is 20 days (IQR 18-25 days).

- *EWG members agreed that, for a screening test which was positive on the first sample, the achievable standard would be 14 days of age and the acceptable standard would be 17 days of age.*
- *EWG members agreed that, for a screening test which was positive on the repeat sample, the achievable standard would be 21 days of age and the acceptable standard would be 24 days of age.*

10.5 EWG Final Recommendations and Revised Standards for Treatment and Follow-up

EWG members agreed that the new standards should be:

New Standard 18. A baby in whom a diagnosis of CHT has been made, should commence treatment with oral levothyroxine by:

a) CHT positive on initial screening sample
Acceptable standard: 17 days of age (≥99% of infants)
Achievable standard: 14 days of age (≥99% of infants)

b) CHT positive on a repeat blood spot sample
Acceptable standard: 24 days of age (≥99% of infants)
Achievable standard: 21 days of age (≥99% of infants)

- *The EWG found Standard 22 (2005) to be inconsistent with the terminology within other bloodspot screening programmes and recommended changing to 'acceptable' and*

achievable' standards. They determined that the timeliness of treatment initiation should prevent severe neurological sequelae but also realistically reflect what was achievable within the current screening programme.

New Standard 19. The starting dose of oral levothyroxine should be 10-15mcg/kg/day, with a maximum dose of 50mcg/day. The objective of treatment is to normalise TSH within the first month. The dose of levothyroxine may need to be reduced if TSH is suppressed or if the baby is showing signs of overtreatment.

Babies with significant endogenous thyroid hormone production may need smaller initial doses.

(See Note 5)

Note 5: Treatment with levothyroxine should lead to normalisation of free T4 and a 50% reduction in TSH within days.[34] However TSH normalisation can take weeks and timing does not correlate well with the administered levothyroxine dosage or the severity of the underlying diagnosis. The aim of treatment is therefore to increase free T4 close to the upper reference range within the first 2 weeks of treatment and to normalise the TSH within the first month.[136] Free T4 concentrations may exceed the normal reference range at the time of TSH normalisation but significant elevation should be avoided. Regular dose adjustments may be required.

- *EWG members agreed that a guide to an appropriate staring dose and upper limit as important to avert the potential overtreatment due to high starting doses described in the literature.*

New Standard 20. Only licensed solutions and tablets of levothyroxine should be used. Suspensions may be unreliable. Parents should be shown how to administer preparations and accompanying written information should be provided.

- *EWG members considered it important to define the types of formulation to be used as suspensions are unreliable in dose but still may be offered to parents. New liquid formulations are now available as alternatives.*

New Standard 21. Once treatment has been started, TSH and thyroid hormone concentration should be checked at approximately 2 weeks, 4 weeks, 8 weeks, 3 months, 6 months, 9 months and 12 months after treatment is started, and thereafter as indicated. More intensive biochemical monitoring may be required.

(See Note 5)

- *EWG members considered it important to define more frequent follow-up during the first year after commencing treatment to ensure that over- and under-treatment was minimised. Note 5 provides a guide to ensure optimal treatment monitoring and consistency.*

11 Economic Effectiveness of Screening, Initial Treatment and Follow-Up Regimes for CHT

11.1 Evidence from the literature review

Only two studies addressing the cost-effectiveness of newborn screening for CHT were retrieved. Carroll and Downs' paper was rated good quality (M+) whilst the Geelhoed's was rated low quality (L). Neither study was undertaken in the UK.

Carroll and Downs (2006)[137] carried out a cost-effectiveness analysis of screening for various inborn disorders in the USA. Through a discounted costs model, estimating quality-adjusted life-years and incremental cost-effectiveness ratio computations, they obtained the following results: For screening for CHT to be cost saving, it would need to have at least 67% sensitivity. Moreover, screening for CH would become costly if the prevalence would decrease to values between 3 and 10 times lower than baseline values. In addition, screening would not be cost saving if the rate of mild developmental delay without treatment was less than one tenth of baseline values or if the risk of severe delay was decreased by approximately one half. Finally, screening for CH would not be cost saving if it was less than 67% effective in preventing severe delay.

Geelhoed and colleagues (2005)[138] undertook a cost-benefit analysis for neonatal screening for PKU and CHT in Australia. They found the annual net saving for screening for CHT was $AUS 1,941,072, while the programme costs were $AUS 581,124 in 2001. Cost savings were primarily attributable to the avoided costs of caring for an intellectually disabled individual.

Summary

The conclusions from both studies were that newborn screening for CHT as currently practised was cost-effective and avoids the costs of providing long-term care to affected individuals in whom the diagnosis is delayed.

11.2 Further Research

Research into the economic effectiveness of newborn screening for CHT in the UK setting is lacking. Ideally, future studies of the economic effectiveness of CHT screening should consider longer-term outcomes and quality of life.

12 Communication with parents

12.1 Introduction

Communication with clinicians and parents was addressed explicitly in the New Standards 10-12, however members of the EWG also considered the leaflets currently produced by the UKNSPC and intended for distribution to parents of children with a presumed positive screening result and after confirmation of the diagnosis.

12.2 Existing leaflets

Two leaflets are currently produced by the UKNSPC:

- 'When Congenital Hypothyroidism is Suspected' – for parents of children with a positive screening result who require further testing
- 'Congenital hypothyroidism and your child' – providing parents with information about the condition and aimed particularly at parents of affected children.

12.3 Revision of parent leaflets

A subgroup of EWG members, including parents, representatives of the UKNSPC and clinicians, was convened. The subgroup reviewed, revised and updated the parent leaflets. These will be available as pdf downloads on the UKNSPC website accessible to parents, laboratory staff and paediatricians.

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Appendix 1: Expert Working Group Terms of Reference and Membership

UK Newborn Screening Programme Centre (UKNSPC) and British Society for Paediatric Endocrinology and Diabetes (BSPED)

Joint Standing Committee on Congenital Hypothyroidism (CHT)

Expert Working Group to review Initial Clinical Referral Standards for CHT 2010 – 2011

1. Terms of reference

1.1 To review existing (2005) UKNSPC standards and guidelines to support confirmatory diagnosis and initial management for babies in whom CHT is suspected

1.2 This will include review of:

- Screening result TSH cut-offs used to determine which infants are referred, not referred or for whom a repeat test might be indicated (borderline).
- Timeliness of referral by laboratory to designated clinician
- Timeliness of first visit to designated clinician when CHT is suspected on first sample
- Timeliness of repeat test for an initial borderline result
- Timeliness of referral to designated clinician when CHT suspected result is preceded by borderline result
- Diagnostic schedule for confirmatory diagnosis of CHT
- Initial treatment including starting dose, formulation and instructions to parents
- Frequency of follow up and repeat blood tests

1.3 To agree consultation and approval process for new standards and guidelines

1.4 To agree timetable for this review

1.5 To support the review process with evidence review and expert consensus where published evidence is lacking

2. Dependencies

2.1 The group will take account of but not revisit the policy on repeat testing of preterm infants as agreed with BAPM.

3. Expected outputs

2.1 Primary output of the group will be:

Revised Standards and guidelines for Initial Clinical Referral – including evidence tables where appropriate.

2.2 The outputs of this review will:

- feed into the CHT laboratory handbook sub group
- need to take account for any recommendations of the BSPED review of managed clinical networks.
- inform parent information and HCP educational material

4. Reporting arrangements

This sub group will report to the Joint Standing Committee for endorsement and recommendation.

Recommendations will be ratified by the Blood Spot Advisory Group (BSAG) and submitted to the Fetal Maternal and Child Health sub Group (FMCH) of the National Screening Committee (NSC) for approval of any changes to current policy.

Appendix 2: Expert Working Group Members and Meetings

12.4 Expert Working Group Members

Dr Tim Cheetham	Chairman, Consultant Paediatric Endocrinologist and representative of the British Society for Endocrinology and Diabetes (BSPED)
Dr Rachel Knowles	Clinical Research Fellow, MRC Centre for Epidemiology of Child Health
Ms Cathy Coppinger	Programme Manager, UK Newborn Screening Programme Centre (UKNSPC)
Ms Radhika Rajani/ Ms Brielle Woods	Administrators, UKNSPC
Professor John Gregory	Consultant Paediatric Endocrinologist and representative of the British Society for Endocrinology and Diabetes (BSPED)
Dr Jeremy Kirk	Consultant Paediatric Endocrinologist and representative of the British Society for Endocrinology and Diabetes (BSPED)
Dr Catherine Peters	Consultant Paediatric Endocrinologist
Ms Jacqui Adkins	Parent
Ms Lynn Booth	Parent
Melanie Downing	Lead Scientist Regional Newborn Screening Laboratory, Sheffield Childrens NHS Foundation Trust. UK Newborn Screening Laboratory Network (UKNSLN) representative
Kate Hall	Clinical Scientist, West Midland Newborn Screening Laboratory UK Newborn Screening Laboratory Network (UKNSLN) representative
Dr Carol Evans	Consultant Clinical Scientist
Ms Shirley Langham	Clinical Nurse Specialist
Dr Laurence Abernethy	Consultant Radiologist
Mr Jez Jones	Thyroid Research Assistant

12.5 Experts attending occasional meetings

Ms Freyja Olafsdottir	PhD Student
Dr Tony Sirimanna	Consultant Paediatric Audiologist

12.6 Expert Working Group meeting dates

14th October 2010

1st March 2011

7th July 2011

16th September 2011

12.7 Subgroup membership

Subgroup Topic	Lead	Membership
Diagnostic Test	Carol Evans	Laurence Abernethy John Gregory Jez Jones
Treatment and Communication	Tim Cheetham Jez Jones	Catherine Peters Cathy Coppinger
Referral Pathway and Clinical Responsibility	Jeremy Kirk	Kate Hall
Screening Test Performance	Rachel Knowles Catherine Peters	John Gregory Kate Hall Shirley Langham Melanie Downing
Communication from the Parent Perspective	Jacqi Adkins Lynn Booth	Cathy Coppinger Radhika Rajani Rachel Knowles Shirley Langham

Appendix 3: Dose and timing of therapy across different studies

Table 1: Starting dose and timing of initiation of therapy

Dose	Age	Reference
2 µg/kg/day	17 days	Gunn et al (1996)[38]
3.2-12.3 µg/kg/day	-	Rovet (2004)[139]
2.5/3.75/5 µg/kg/day	-	Vogiatzi & Kirkland (1997)[135]
4.5-4.6 µg/kg/day	18-34.88 days	Toublanc et al (1998)[43]
5.1 µg/kg/day	24 days	Toublanc et al (1997)[140]
5.1 µg/kg/7.9 µg/kg/9.1 µg/kg	18.3 days/12 days	Rovet & Ehrlich (1995)[127]
5.6 ± 1.6 µg/kg/d	22.8 ± 6.8 days	Leger at al (2001)[61]
6.4 ± .2 µg/kg/d	26 ± .9 days	Salerno et al (2008)[49]
6.6 ±.9 µg/kg/d	26 ± 4 days	Salerno et al (2004)[48]
6.6 µg/kg/d (range 5.3-9.3 µg/kg/d).	14.5 days (range 2-22 days)	Campos et al (1995)[36]
6.7-8 µg/kg	13.5-17 days	Rovet & Alvarez (1996)[63]
6.8 ± 1.8 µg/kg	28.2 ± 10.8 days	Salerno et al (1999)[46]
6.8 µg/kg/day	24 ± 12 days	Moreno et al (1989)[120]
6.8 µg/kg/d	Mean 20 days	Kempers et al (2007)[72]
7 ± 1.8 µg/kg	25 ± 5 days	Salerno et al (2001)[47]
7.6 ± 1.4 µg/kg/day	19.5 ± 14.8 days	Mayayo et al (1988)[141]
7.7 µg/kg (normal hearing), 7.1 µg/kg(hearing impaired)	13.5 days (normal hearing), 22.3 days (hearing impaired)	Rovet et al (1996)[107]
7-10 µg/kg/day	35 ± 9.8 days	Weber et al (1996)[121]
7-10.6 µg/kg/day	10.8-18.1 days	Bongers-Schokking et al (2005)[112]
31/120 used 7.6µg/kg/d, 28/120 used 15 µg/kg/d, 53/120 used 11.4 µg/kg/d.	-	Jones & Donaldson (2009)[130]
8 µg/kg/d	17 days	Law et al (1998)[13]
8.1mg/kg/7.8mg/kg	16.7days/16.9days	Rovet et al (1987)[142]
8.4 ± 2 µg/kg/d	33 ± 14 days	Battisti et al (1996)[58]
8.4 ± 3.3 µg/kg/d	24.4 ± 29.9 days	Oerbeck et al (2005)[41]
8.4 ± 3.4µg/kg	18.9 ± 8.6days	Heyerdahl et al (1991)[60]
8.5 µg/kg/day	18.9 ± 8.6 days	Heyerdahl et al (1996)[71]

Dose	Age	Reference
8.5 µg/kg/day	24.4 ± 29.2 days	Oerbeck et al (2003)[42]
8.5 ±3.3 µg/kg/d	18.9 ± 8.6 days	Heyerdahl (1996)[53]
8.8 ± 2 µg/kg	12.2 ± 4 days	Rovet et al (1989)[143]
8.8 µg/kg/day	16 days	Alvarez et al (2004)[30]
8-9 µg/kg/day	12-14 days	Bakker et al (2002)[34]
8-10 µg/kg	17 days (range 0-114 days)	Tillotson et al (1994)[40]
8-10 µg/kg/d	15 ± 7 days	Ilicki & Larson (1988)[22]
8-10 µg/kg/d	28 days (range 15-45 days)	Bargagna et al (2000)[132]
8-10 µg/kg/d	30 ± 10 days	Bargagna et al (1999)[122]
8-10.6 µg/kg/d	13-17 days	Connelly et al (2001)[35]
8-10µg/kg/d	16.6 ± 16.2 days	Rovet et al (1992)[62]
9 ± 1.7 mcg/kg/d	17.9 ± 21.9 days	Song et al (2001)[68]
9.03 µg/kg/d	Median 25 days	Gibert Agullo et al (2010)[144]
9.1mg/kg	31 days	Nakamizo et al (2007)[9]
9.2 µg/kg/d (range 4-12)	13 days (range 8-30 days)	Bongers-Schokking et al (2000)[111]
9.3 ± 5 µg/kg/d	16.4 ± 22 days	Rovet (1999)[64 69]
9.3 ±5mg/kg	16.25 days	Rovet & Hepworth(2002)[145]
9.8 µg/kg	26.6 days	Delvecchio et al (2007)[51]
10 µg/100cal	29 days	NECHC (1984)[134]
10 µg/kg/day	9 days	Mirabella et al (2005)[146]
10.5 ±0.8µg/kg/d / 7.1 ±1.8µg/kg/d	10.8 days/ 17 days	Bongers-Schokking (2001)[131]
10µg/kg/day	14 days	Brown et al (2002)[114]
10-14 µg/kg/d	4 weeks	Germak & Foley (1990)[55]
10-15 µg/kg/d	8.21 ± 7 days	Alvarez (2010)[57]
10-15 µg/kg/d	9 days (range 5-18 days)	Dimitropoulos (2009)[32]
112.2-12.2 µg/kg/d	13-14 days	Simoneau-Roy et al (2004)[113]
12 µg/kg (7.2-17)	7 days (range 4-15 days)	Arenz et al (2008)[108]
12. µg/kg/d (severe), 11.1µg/kg/d (moderate)	11 days (moderate), 14 days (severe)	Dubuis et al (1996)[31]
12.5-72 µg/d	7-14 days(n=50), 3-6 weeks(n=10)	Winkler et al (1993)[67]
50 µg/d	18 days (range 10-36 days)	Fisher & Foley (1989)[52]

Dose	Age	Reference
Athyreosis: 15 µg/kg/d, Ectopia: 12 µg/kg/d, Dyshormonogenesis: 10 µg/kg/d	2-3 days (positive screen) or 14 days (borderline)	Mathai et al (2008)[29]
Group 1: 25 µg/kg, Group 2: 30-40 µg/kg, Group 3: 50µg/kg	12 days	Jones et al (2009)[130]
Group 1: 6.3 µg/kg/d, Group 2: 9.1 µg/kg/d, Group 3: 13.4 µg/kg/d	21-25 days	Salerno et al (2002)[45]
Group 1; 37.5 µg/d. Group 2: 62.5 µg/d for 3 days, followed by 37.5 µg/d. Group 3: 50 µg/d	10.9 days	Selva et al (2002)[110]
-	28-29 days	Van der Sluijs et al (2008)[125]
-	27± 7.6 days	Murphy et al (1986)[70]
-	23-52 days	Kooistra et al (2004)[128]
-	23.9 ± 10.8 days	Adachi et al (2003)[119]
-	28.2 days	Bargagna et al (2006)[126]
-	16.7 days (range 8-130 days)	Rovet & Hepworth (2001)[147]
-	Median 23 days (4-41 days)	Fuggle et al (1991)[148]
-	9 days (1988), 9 days (1992)	Hopfner et al (2005)[11]
-	24 days (low confirmatory T4) 37 days (intermediate T4)	Kooistra et al (1996)[117]
-	15-91 days	Illig et al (1987)[123]
-	12-46 days	Kooistra et al (1994)[116]
-	12-16 days	Rovet et al (2000)[65]