The Down Syndrome Medical Interest Group

Thyroid Disorder in Children and Young People with Down Syndrome

Surveillance and when to initiate treatment

April 2020

RCPCH Endorsed
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The views of CYP who have Down syndrome were obtained through focus groups facilitated by Down's Syndrome Association and Down's Syndrome Scotland.

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The DSMIG (U.K. and Ireland) wishes to thank all expert peer reviewers for their valuable feedback on the draft scope and draft guideline.

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Stakeholders

The DSMIG (U.K. and Ireland) wishes to thank all stakeholders for their valuable feedback on the draft scope and draft guideline. A complete list of stakeholders is given in Appendix A.

Acronyms and Abbreviations

BMI	Body mass index
CI	Confidence interval
CYP	Children and young people up until their 19th birthday
DSMIG	Down Syndrome Medical Interest Group
DSA	Down's Syndrome Association
GDG	Guideline development group
HLA	Human leucocyte antigen
HT	Hashimato's thyroiditis
NICE	National Institute for Health and Care Excellence
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomised control trial

SD	Standard deviation
SDS	Standard deviation score
T3	Thyroxine 3
T4	Thyroxine 4
TFT	Thyroid function test
TRH	Thyroid releasing hormone
TSH	Thyroid stimulating hormone
fT4	Free T 4 (free thyroid hormone 4)
TT4	Total T 4 (total thyroid hormone)
fT3	Free T 3 (free thyroid hormone 3)
TG antibodies	Thyroglobulin antibodies
TPO antibodies	Thyroid peroxidase antibodies
TRAb antibodies	Thyroid stimulating hormone receptor antibodies

Glossary

Antibodies	Proteins produced in the blood in response to the presence of an antigen or 'foreign substance' e.g. bacteria or a virus
Auto-antibodies	Proteins produced in the blood against the body's own tissues e.g. the thyroid gland. This is not a normal response
Central hypothyroidism	Includes secondary and tertiary hypothyroidism, caused by an abnormality of the pituitary and hypothalamic gland, respectively
Diagnostic overshadowing	The tendency for clinicians to attribute symptoms of a person with learning disability to their underlying cognitive deficits or condition and hence to under-diagnose the presence of co-morbid psychological pathology. It has also been defined as the tendency to attribute any new problems identified to the primary diagnosis once a diagnosis of a major condition has been made, thereby leaving other co-existing conditions undiagnosed.
Decompensated hypothyroidism	Severe hypothyroidism with manifest clinical signs and symptoms
Euthyroid (also referred to as euthyroidism)	A normally functioning thyroid gland with TSH and serum free thyroxine T4 within the defined reference range
Goitre	A visible enlargement of the thyroid gland
Graves' disease	An autoimmune disorder of the thyroid gland causing hyperthyroidism
Hashimoto's disease	An autoimmune disorder of the thyroid gland, causing hypothyroidism

Hypothyroidism	An underactive thyroid gland, with TSH above the defined upper limit of the reference range and a serum free thyroxine T4 below the reference range
Hyperthyroidism	An overactive thyroid gland, with TSH below the defined upper limit of the reference range, with a serum free T4 above the reference range
Isolated hyperthyrotropinemia / isolated raised TSH	A TSH above the local laboratory-defined normal reference range with a serum free T4 within the normal range
Lymphadenopathy	Enlargement of the lymph nodes
Secondary hypothyroidism	Failure of the pituitary gland to secrete TSH
Subclinical hypothyroidism (also known as compensated hypothyroidism)	A marginally underactive thyroid gland, TSH above the local laboratory-defined normal reference range but below 10mu/l, with a serum free thyroxine T4 within the reference range
Thyroid dysgenesis	Absent or severely underdeveloped thyroid gland
Thyroid stimulating hormone	A hormone released from the pituitary gland in the brain which controls the release of the thyroid hormone (free T4 and T3) from the thyroid gland

Who is the guideline for?

This guideline contains recommendations for the care provided by health professionals to CYP with Down syndrome. It can also be used in the education and training of health professionals. The guideline can help the parents/carers of CYP with Down syndrome to make informed decisions and improve communication between patients, their parents/carers and health professionals.

This guideline should be read alongside the NICE Thyroid Disease guidance (November 2019) and NICE Transition from Paediatric to Adult Services guideline (February 2016).

Summary of all recommendations

Information for children and young people, parents and carers

Offer information at each contact to parents/carers and children and young people with Down syndrome on thyroid disorders in order to explain the offer and importance of ongoing surveillance, for example using the following resources:

https://www.btf-thyroid.org/parents-and-carers Last accessed 22.11.19
https://www.btf-thyroid.org/hypothyroidism-leaflet Last accessed 22.11.19
https://www.btf-thyroid.org/hyperthyroidism-leaflet Last accessed 22.11.19
https://www.btf-thyroid.org/thyroid-nodules-and-swellingsleaflet Last accessed 22.11.19
https://www.downs-syndrome.org.uk/download-package/thyroid/ Last accessed 22.11.19

Inform parents/carers that blood test results will show what the child's or young person's thyroid function is at the time of testing and that thyroid function can change over time so further tests will be offered throughout life or if the child or young person develops signs or symptoms.

General recommendations on performing blood tests

Take measures to minimize any potential associated distress when performing blood tests. These measures should include:

- Informing the child or young person (where appropriate) and their parents/carers of the purpose of the test and the possible outcome of the tests including the need for repeat or follow up testing. Explain when and how (by phone or letter) to expect the results of the tests
- Before the blood test is taken explain the process of taking a blood test and inform parents/carers where to find child-friendly online resources showing what happens during a blood test
- Providing support and comfort as needed, if the child or young person is anxious
- Making any reasonable additional adjustments needed to support the blood-taking process
- Ensuring that the blood test being performed by a skilled, experienced practitioner

Also consider:

- The use of distraction techniques e.g. pictures, bubbles, the presence of a play therapist
- The use of topical local anesthetic (cream or spray) to numb the area and the application of a plaster afterwards
- The use of rewards

See, for example: http://www.lchtv.com/blood-taking
https://www.downs-syndrome.org.uk/for-families-and-carers/health-and-well-being/giving-blood-samples/ (last accessed 22.11.19)

Decide whether testing will be venous (TSH, free T4 and thyroid peroxidase (TPO) antibodies) or a dried blood spot test (TSH) in accordance with the clinical presentation, local arrangements and taking into account the preferences of the child or young person and their parents/carers.

Offer venous blood tests for TSH, free T4 and thyroid peroxidase (TPO) antibodies if a child/young person has any signs/symptoms suggestive of hypothyroidism. Do not perform a dried blood spot test in this instance.

Offer venous blood tests for TSH, free T4, thyroid peroxidase (TPO) antibodies and thyroid stimulating hormone receptor antibodies (TRABs) if there is a clinical suspicion of hyperthyroidism.

Time blood tests for routine surveillance to coincide with other blood tests or appointments wherever possible, for example at the annual health review, to minimize any disruption and distress to the child or young person and family. However, it is important to remember an illness can affect the concentration of TSH, free T4 and free T3.

Discuss reference ranges for thyroid hormones with the local laboratory as this will vary depending upon the assay method employed and the child or young person's age.

Neonatal screening

Follow the current national newborn screening blood spot programme for screening for congenital hypothyroidism.
https://www.gov.uk/government/publications/health-professional-handbook-newborn-blood-spot-screening/7-conditions#congenital-hypothyroidism (last accessed 22.11.19)

Do not undertake additional blood tests for thyroid dysfunction in the neonatal period in babies with Down syndrome unless there are signs and/or symptoms of thyroid dysfunction or where additional testing is recommended by the national newborn screening programme, such as for premature or sick neonates.

Ongoing surveillance (from 4-6 months of age)

Offer all infants with Down syndrome thyroid function testing at 4-6 months of age, at 12 months of age and annually thereafter, unless they are already receiving treatment for thyroid disorder or develop signs and symptoms of thyroid dysfunction when earlier testing would be indicated.

Decide the frequency of any follow-up blood tests on an individual basis taking into account initial blood test findings and any signs/symptoms of thyroid dysfunction, including presence or absence of a goitre.

Abnormal blood test findings

The timing of repeat blood tests following an initial abnormal finding for TSH and free T4 should be made according to clinical judgement regarding urgency and bearing in mind that in some instances an abnormal finding may be transient.

Dried blood spot test TSH concentration above local laboratory-defined normal reference range on surveillance sample:

- Offer a venous blood test for TSH, free T4 and thyroid peroxidase (TPO) antibodies within 5 working days of the initial blood test.

- Consider initiating treatment whilst awaiting blood test results if TSH is very high and there is clinical suspicion of hypothyroidism.

Initial venous TSH concentration above 10mU/l, and low free T4:

- Offer immediate repeat venous blood test to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies.

- Consider initiating treatment whilst awaiting blood test results if TSH is very high and there is clinical suspicion of hypothyroidism.

Formulate an individualised management plan for the child or young person if blood test results confirm a diagnosis of hypothyroidism and consider discussing the plan with a clinician with expertise in paediatric endocrinology.

Initial venous TSH concentration above 10mU/l with normal free T4

- Offer a repeat venous blood test to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies as a TSH concentration above 10mU/l with normal free T4 is likely to be a form of hypothyroidism, and discuss with a clinician with expertise in paediatric endocrinology.

Initial venous TSH concentration above local laboratory-defined reference range but below 10 mu/l, and low free T4:

- Offer a repeat blood test as soon as possible, to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies.

- Formulate an individualised management plan for the child or young person if blood tests confirm a diagnosis of hypothyroidism and consider discussing the plan with a clinician with expertise in paediatric endocrinology.

Initial venous TSH concentration above local laboratory-defined reference range, but below 10 mu/l and normal free T4:

- Offer an infant/child under the age of 3 years a repeat TSH and free T4 test in 1-3 months. Include thyroid peroxidase (TPO) antibodies in order to ascertain a baseline.

- In a child or young person aged 3 years and over offer:
    - a repeat venous blood test in 6 months to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies if there are no clinical signs and/or symptoms suggestive of thyroid dysfunction and thyroid antibodies are negative.
    - a repeat blood test sooner than 6 months to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies if clinical signs and/or symptoms develop.

Return to annual surveillance if three consecutive repeat tests show TSH and free T4 remain stable and there are no signs and symptoms suggestive of thyroid dysfunction.

Initial venous TSH within or below the local laboratory-defined reference range, and free T4 below the reference range:

- Offer repeat venous blood tests as soon as possible for TSH, free T4 and thyroid peroxidase (TPO) antibodies.

Seek advice promptly from a paediatric endocrinologist if repeat blood test findings show that the abnormality persists as this may be indicative of a more unusual form of hypothyroidism or central hypothyroidism and further specialized investigations are likely to be needed.

Blood test shows a normal TSH and normal free T4 but raised thyroid peroxidase (TPO) antibodies:

- Offer a venous blood test to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies.
- The timing of these repeat tests should be:
    - in 6 months for children and young people aged 3 years and over
    - in 1 – 3 months in children aged less than 3 years.

Offer a repeat blood test sooner if there are clinical concerns.

Return to annual surveillance if there are no signs and/or symptoms suggestive of thyroid dysfunction.

Hyperthyroidism

Venous TSH below local laboratory-defined reference range and high free T4, or clinical symptoms of hyperthyroidism:

- Seek advice from a paediatric endocrinologist
- Offer a venous blood test for TSH, free T4, free T3, thyroid peroxidase (TPO) antibodies and TSH receptor antibody (TRAB) levels and seek advice from a paediatric endocrinologist if there are any clinical signs and/or symptoms of hyperthyroidism.

Do not routinely test for free T3 as part of ongoing surveillance.

Presence of a goitre

If there is clinical evidence of goitre:

- Offer venous blood testing for TSH, free T4 and thyroid peroxidase antibodies.
- Offer an ultrasound scan.
- Monitor closely for cervical lymphadenopathy.

Seek advice from a paediatric endocrinologist if there are any abnormal findings or clinical concerns.

Do not routinely perform ultrasound surveillance of the thyroid gland in the absence of goitre.

Audit

Staff responsible for commissioning or providing surveillance services for children with Down syndrome should conduct a yearly audit to include the timing, frequency, types of blood tests and test results carried out for children and young people with Down syndrome, and children's and young people's and parents experience of care The test result should also be correlated to clinical signs, symptoms and outcomes. This is usually within the remit of the local secondary paediatric services.

Audit should include pooling of individual patient data regarding antibody levels, and reporting how they relate to other blood test findings and clinical signs and symptoms of thyroid dysfunction.

Research recommendations

What is the incidence of thyroid dysfunction in children and young people who have Down syndrome and is thyroid dysfunction more common in the first year of life?

What is the natural history of thyroid dysfunction in children and young people who have Down syndrome?

What is the natural history of thyroid autoimmunity in children and young people with Down syndrome? How often should thyroid antibodies be evaluated?

Recommended programme for surveillance

The following provides a brief overview of the recommended surveillance programme for thyroid dysfunction in CYP with Down syndrome:

Birth: Follow the national newborn blood spot screening for congenital hypothyroidism

4-6 months: Surveillance for thyroid dysfunction to commence

12 months: Surveillance repeated and to continue annually life-long thereafter

If there is a clinical suspicion of thyroid dysfunction at any stage offer venous blood tests for TSH, free T4 and thyroid peroxidase (TPO) antibodies

1. Introduction

At all ages thyroid disorders occur more frequently in people with Down syndrome than in the general population. If undiagnosed, thyroid disorders can constitute a significant cause of preventable secondary neurodevelopmental impairment and other health issues, including mental health, e.g. behavioural challenges, low mood, anxiety, depression. The prevalence of hypothyroidism in Down syndrome has been reported to vary between 15.1% to 17.5% (Erlichman et al 2016, Purdy et al 2014) in the first year of life and 5.5% in childhood (Noble et al, 2000; McGowan et al, 2011) compared to 0.135% in the general child UK population. Hyperthyroidism is also more common and is more likely to occur in late teenage years or early adulthood.

The diagnosis of thyroid disorders in CYP with Down syndrome based on clinical presentation is unreliable due to diagnostic overshadowing of commonly presenting symptoms e.g. constipation, dry skin etc. Timely biochemical surveillance is essential for early detection and intervention. The treatment and management protocols for thyroid dysfunction in CYP who

have Down syndrome is the same as for CYP who do not have Down syndrome and thus is not covered within the scope of these guidelines.

1.1 Current practice in the UK

All newborns with Down syndrome are included within the newborn blood spot screening programme for congenital hypothyroidism.

As thyroid disorders are significantly more common in CYP with Down syndrome and clinical symptoms and signs (including a goitre/a palpable thyroid) may not be apparent in this population, the DSMIG recommended life-long surveillance for thyroid dysfunction from the age of one year (DSMIG U.K. and Ireland, 2001).

1.2 Clinical need for the guidance

The potential health impact of the guideline will be a reduction in the impact of unrecognised and untreated thyroid disorder in CYP who have Down syndrome. Down syndrome has an incidence of 1:1000 live births in the UK (Down's Syndrome Association website; accessed 20.01.20). The occurrence of hypothyroidism in CYP is reported as between 5.5% and 10%, (King et al, 2014) and hyperthyroidism as approximately 1% (Goday-Arno et al, 2008). This health impact will include improved cognitive functioning in CYP who are identified and treated (particularly those who are identified early, before the age of 3 years), and an associated improvement in behaviour that challenges. Timely treatment can also improve psychological symptoms such as low mood, anxiety and depression. In addition timely initiation of treatment will lead to a decrease in signs and/or symptoms associated with thyroid disorder including constipation, tiredness and lethargy and dry skin.

The DSMIG guidance acknowledged the controversy around the timing, frequency and type of blood tests partly due to a lack of evidence for the reliability and availability of the dry whole blood spot TSH testing. Given that prompt detection and management of hypothyroidism could potentially prevent additional intellectual and health impairments in CYP with Down syndrome, and the reported variation in practice, the DSMIG considered it important to commission the development of high-quality evidence-based guidance on the surveillance and initiation of treatment of thyroid dysfunction.

The on-going management of thyroid dysfunction in CYP with Down syndrome is similar to the general population and was therefore not covered in the scope of this guideline.

It is recognised that blood testing can be distressing for CYP and their parents/carers and thus the process and procedures involved in blood testing are included in the general recommendations.

1.3 Aims and objectives

Aim: To improve surveillance and timely initiation of treatment of thyroid disorder in CYP who have Down syndrome.

Objectives:

1. To increase the proportion of CYP with Down syndrome who have thyroid disorder who are correctly identified.
2. To lower the mean age at which CYP with Down syndrome who have thyroid disorder are identified.
3. To increase the proportion of CYP with Down syndrome who have thyroid disorder for whom treatment is initiated at the optimum time for treatment to have the maximum benefit.

2. Methods

2.1 Introduction

The guideline aims to produce evidenced based guidance to support the surveillance of thyroid function in CYP with Down syndrome. The guideline population is defined as CYP up until their 19th birthday.

The guideline was generously funded by the Down syndrome Medical Interest Group (UK and Ireland).

2.2 Declarations of interest

All members of the Guideline Development Group declared any interests at the beginning of each meeting (see Appendix I)

The DSMIG is a stakeholder and in that role formally commented on the draft recommendations during the consultation period of the draft guideline.

2.3 Developing the clinical questions

The scope identified the clinical areas to be covered by the guideline. The technical team formulated structured review questions within each of the clinical areas with input from the chair and clinical leads.

A review protocol was developed based on a framework of **P**opulation, **I**ntervention, **C**omparison and **O**utcome (PICO). The technical team and clinical leads developed a protocol which defined the parameters for the literature search and the inclusion/exclusion criteria for the systematic review (see Appendix C).

2.4 List of review questions

The following four clinical questions were addressed:

1. What blood tests should be undertaken as part of routine surveillance to identify thyroid disorders in CYP with Down syndrome?
2. When should routine surveillance blood tests commence in CYP with Down syndrome and how often should they be repeated?
3. At what thresholds should treatment be initiated when hypothyroidism has been detected, including clinical symptoms and biochemical thresholds?
4. At what thresholds should treatment be initiated when hyperthyroidism has been detected?

2.5 Identifying the evidence

A simple, sensitive search was developed based on the review protocol combining terms for CYP, Down syndrome and thyroid dysfunction (see Appendix D for search strategy). Literature searches were conducted in the Web of Science which includes the following literature databases: Medline; Science Citation Index Expanded; Arts and Humanities Citation Index; Conference Proceedings Citation Index – Science edition; Conference Proceedings Citation Index – Social Science + Humanities edition; Emerging Sources Citation Index (2015–); Book Citation Index (2005–)); BIOSIS Citation Index; BIOSIS Previews; Cochrane Central Database of Controlled Trials (CENTRAL) [Cochrane Library]; SciELO Citation Index.

Searches were limited to the English language. There was no searching of grey literature, nor was hand searching of journals undertaken. Searches were carried out to identify literature published from 1st January 1989 to 10th April 2019.

Due to the high degree of overlap between the clinical focus of the review questions one broad, sensitive search of electronic literature databases was conducted to identify studies relating to all four questions. The electronic search returned 1,192 citations. Screening of abstracts identified 30 references for consideration for inclusion in the systematic review. An additional 3 papers were submitted for consideration by the guideline development group chair. Based on the review protocol eleven of these studies were excluded and 22 were included in the guideline review (see Appendix E for PRISMA flow diagram). Reasons for exclusion of excluded studies are given in the excluded studies table (Appendix H).

2.6 Reviewing and synthesising the evidence

Information on study design, methods, participants, clinical interventions and findings were extracted directly into an evidence table (see Appendix F). Details of study methods extracted included any definitions of normal thyroid function/dysfunction with thresholds for thyroid function blood tests. In addition, laboratory assay methods were recorded where this had been reported.

A complete narrative summary of the evidence base was drafted (see section 3 below) based on a brief description of the study, participants and key findings relating to the clinical questions. This was divided into sub-sections to reflect the evidence base and to aid consideration of the evidence for each of the 4 clinical questions. In order to avoid repetition all 4 clinical questions are addressed in the one narrative summary since all questions are inter-related and most studies report findings relating to at least 3 questions.

Appraisal of the level of certainty ascribed to the findings of each study was derived using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Guyatt et al, 2011), a quality appraisal approach developed for use in guidelines. The principles of GRADE include assessment of risk of bias (taking into consideration selection bias, performance bias, detection bias, attrition bias and reporting bias), inconsistency of findings (heterogeneity), indirectness (poor applicability of the study population, intervention, control or outcomes), imprecision (judged based on width of confidence intervals and/or adequacy of sample size) and publication bias. The four possible grades of

the certainty of evidence ascribed using this system are high, moderate, low and very low (Balsham et al, 2011). See GRADE tables (Appendix G) for details of quality appraisal and reasons for downgrading of evidence level for each of the relevant findings from the included studies.

2.7 Developing recommendations

Recommendations were derived by the guideline development group and explicitly linked to the evidence that supported them. In the first instance drafts of the systematic review (evidence table and narrative review) were shared with the guideline group chair and clinical leads and from time to time additional input was sought from subject or lay experts. This iterative work between meetings led to the development of concise evidence statements and a list of issues for consideration by the guideline development group.

The evidence table, narrative summary, evidence statements and key points for consideration were then presented to the group for discussion at guideline group meetings. All recommendations were made based upon GDG interpretation and discussion of the evidence, informed by clinical knowledge and experience along with expert input from CYP's representatives. Following this discussion recommendations were drafted live at the meetings and the wording agreed by the group. Where there was disagreement between group members further informal discussion was conducted until a consensus was reached and a form of wording drafted that the whole group could agree. Editing of recommendations was carried out between meetings and changes shared with the guideline group and agreed by email.

Key points from the guideline group's discussion and decision-making leading to recommendations are reported in the consideration of evidence (section 3.6). This section includes consideration of the evidence findings, including their applicability to clinical practice, benefits and risks associated with interventions, the experiences of CYP and their families/carers and resource implications. Where the evidence reviewed linked directly to a recommendation this is cross-referenced in the consideration of evidence (sections 3.4 and 3.7). Some recommendations have been drafted based upon an overall consideration of a body of evidence rather than on a particular finding, again this association is cross-referenced. Recommendations have also been drafted by the GDG in order to encourage good practice. These recommendations are based upon the clinical experience and expertise of professionals in the group and the views and experiences of care expressed by CYP's representatives and do not link specifically to the evidence reviewed.

The strength of recommendations is reflected in their wording, as used in NICE clinical guidelines. The term "offer" is used to represent a strong recommendation and "consider" represents a less strong recommendation. The body of evidence for this guideline is predominantly of low and very low certainty as defined using the GRADE methodology. This is usual for evidence based upon observational studies, many of which rely upon the retrospective examination of medical records. In order to take this floor effect into consideration, and so as not to undermine the usefulness of the guideline, the strength of

recommendations is not based solely upon the level of certainty of findings but takes into account the overall body of evidence. Where there were three or more studies providing evidence for a recommendation supported by GDG consensus a strong recommendation was made. Additionally, where good practice recommendations regarding provision of information and how to minimize the distress associated with blood tests were made with the full agreement of all GDG members, including CYP's representatives, these were also worded as strong recommendations. Where there was more limited supporting evidence or some disagreement amongst GDG members (but with overall consensus) a less strong recommendation was made.

2.8 Stakeholder involvement

Stakeholders were invited to comment on the draft scope and draft guideline. Comments on the draft scope were reviewed by the technical team, chair and clinical leads and, where agreed appropriate, amendments made based on the comments received. The draft full guideline was available online for consultation 26th September – 23rd October 2019. Following consultation, all stakeholder comments were collated and considered initially by the guideline chair, clinical leads and technical team. Where potential changes to recommendations were indicated in light of stakeholder feedback relevant comments were discussed by the full guideline development group and amendments agreed by informal consensus. Minor changes e.g. clarification of meaning, layout and presentation, ordering of sections, typographical errors were discussed and agreed between the technical team and guideline group chair with the support of the clinical leads where necessary.

2.9 Young people, parent and carer participation

The guideline development group (GDG) included a parent of a young person with Down syndrome as a full member. At each meeting items relevant to service users were discussed and a dedicated opportunity made for input from the parent/carer representative in addition to her participation in ongoing discussion. An invitation was extended to a few young people with Down syndrome to participate as a GDG member, but unfortunately, despite repeated efforts on all sides, this was ultimately not possible. However, in order to facilitate direct feedback on the guideline recommendations from young people with Down syndrome and their families, three focus groups were held during the consultation period, one organised and facilitated by the Down's Syndrome Association Scotland involving five young people with Down syndrome and two facilitated and organised by the Down Syndrome Association involving 25 young people with Down syndrome in Devon (n=9) and in London (n=16). A short summary of the feedback received from the young people at these meetings is given in Appendix L. In addition, stakeholders including voluntary sector organisations and those representing young people, families and carers were specifically invited to comment on the draft guideline from the users' perspective. All feedback from the focus groups and stakeholder comments was collated and carefully considered by the GDG in order to ensure the views of CYP and their families and carers are represented in the consideration of evidence and the guideline recommendations.

2.10 External peer review

Consultation on the scope took place in Spring 2019. During this time subject experts were invited to comment.

The draft guideline was peer reviewed by three external experts, including two expert clinicians and a family representative. External expert advice was also provided regarding laboratory reference values for thyroid function tests.

Feedback from peer reviewers was considered by the guideline group and amendments made to the final version of the guideline following discussion of all feedback from expert peer reviewers and stakeholders.

2.11 Guideline endorsement

The guideline has been developed with formal stakeholder support from the RCPCH and has received RCPCH endorsement

https://www.rcpch.ac.uk/sites/default/files/2018-03/setting_standards_for_development_of_clinical_guidelines_-_2016.pdf).

2.12 Guideline update

Five years after publication (in 2025) the DSMIG will consider the need to update the guideline in light of any new evidence or other relevant information. This will be carried out earlier should the DSMIG become aware of important new evidence before five years have elapsed.

3. Surveillance and when to initiate treatment

3.1 Introduction

The GDG acknowledged the existing published guidance on Thyroid Disorders in Children by the DSMIG U.K. and Ireland (2001), the American Academy of Paediatrics (2011), the European Society for Paediatric Endocrinology Consensus Guidelines on Screening, Diagnosis and Management of Congenital Hypothyroidism (2013) and the NICE guidance on Thyroid Disease: Assessment and Management (2019). The guideline group noted that the NICE guideline does not address CYP with Down syndrome specifically and that recommendations for CYP with Down syndrome may well differ from those meant for the general population of CYP.

The GDG was aware of considerable variation in practice in the timing, frequency and type of blood tests being undertaken as a part of surveillance of thyroid disorders in CYP with Down syndrome in the U.K. (personal communciation DSMIG, Steering Group Committee). The GDG also acknowledged the variations in the laboratory platform assays and reference ranges for both TSH and free T4 concentrations...

The guideline scope extends from birth to a young person's 19th birthday. In utero detection of thyroid disorders and surveillance in adulthood is not included within the scope of this guideline and thus are not addressed here. The guideline does not cover the following scenarios:

1. Pre-term babies, in utero detection and thyroid dysgenesis. These issues are covered within the scope of the national newborn screening programme.
2. Central hypothyroidism: Secondary (pituitary) and tertiary (hypothalmic) causes of hypothyroidism. These conditions are rare, and although they should be detected by the surveillance progamme, a specific literature search was not conducted for them, as they should be managed as for any CYP, seeking specialist advise from a paediatric endocrinologist

3.1.1 Presentation of evidence and recommendations

The guideline evidence and recommendations are presented as follows:

- Narrative summary of evidence for all 4 clinical questions
- Evidence statements for clinical questions 1 and 2 (what tests to perform and when to carry them out)
- Consideration of evidence for questions 1 and 2
- Recommendations for questions 1 and 2
- Evidence statements for clinical questions 3 and 4 (thresholds for treatment for hypothyroidism and hyperthyroidism)
- Consideration of evidence for questions 3 and 4
- Recommendations for questions 3 and 4

3.2 Narrative summary of evidence for the 4 clinical questions

Clinical questions:

1. What blood tests should be undertaken as part of routine surveillance to identify thyroid disorders in CYP with Down syndrome?
2. When should routine surveillance blood tests commence in CYP with Down syndrome and how often should they be repeated?
3. At what thresholds should treatment be initiated when hypothyroidism has been detected, including clinical symptoms and biochemical thresholds?
4. At what thresholds should treatment be initiated when hyperthyroidism has been detected?

In order to avoid repetition the narrative summary addresses all four clinical questions together as the evidence for them has a very high degree of overlap i.e. many of the reviewed studies included evidence for at least three of the clinical questions. The narrative summary is divided into the following sections:

- Neonatal screening
- Ongoing surveillance
- Predictive value of thyroid function tests
- Prevalence and course of thyroid dysfunction, and the role of thyroid antibodies

For details of the included studies see the evidence table in Appendix F.

For GRADE assessment of certainty of evidence findings see tables in Appendix G.

Excluded studies are listed in Appendix H.

3.2.1 Neonatal screening

(2 studies)

A retrospective observational study conducted in Israel aimed to determine whether thyroxine (T4)-based screening followed by TSH measurements in infants with TT4 <10th percentile identified congenital hypothyroidism in all neonates with Down syndrome (Erlichman et al, 2016). TT4 measurements were obtained from the National Screening Programme between 1998 and 2007 for 159/190 (83.7%) children with Down syndrome. Demographic and clinical data were collected from medical records and telephone interviews conducted with the primary care doctor of each child to obtain details of laboratory tests, age at diagnosis and any treatment given. The screening programme required TSH to be measured in infants whose TT4 values were <10th percentile of the same day's analysis, thus by definition TSH was measured in 10% of general population compared with 27.6% of infants with Down syndrome. Forty-four infants with Down syndrome had venous TSH measured. TT4 concentrations did not correlate with TSH concentrations in infants who had both measured. Twenty-four of the 32 infants who were started on thyroxine therapy continued treatment after subsequent testing, giving a prevalence of 15.1%. Values of TT4 at screening were nearly identical between children who eventually were treated (11.2 $\pm$ 3.9 mcg/dL) and those who never received treatment (11.3 $\pm$ 3.0 mcg/dL; p = 0.59). TSH concentrations at screening were significantly higher in the treated group (18.2 $\pm$ 18.1 mU/L; n = 12) than in the untreated group (9.2 $\pm$ 12.0 mU/L; n = 32) (p value not reported). Twenty infants began L-thyroxine therapy within the first month of life. Of these, 10 had been diagnosed by initial screening at birth, based on low TT4 and confirmed by high TSH; 10 were diagnosed after discharge based on subsequent testing; only one of this group had transient hypothyroidism. [Evidence level: low]

An earlier Swedish retrospective observational study sought to determine whether TSH concentrations measured at neonatal screening using a dried blood spot test were associated with the development of hypothyroidism during childhood (Myrelid et al, 2009). The study sample comprised children with Down syndrome born between 1986 and 1996 who were followed up for 10 years by means of hospital record examination. Full sets of study data were available for 62 children. None of the children with Down syndrome had a capillary TSH concentration ≥ the threshold of 40 mU/l. Twenty-two children with Down syndrome were started on thyroxine therapy during the follow up period, giving a prevalence of 35.5%. Four of these children were positive for autoantibodies (thyroperoxidase (TPO) and thyroglobulin (TG)). Examination of records for the 22 children on therapy showed 7 had hypothyroidism (TSH above reference level and T4 below reference level); 6 children had subclinical hypothyroidism (TSH above reference level and T4 on the lower limit) with symptoms of hypothyroidism; and 9 children had symptoms of hypothyroidism (with normal TSH

concentration and T4 concentration close to the lower reference limit). Neonatal TSH or TSH standard deviations did not differ significantly between children who went on to develop hypothyroidism and those who remained euthyroid. [Evidence level: very low]

3.2.2 Ongoing surveillance

(4 studies)

A retrospective observational study conducted in the USA investigated the incidence of hypothyroidism in infants with Down syndrome when tested at birth and then again prior to 6 months of age (Purdy et al, 2014). Medical records for infants with Down syndrome admitted to the study hospital between May 2000 and March 2012 with a normal thyroid screening result at birth were examined to cross-link demographic data and thyroid hormone laboratory tests performed before 4 months of age (n=80; age range 3 – 120 days). One baby was born with hypothyroidism and excluded from the analysis. Four categories of thyroid function were defined: euthyroid (normal TSH and normal TT4); primary hypothyroidism (high TSH and low TT4); compensated hypothyroidism: high TSH and normal TT4); sick thyroid syndrome (low TSH and low TT4). Thresholds for thyroid hormone concentrations are not reported. Fifty-four (67.5%) of the infants retested before 4 months of age remained euthyroid; 14 (17.5%) were diagnosed with primary hypothyroidism and treated with supplemental T4; and 12 (15%) were found to have compensated hypothyroidism. Two infants were diagnosed with sick thyroid syndrome. The overall prevalence of thyroid dysfunction (congenital hypothyroidism and primary hypothyroidism) was 18.5%. The incidence of hypothyroidism was not associated with gender, cardiovascular or gastrointestinal disorder. [Evidence level: low]

A prospective observational study was conducted by Noble et al (2000) to establish the feasibility of a school-based screening programme for thyroid dysfunction in CYP with Down syndrome (UK, Scotland). All CYP with Down syndrome in two Scottish health boards were entered onto a register over the two school years 1997-8 and 1998-9 and invited via a letter to their parents/carers to take part in an annual screening programme using capillary blood testing. Two hundred of 214 CYP with Down syndrome were screened (93.5%). An additional 9 CYP were tested outside of the screening programme so by the end of the 2 years 209/214 CYP with Down syndrome (97.7%) had been tested. The capillary TSH threshold for referral was 10mU/l. Over the 2 years of study 15 CYP were referred for further testing, aged between 5 and 18 years (median 13). The raised capillary TSH concentrations were confirmed by venous testing in all cases, and all but one had either positive microsomal or TPO antibodies consistent with Hashimoto's thyroiditis. Of the 10 CYP referred in year 1, thyroglobulin antibodies were negative in five of the CYP and strongly positive (1/1600) in two. Of the 15 CYP referred in total, six had markedly raised TSH values (36 – 132 mU/l) with subnormal fT4 concentrations of 5.2 – 8.9 pmol/l (normal range 9 - 26) and 1 further child/young person had symptoms of hypothyroidism although fT4 was normal and TSH only mildly raised (14.8mU/l). All seven CYP were started on thyroxine treatment. None of these seven CYP had visited their GP in relation to their thyroid function. Eight CYP had mildly raised venous TSH concentrations (7.3 – 12.7 mU/l) with normal fT4 (median 11.6, range 9.4 – 19.7 pmol/l). None of these CYP had clinical features of hypothyroidism and none were treated initially. On venous retesting

one year later fT4 remained >9 pmol/l in all CYP. However, 4 of these CYP were started on thyroxine therapy because TSH values had risen accompanied in 2 cases by the onset of tiredness/lethargy. TSH fell in three of the four remaining CYP and there was a marginal rise in one; all remained untreated. The overall prevalence of thyroid dysfunction based on CYP receiving thyroxine therapy was therefore 5.5% (11/200). [Evidence level: moderate]

A second study conducted in Scotland sought to determine the uptake of a community-based capillary (dried blood spot) TSH screening programme and the optimal frequency of screening (McGowan et al, 2011). This retrospective longitudinal study examined proformas for all CYP referred for follow up from the national capillary TSH screening programme from 1997 to 2009. The capillary TSH threshold for referral was ≥4 mU/l in whole blood (from 2002 onwards); and the reference ranges for venous blood tests were: TSH 0.55-5.8 mU/l and fT4 9-26 pmol/l. Ninety-eight of the 132 CYP (77%) referred had a full set of data available for analysis. The estimated uptake of screening amongst all CYP with Down syndrome was 56%, with the proportion of pre-school children screened ranging from 16.7% - 24.1% (2005 to 2009). The prevalence of thyroid dysfunction for the population of all CYP with Down syndrome was 5.7% with age at referral of 9.4 years (range 0.9 – 17.9 years). Thirteen of the children referred were pre-school (age 2.1 years, range 0.9 - 3.3 years), four of whom were started on treatment immediately (three had pre-treatment venous TSH >11.0 mU/l). Two of these 13 children were symptomatic. Of the 98 CYP referred 57% had tested negative the previous year. Of 22 CYP with venous TSH <6 mU/l two were started on treatment immediately by their clinician. A further five were subsequently started on treatment, three of whom were asymptomatic. Of 27 CYP with venous TSH 6-10.9 mU/l 12 of 22 tested were found to be antibody positive; 11 were started on treatment, three immediately and eight subsequently. Of 25 CYP with venous TSH 11.0-20.9 mU/l four had decompensated hypothyroidism; 17 of 19 tested were antibody positive. Twenty of these CYP were treated, 15 initially and 5 subsequently. Of 24 CYP with venous TSH >21 mU/l 12 had decompensated hypothyroidism. Sixteen of 19 CYP tested were antibody positive. Twenty-two of these CYP were reported as receiving thyroxine treatment (n=2 incomplete data). A significant negative correlation was found between venous fT4 and age ($R=-0.35$; $p<0.001$). No significant correlation was seen between age and capillary TSH ($R=0.14$; $p=0.17$) and a borderline significant correlation between age and venous TSH ($R=0.19$; $p=0.05$). A significant correlation was found between venous TSH concentration and TPO antibodies ($R=0.417$; $p<0.001$). In a comparison of CYP with and without symptoms a significantly higher TSH was found in CYP with symptoms ($p=0.03$). The authors note some inconsistencies in management of CYP with elevated venous TSH, with some being started on treatment when the venous TSH <6 mU/l whilst others with a higher concentration were not. [Evidence level: low/very low]

A similar Scottish retrospective longitudinal observational study was conducted to identify a capillary TSH concentration below which low venous fT4 (<9 pmol/l) and/or frank venous raised TSH concentration (>10 mU/l) would be unlikely (McGowan et al, 2015). Data was collected from proformas submitted to the Scottish screening programme between 2003 and 2013 for CYP with Down syndrome with a capillary TSH ≥4 mU/l. During the study period 99 CYP meeting the inclusion criteria were identified, 76 were school age (≥5 years) and 23 were

preschool (<5 years); median age at referral 9.4 years (range 0.9 to 18.1 years). Twenty CYP had symptoms that could have been thyroid related, 43 had no symptoms (6 had possible symptoms; 30 sets of missing data). The height and weight of CYP with symptoms were not significantly different from those without symptoms (n=70). When growth was examined in relation to venous TSH values of <10, 10 - 20, and >20 mU/L no differences were found for median height SDS (-0.04, -0.179 and 0.279; p=0.49]) or median weight SDS (0.084, 0.499 and 0.285; p=0.86). As expected, the correlation between capillary and venous TSH was high (Pearson correlation +0.814; p=0.01). The correlation between capillary TSH and fT4 was less high although still statistically significant (-0.522; p=0.01). Receiver-operator curve analysis was conducted to show the sensitivity and specificity for different thresholds of capillary TSH to predict venous TSH >10mU/l; these ranged from a sensitivity of 95.9% with a specificity of just 5.8% for a capillary TSH threshold of 4.06 mU/l to a sensitivity of 71.4% and a specificity of 84.6% for a threshold of 6.32 mU/l. Although sensitivities improved, capillary TSH values of below 5.15 mU/l gave specificities of less than 60%.

Venous TSH and fT4 concentrations were stratified according to capillary TSH for pre-school and school age CYP as seen in table 1. Decompensated hypothyroidism was defined as venous fT4<9 pmol/l and venous TSH elevation as >10 mU/l.

Table 1. Venous (ven) fT4 and TSH concentrations in 99 children with Down syndrome according to capillary TSH concentrations on hypothyroid screening

Cap TSH (mU/l) [n]	Ven fT4 median (range) pmol/l	Ven TSH median (range) mU/l	Ven fT4 <9 pmol/l		Ven TSH >10 mU/l	
			<5 years	≥5 years	<5 years	≥5 years
4 – 5.9 [n=53]	14.0 (7.45 – 20.0)	7.1 (1.15 – 25.9)	0 / 15	1 / 38	4 / 15	9 / 38
6.0 – 10.9 [n=24]	13.15 (8.5 – 18.0)	11.94 (1.5 – 92.0)	0 / 5	2 / 19	3 / 5	14 / 19
11.0 – 20.0 [n=10]	12.0 (9.9 – 17.7)	13.0 (2.7 – 59.0)	0 / 0	0 / 10	0 / 0	7 / 10
>20.0 [n=12]	7.6 (4.4 – 14.0)	85.2 (63.7 – 151.0)	1 / 3	5 / 9	3 / 3	9 / 9

[Evidence level: low]

A prospective, observational study tested the feasibility and acceptability of screening for hypothyroidism using finger prick capillary blood testing for TSH in infants and CYP (Murphy et al, 2008). Data were collected from 394 CYP born between January 1981 and December 1997, 305 of whom received the fingerprick test. The overall prevalence of thyroid dysfunction was 4.6% (18/394) including six CYP who were newly diagnosed during the study, five from the fingerprick screening test and one following presentation at A&E with clinical symptoms of constipation. The mean age of CYP newly diagnosed was 10.8 years (range 7.7 – 16.1 years). Five CYP were positive for thyroid microsomal or TPO antibodies and three showed clinical signs/symptoms of hypothyroidism (fatigue, poor growth and constipation) but these had been attributed to Down syndrome itself rather than hypothyroidism. Ten CYP had been previously diagnosed with hypothyroidism; three of these CYP had presented with clinical signs/symptoms, six had been positive for antibodies and four had been under the age

of 3 years at the time of diagnosis. Two CYP had been previously diagnosed with hyperthyroidism, one of who had presented with clinical signs. CYP with a capillary TSH >10 mU/l were followed up with a venous sample for TSH, fT4 and antibodies (microsomal antibodies earlier in the study and TPO antibodies later in the study). The finger prick test was found to be feasible and accepted by most CYP with only 4/309 declining the test. [Evidence level: moderate]

3.2.3 Predictive value of thyroid function tests

(2 studies)

A prospective longitudinal study conducted in India sought to determine the predictive value of venous TSH concentration at time of diagnosis of thyroid dysfunction in young children with Down syndrome in determining persistent hypothyroidism (Sankar et al, 2018). Forty-seven of 192 children with Down syndrome (24.5%) aged under 3 years referred to the study hospital were found to have a venous TSH concentration >5mU/l and treated with thyroxine. Total T4 (TT4) concentrations were also tested with the normal range defined as 4.5 – 12.5 µg/dl. Four of these children were diagnosed with overt hypothyroidism (mean TSH 46.5 mU/l (SD 41.), giving a prevalence of 2.1% at mean age 11.5 months. A further 43 children were diagnosed as having subclinical hypothyroidism (mean TSH 10.5 mU/l (SD 3.8). Two of the four children with overt hypothyroidism were positive for anti-TPO antibodies, as were 6/43 children with sub-hypothyroidism. Anti-thyroglobulin antibodies were negative in all children. Thirty-four of these children were evaluated later at the age of 3 years for persistent hypothyroidism. Most children (n=25; 73.5%) were found to have normalized TSH concentrations whilst the remaining 9 children (26.5%) were found to have high TSH suggestive of hypothyroidism. The overall prevalence of hypothyroidism (persistent hypothyroidism at 3 years of age) was 7.1%. Receiver-operator curve (ROC) analysis indicated that a venous TSH threshold of 11.6 mU/l predicted persistent hypothyroidism with a sensitivity of 77% and a specificity of 92%. Values for alternative cut-off values are not reported and the ROC plot is not shown. [Evidence level: low]

An earlier UK prospective longitudinal study assessed whether findings from thyroid function tests performed earlier in childhood could predict later hypothyroidism during adolescence (Gibson et al, 2005). Thyroid function was assessed using blood tests for TSH, thyroid binding globulin, TT4, thyroglobulin, thyroid microsomal antibodies and clinical symptoms. Definitions used in the study were as follows:

- Hypothyroidism: low thyroxine and TSH ≥ 6 mu/ml
- Isolated raised TSH (IR-TSH): normal thyroxine and TSH ≥ 6 mu/ml
- Normal thyroid function: normal thyroxine and TSH < 6 mu/ml
- Positive autoantibodies: titre > 1:64

The first round of data collection was carried out 1988-1987 with a second round from 1990-1993. One hundred and three CYP with Down syndrome were tested on both occasions with ages ranging between 6 – 14 years (median 9.8 years) at first testing and 10 – 20 years at second testing (median not reported). Findings were as follows:

Table 2. Summary of findings: children with available results at second testing					
Thyroid function 2nd test					
Thyroid function 1st test		Hypo-thyroid	IR-TSH	Normal	**Total**
	Hypothyroid	0	0	0	0
	IR-TSH	1	5	14	20
	Normal	2	4	77	83
	Total	3	9	91	103

If IR-TSH at second testing is considered normal (i.e. for second testing the IR-TSH column and the normal column are combined) the sensitivity of the thyroid testing is 50% and the specificity 82%. The overall prevalence of thyroid dysfunction (CYP receiving ongoing thyroxine therapy) was 3.8%. Eight CYP tested positive for antibodies at the first testing (all 8 were positive for anti-microsomal antibodies and 2 were additionally positive for thyroglobulin antibodies). Of these eight, five remained positive at second testing, three retained IR-TSH and one developed hypothyroidism. Two CYP initially negative for antibodies became positive at second testing. The association between positive autoantibodies on first testing and an abnormal second test (hypothyroidism, IR-TSH, and positive antibodies) was significant (Fisher's exact test $p<0.05$). The association between positive antibodies on first screen and hypothyroidism at second test was not significant. Symptoms associated with hair growth, skin, appetite, bowel function, height and weight were found not to be related to thyroid dysfunction or autoantibody status. [Evidence level: very low]

3.2.4 Prevalence and course of thyroid dysfunction, and the role of thyroid autoantibodies

(12 studies)

A prospective longitudinal study conducted in Italy investigated the development of thyroid dysfunction in children with Down syndrome (Iughetti et al, 2014). The thyroid function of children was tested annually from birth for 10 years and blood samples analysed for TSH, fT4, thyroglobulin antibodies and TPO antibodies, and thyroid ultrasonography performed when congenital thyroid abnormalities were detected at birth, or at age 2 years for other children and when abnormal blood test results were obtained. Congenital hypothyroidism was diagnosed based on the neonatal screening measurement of TSH ≥ 20µIU/ml on dry blood spot testing and confirmed by plasma thyroid function test after 8 days of life (threshold not reported). All children with Down syndrome were grouped annually according to fT4 and TSH concentrations as follows:

- Euthyroidism: normal fT4 and TSH ≤ 5µIU/ml

- Hypothyroidism: low fT4 and TSH ≥ 10µIU/ml
- Subclinical hypothyroidism: normal fT4 and TSH > 5µIU/ml
- Hyperthyroidism: high fT4 and low TSH

Neonatal testing confirmed congenital hypothyroidism in 10/145 children (6.9%; all had abnormal characteristics on ultrasound); 4 children had hypothyroidism (2.7%; all had normal ultrasound characteristics) and 27 had subclinical hypothyroidism (18.6%; 2 of these children had thyroid hypoplasia and 1 year later developed thyroid autoantibodies). The remaining 104 children (71.7%) had normal thyroid function. Subclinical hypothyroidism had a fluctuating course between normal, compensated and overt hypothyroidism and its probability was found to be fairly stable over the 10 years, being 22% at the 1st year and 24% at the 10th year. The probability of overt hypothyroidism increased from 7% at the 1st year to 24% at the 10th year ($p<0.001$; ordinal logistic regression). The overall prevalence of thyroid dysfunction (congenital hypothyroidism, hypothyroidism and hyperthyroidism) was 9.7% (14/145).

Of the 104 children with normal thyroid function at birth 64 (61.5%) still had normal thyroid function at 10 years, 17 developed subclinical hypothyroidism and 17 developed hypothyroidism. One child developed hyperthyroidism and was removed from the analysis. In the subclinical hypothyroidism group one third had developed normal thyroid function by the end of the study (without replacement therapy) whilst another third developed hypothyroidism. The probability of positive thyroglobulin antibodies increased from 3% at 1st year to 25% at the 10th year with corresponding figures of 5% and 37% for TPO antibody ($p<0.001$, binary logistic regression). Two different natural course patterns were found for euthyroidism and subclinical hypothyroidism depending upon the presence or absence of thyroid antibodies. Sixty per cent (22/37) of children with normal thyroid function who tested positive for thyroid antibodies developed a thyroid dysfunction (including one case of hyperthyroidism), whereas 73% of this group who tested negative for thyroid antibodies remained euthyroid (49/67) ($p=0.002$). Among the children with subclinical hypothyroidism at the first visit, 50% (7/14) of those who were thyroid antibody positive still had subclinical hypothyroidism at the last visit, whereas 28.6% (4/14) developed hypothyroidism. In the 13 children with subclinical hypothyroidism who were thyroid antibody negative 5 (38.5%) developed hypothyroidism whilst 6 (46.1%) became euthyroid. Thyroglobulin antibody positivity was found to be associated with a higher odds of more severe rather than less severe hypothyroidism (OR=3.6 [95% CI 1.2 to 11.0], $p=0.02$). TPO antibody positivity was a better predictor of more severe hypothyroidism (OR=6.1 [95% CI 2.3 to 16.1], $p<0.001$). Adding thyroglobulin antibody positivity to TPO antibody positivity was associated with no improvement in the prediction of the severity of hypothyroidism as compared to TPO antibody positivity alone.

To assess the possibility that the concentration of initial TSH were predictive of a future thyroid dysfunction requiring thyroxine therapy the 1st year TSH values were correlated with the last ones taken before beginning treatment. The TSH concentrations at 1st year (4.92 ± 1.83 µIU/ml) and the ones just before therapy (12.3 ± 13.5 µIU/ml) were not significantly

correlated (Spearman's rho=0.234, p=0.098). Similar results were observed analysing data according to 1st year thyroid function for euthyroidism (Spearman's rho=0.060, p=0.7322) and subclinical hypothyroidism (Spearman's rho=0.317, p=0.230). [Evidence level: low]

A retrospective longitudinal study conducted in the USA investigated the timing and prevalence of thyroid disorders in CYP with Down syndrome with the aim of re-examining screening recommendations (Pierce et al, 2017). The medical records of all CYP with Down syndrome attending one of 2 clinics at the research university between November 2007 and January 2015 were reviewed and results of thyroid function blood tests, clinical and demographic data noted. The prevalence of thyroid disorder (congenital hypothyroidism, overt hypothyroidism, unknown hypothyroidism and hyperthyroidism) was 12.6% (71/565). An additional 76 CYP (13.5%) were noted to have subclinical hypothyroidism. The median age at diagnosis of hypothyroidism was 4 years 10 months and the median age for the diagnosis of hyperthyroidism was just under 9 years. Representative reference ranges after 1 month of age: TSH 0.5 to 5.0 µIU/ml and fT4 0.8 to 1.8 ng/dl, although the authors note that classifications of "high" and "low" concentrations for diagnosis of thyroid disease were decided by individual laboratories. Among those diagnosed with hypothyroidism outside of newborn screening, n=11 (7.5% of all acquired hypothyroidism) were diagnosed before 6 months of age. A Kaplan-Meier estimate was calculated for the development of thyroid disease with increasing age which suggested that 25% CYP with Down syndrome would have thyroid disease by the age of 7.5 years and 50% by adulthood (reporting suggest this includes subclinical hypothyroidism although it is not clear). Clinical findings support this estimate. If the estimate is restricted to CYP with TSH >10 µIU/ml at diagnosis the figures are 25% developing thyroid disease by 10 years of age and 50% by adulthood. The proportion of CYP found to be antibody positive is also reported. CYP with overt hypothyroidism were significantly more likely to be antibody positive than those with subclinical hypothyroidism (p=0.02) and those with isolated hyperthyrotropinemia (p=0.01) (note: numbers in the subgroups are very small e.g. n=5 with overt hypothyroidism). [Evidence level: very low]

A retrospective longitudinal study conducted in Italy sought to describe Hashimoto's thyroiditis in CYP with Down syndrome and compare it with Hashimoto's thyroiditis in a control group of CYP without Down syndrome (Aversa et al, 2015). The medical records of 699 CYP diagnosed with Hashimoto's thyroiditis were reviewed and the subgroup of 146 CYP with Down syndrome were clinically reassessed for thyroid function patterns, serum fT4 and TSH concentrations and ultrasound examination of the thyroid gland. The median follow-up time of this reassessment was 5.1 years (range 3.5 – 6.4 years). The 87 CYP with Down syndrome who were receiving L-T4 therapy at the time of re-evaluation were assessed 6 weeks after treatment withdrawal. Female predominance and age of diagnosis were significantly lower in CYP with Down syndrome compared with the control group. The prevalence of a family history of thyroid diseases was significantly higher in the control group, whilst the rates of CYP with associated extra-thyroidal autoimmune diseases were significantly higher in the group with Down syndrome. Alopecia was relatively frequent in CYP with Down syndrome, whereas it was very uncommon in the control group (11.4% vs 0.9%; p<0.001). Thyroid function test results showed that the most frequent hormonal patterns at Hashimoto's thyroiditis presentation were subclinical hypothyroidism in CYP with Down

syndrome and euthyroidism in the control group. Overall, the prevalence rates of thyroid dysfunctions were higher in CYP with Down syndrome diagnosed with Hashimoto's thyroiditis compared with controls (86.3% vs 45.7%; p <0.001). When the thyroid function patterns found in CYP with Down syndrome at Hashimoto's thyroiditis presentation were compared with those detected approximately 5 years later, a further significant decrease in the prevalence rate of euthyroidism was recorded. Details of findings in table 3 below:

Table 3. Prevalence rates of different thyroid hormone patterns in CYP with Down syndrome (n=146) at the time of Hashimoto's thyroiditis (HT) diagnosis and at re-evaluation after a median time interval of 5.1 years

	Euthyroidism n (%)	Subclinical hypothyroidism n (%)	Overt hypothyroidism n (%)	Hyperthyroidism n (%)	Overall dysfunctions n (%)
At HT diagnosis	20 (13.7)	92 (63.0)	28 (19.2)	6 (4.1)	126 (86.3)
At re-evaluation	5 (3.4)	92 (63.0)	37 (25.4)	12 (8.2)	141 (96.6)
p value*	0.002	1.000	0.205	0.144	0.002

*Chi-squared test

All the 12 CYP who, at re-evaluation, were included in the hyperthyroid subgroup, had developed from Hashimoto's thyroiditis presentation onwards a classical picture of Graves' disease and needed methimazole therapy. The switch from Hashimoto's thyroiditis to Graves' disease in these 12 CYP was confirmed by the finding of positive TSH receptor autoantibodies at the time of re-assessment. [Evidence level: low/very low]

An earlier retrospective longitudinal UK study aimed to describe the presentation and clinical course of Hashimoto's thyroiditis in CYP with Down syndrome (Popova et al, 2008). The medical records of CYP receiving care in 2 Scottish health regions were examined and those diagnosed with Hashimoto's thyroiditis (N=38) included in the study. Twenty-nine of these 38 CYP (76%) were identified through the neonatal capillary TSH screening programme. The median age at diagnosis was 12.3 years (range 2.1 to 17.7) and the median follow-up period was 6.4 years (range 2.1 to 14.2 years). Prevalence of Hashimoto's thyroiditis was calculated for the cohort screened between 1997 and 2004 and calculated to be 7.5% (29/385). Twenty-one (55%) of the 38 CYP diagnosed were asymptomatic with a median TSH of 14.2 mU/l (range 7.8 to 29.3); a further 6 CYP had symptoms (median TSH 14.2 mU/l (range 7.8 to 29.3). Six CYP were commenced on thyroxine therapy based on symptoms or TSH concentration >20mU/l. The majority of CYP (29/30) tested positive for TPO antibodies, 4/10 tested positive for thyroglobulin antibodies. Of the 21 CYP diagnosed with compensated hypothyroidism six were treated with thyroxine initially and remained on treatment. Eleven of the 15 who were initially untreated were placed on treatment within the next 4 years. One young person developed incipient hyperthyroidism at 14.3 years but after 3 months reverted to biochemically compensated but symptomatic hypothyroidism and received thyroxine therapy. Fifteen of the 16 CYP who were diagnosed with compensated hypothyroidism remained euthyroid on thyroxine therapy throughout follow-up, thus within 4 years of follow

up 91.9% (34/37) CYP were receiving ongoing thyroxine therapy. [Evidence level: low/very low]

A prospective longitudinal Australian study aimed to describe the prevalence and course of thyroid disorder in CYP with Down syndrome (Selikowitz et al, 1993). All CYP with Down syndrome attending the study hospital June 1985 to June 1987 were recruited into the study and 101 (94.4%) followed up for five years. The prevalence of all thyroid dysfunction in the study sample was 11% (11/101). At study entry three CYP were diagnosed with thyroid dysfunction (one congenital hypothyroidism; two compensated hypothyroidism) and over the course of the study a further 8 CYP developed compensated hypothyroidism. Of the ten CYP with compensated hypothyroidism: four CYP resolved spontaneously, none had raised thyroid auto-antibodies; five CYP continued with compensated hypothyroidism, two of these had raised auto-antibodies; one CYP developed uncompensated hypothyroidism, raised anti-thyroglobulin antibodies and anti-microsomal antibodies. [Evidence level: low/very low]

A longitudinal retrospective review of medical records at a regional university hospital in Brazil described the prevalence of thyroid dysfunction according to age in a cohort of 81 CYP with Down syndrome (Schmitt-Lobe et al, 2018). The prevalence of any type of thyroid disorder was found to be 70.4% (57/81), with a prevalence of Hashimoto's thyroiditis (defined as TSH >6 µUI/mL and low fT4 with TPO antibody and/or thyroglobulin antibody positive) of 11.1% (9/81). The mean age at time of diagnosis of any thyroid dysfunction was 5.19 years, including six infants diagnosed with congenital hypothyroidism. Prevalence by age at diagnosis for any type of thyroid dysfunction was as follows:

Table 4. Age at diagnosis of thyroid dysfunction and overall prevalence (n=57/81)

Age range (years)	Mean age (SD) (years)	Number diagnosed	Prevalence (%)
0 - 4	1.66 (1.19)	31	31/81 (38%)
5 - 9	7.32 (1.29)	13	44/81 (54%)
10 - 15	12.7 (1.56)	12	56/81 (69%)
>15	17	1	57/81 (70%)

[Evidence level: very low]

An earlier Swedish longitudinal observational study investigated the prevalence and course of thyroid dysfunction in CYP aged 1 – 25 years (Karlsson et al, 1998). It appears the study was a retrospective review of medical records at the study University Hospital although the description of the methods used is unclear. Hypothyroidism is not well defined and subclinical hypothyroidism is not separately described. The prevalence of thyroid dysfunction (hypothyroidism and hyperthyroidism) was 35.3% (30/85), with two CYP having hyperthyroidism. The prevalence of hypothyroidism by age was as follows:

Table 5. Cumulative % of CYP developing hypothyroidism

Age (years)	Cumulative %
0	1
1	8
2	11

3	11
4	13
6	13
8	16
10	18
12	19
14	25
16	27
18	29
20	31

Half of the CYP with hypothyroidism developed the condition before the age of 8 years. Of these CYP one of the 11 tested for autoimmunity had a detectable serum TPO antibody level, none were found to be positive for thyroglobulin antibodies. Of the 14 CYP aged over 8 years when diagnosed with hypothyroidism 11 had raised concentrations of thyroglobulin antibodies or TPO antibodies, or both. [Evidence level: very low]

A Swedish retrospective observational study investigated the extent to which thyroid autoantibodies contribute to thyroid dysfunction in CYP with Down syndrome (Ivarsson et al, 1997). Medical records of a sample of 70 CYP with Down syndrome (mean age 10.5 years; range 1 – 19) and a control group of 386 CYP (mean age 12 years; range 11 - 13) were examined to determine findings from thyroid function tests and blood tests for thyroid autoantibodies. Thyroid autoimmunity was found in 39% CYP with Down syndrome compared with 16% of CYP in the control group ($p<0.0001$). Seventeen CYP with Down syndrome were hypothyroid and receiving thyroxine therapy, giving a prevalence of 24%. Antibody analyses were done before or within the first year of treatment for 12 CYP. Nine out of 17 CYP had thyroglobulin antibody and TPO antibodies detected, one child/young person had thyroglobulin antibodies only and one had TPO antibodies only. These 11 CYP had TSH values ranging from 5.8 – 197 mU/l (normal range: 0.4 – 4.0 mU/l). Six of the 17 CYP had no antibodies detected and TSH values ranging from 4.6 – 23.0 mU/l when treatment was started. CYP over 12 years of age were significantly more likely to have thyroid autoantibodies detected than those under 12 (unclear which category includes CYP aged 12) (57% vs 20%; $p<0.01$). No significant sex differences were found. [Evidence level: very low]

A US cross-sectional observational study has investigated the association of thyroid autoantibodies with thyroid dysfunction in individuals with Down syndrome (Zori et al, 1990). The total sample of 61 individuals was divided into three age groups: children under 10 years, CYP aged 10 - 20 years and individuals aged over 20 years (it appears from the reporting that children aged 10 years were included in the 10 - 20 years group). Thyroid dysfunction was defined as venous TSH ≥5 µIU/ml or previously diagnosed Hashimoto's thyroiditis or Graves' disease. Using this definition, the prevalence of thyroid dysfunction in children aged less than 10 years was 68% (15/22) and in CYP aged 10-20 years was 72% (13/18). Children aged under 10 years tended to have higher TSH concentrations than individuals aged over 10 years (including adults) ($p=0.06$; Fisher's exact test). Seventeen individuals had thyroid autoantibodies (12 thyroid microsomal antibodies only, one thyroglobulin antibodies and four

both types of antibody), including 12 CYP aged ≤20 years. In individuals with thyroid dysfunction 12/25 (48%) over the age of 10 years had thyroid autoantibodies compared with 3/15 (20%) of those aged under 10 years (p=0.06). All eight individuals with TSH>10 µIU/ml or previously diagnosed thyroid disease had thyroid autoantibodies compared with 2/8 children under 10 years (p=0.001). [Evidence level: very low]

Subclinical hypothyroidism

A prospective longitudinal study has been conducted in Israel to determine whether subclinical hypothyroidism or low fT4 are associated with detrimental clinical outcomes (Tenenbaum et al, 2012). The investigators recruited and followed up CYP with Down syndrome attending annual outpatient clinics at the study hospital between 2004 and 2010. A total of 157 CYP were included in the study, median age 5.9 years. Of the 134 CYP who had complete thyroid function test results available 36.6% (n=49) were found to have thyroid dysfunction, comprising either subclinical hypothyroidism (n=20, 14.9%) or hypothyroidism receiving thyroxine (n=29, 21.6%). Biochemical and clinical signs and symptoms of hypothyroidism were compared between the group of CYP with subclinical hypothyroidism and the group without hypothyroidism (n=85). The group of CYP without hypothyroidism was found to be significantly older than the group with subclinical hypothyroidism (8.9 vs 4.7 years; p=0.04) and, as would be expected their average TSH was significantly lower (9.0 (SD 2.2) vs 3.6 (SD 1.5) mIU/l; p=0.0001) although there was no difference between average fT4 concentrations (16.0 (SD 2.7) vs 16.6 (SD 3.3) pmol/l respectively). The degree of hypotonia was found to be significantly higher in CYP with subclinical hypothyroidism compared to those without hypothyroidism (p=0.002). No significant differences were found between the groups for BMI or the occurrence of constipation, dry skin, bradycardia or anaemia. In order to investigate TSH concentrations as a predictor of clinical outcome the 128 CYP with absolute TSH concentrations within the normal range and not receiving thyroxine were divided into 2 groups: euthyroid submedian TSH (TSH <3.6 mIU/l) and euthyroid supramedian TSH (TSH ≥3.6 mIU/l). No significant differences were found between the two groups for any hypothyroidism-related symptoms or average fT4 concentrations. Average age of CYP in euthyroid submedian group 3.19 years older than the supramedian group (p=0.05), although no correlation was found between age and TSH concentrations (Pearson's correlation coefficient = -0.096, p=0.40). [Evidence level: low/very low]

A retrospective observational study conducted in Spain by Claret et al (2013) sought to confirm that subclinical hypothyroidism in CYP with Down syndrome is usually transitory and to identify factors associated with spontaneous remission. The overall prevalence of thyroid dysfunction (hyperthyroidism, subclinical hypothyroidism, overt hypothyroidism, including treated and untreated CYP) in the total sample of CYP with Down syndrome was 7.8% (149/1903). A review of clinical records from 1993 to 2008 identified a sample of 53 children with Down syndrome who had been diagnosed with hypothyroidism before the age of 5 years. Data for TSH concentrations, fT4 concentrations, TPO antibodies, thyroglobulin antibodies and details of clinical symptoms were extracted for children at diagnosis and

during follow up (mean follow up 54 ± 19 months). Definitions used in the study were as follows:

- Subclinical hypothyroidism: TSH 5.5-25 µU/ml (6 months - 4 years) or 4.13-25 µU/ml (4 - 7 years), fT4 11.45 – 24.07 pmol/l (6 months - 4 years) or 12.35 – 23.94 pmol/l (4 - 7 years) [reported as fT4 0.89-1.87 ng/dl (6 months - 4 years) or 0.96-1.86 ng/dl (4 - 7 years) in paper].
- Overt hypothyroidism: TSH elevation with low fT4 and/or TT3.

Mean age at diagnosis was 2.4 ± 1.1 years (range 0.3 - 4.9) and the average interval between diagnosis of thyroid dysfunction and documentation of remission was 13.2 ± 11.1 months, with most cases resolving between 4 and 5 years of age. Fourteen of the 53 children with hypothyroidism were treated with levothyroxine. Positive anti-TPO anti-thyroglobulin antibodies were detected in 12 cases (22.6%) at a median age of 2.8 (range 1.6–4.9) years. There was a higher incidence of medical co-morbidities including heart disease in CYP diagnosed with hypothyroidism before the age of 5 years and 24.5% (95% CI 12.9 to 36.1) had a positive family history of thyroid disease. Hypothyroidism resolved in 39 of the 53 children, including four of the 14 who were initially treated for hypothyroidism. Factors associated with the remission of subclinical hypothyroidism are summarized in the table below:

Table 6. Summary of factors associated with remission of subclinical hypothyroidism

	Remission	Persistence	*p*
N (%)	39 (73.6%)	14 (26.4%)	_
Median age at diagnosis (range) (years)	2.2 (0.3–4.9)	2.2 (1.1–4.7)	0.95
Median age at the last recorded visit (range) (years)	6.7 (3.5–11.4)	6.5 (3.7–10.9)	0.67
Symptoms/signs at diagnosis, n (%)	11 (28.2%)	8 (28.6 %)	0.72
Median TSH concentration at diagnosis (range) (µU/ml)	6.9 (4.2–9)	9.1 (5.4–23.9)	0.13
Median fT4 concentration at diagnosis (range) (ng/dl)	1.1 (1–1.7)	1 (0.9–1.5)	0.58
Absence of goitre, n (%)	37 (94.9%)	4 (28.6%)	<0.05
Negative for antibodies to TPO/TGB, n (%)	35 (89.7%)	6 (42.9%)	<0.05

None of the children progressed to overt hypothyroidism during the period of observation. [Evidence level: low/very low]

A prospective longitudinal observational study conducted using the placebo arm of an RCT aimed to describe the aetiology and course of thyroid function in infants with Down syndrome from birth to 26 months (van Trotsenburg et al, 2006). This Dutch study investigated the thyroid function of 90 infants (of 97 recruited) with a normal congenital hypothyroidism screening result from 0.8 months to 26 months and compared findings with figures seen in age-comparable groups of infants without Down syndrome (figures obtained from evidence literature review) and/or infants in the intervention arm (thyroxine therapy) of the trial. The study found that the mean plasma TSH concentrations of the infants with Down syndrome decreased from 5.45 mIU/l at age 0.8 months to 4.53 mIU/l at 6 months and stabilized between 4.24 and 4.52 mIU/l after 6 months. All these figures are above the laboratory reference interval for plasma TSH (0.4 to 4.0 mIU/l) and were significantly higher than the comparison group of infants without Down syndrome ($p<0.001$). Frequency distributions of TSH concentrations were seen to be shifted entirely to the right compared to the general population (rather than being due to elevated TSH concentrations in a sub-sample of CYP with Down syndrome). Individual TSH concentrations fluctuated over time from "normal" to "elevated" and vice versa. Only 9.3% CYP with Down syndrome had all TSH measurements within the laboratory's reference interval. From age 0.8 months to age 6 months the mean plasma fT4 concentrations decreased approximately 20%. After six months values stabilized around 14.2 pmol/l. The mean fT4 concentrations and fT4 frequency distributions for infants in the study group were in the lower two thirds of the reference interval. Few infants were found to be TPO antibody positive. At the age of 24 months the study placebo group contained 4/92 infants who were anti-TPO antibody positive, the intervention (thyroxine therapy) group of the RCT had 6/92 infants who were anti-TPO antibody positive (overall prevalence of TPO antibody positivity: 5.4%). In the study placebo group TSH concentration did not differ significantly between infants who were anti-TPO antibody positive and those who were anti-TPO antibody negative (anti-TPO antibody positive: TSH 5.35 (1.82) mIU/l and anti-TPO antibody negative: TSH 4.93 (2.59) mIU/l; $p=0.75$). [Evidence level: moderate]

Overactive thyroid gland (Graves' disease)

Researchers in Italy have investigated the course of Graves' disease in CYP with Down syndrome (n=28) and compared this with its course in a control group of CYP without Down syndrome (n=109) (DeLuca et al, 2010). A retrospective review of medical records for CYP referred to one of 6 study clinics between 1995 and 2005 was carried out and demographic details, thyroid function test results and clinical signs of hyperthyroidism recorded. Follow up was similar for the 2 groups being 4.0 years for the CYP with Down syndrome and 4.4 years for the control group. Mean age at time of diagnosis with Graves' disease was significantly younger in the CYP with Down syndrome compared with controls, 9.9 years vs 11.5 years ($p<0.05$), and the proportion of females with the condition was lower in the Down syndrome group (50% vs 82%; $X^2=12$, $p<0.0005$). There was no significant difference in the prevalence of clinical signs and symptoms (including exophthalmos), fT4 concentrations and TSH receptor

autoantibodies between the 2 groups at diagnosis. The subsequent clinical course of Graves' disease was less severe in the CYP with Down syndrome, with significantly fewer relapsing after their first cycle of treatment with methimazole (7.1% vs 31.2%; p<0.005) and with a higher rates of persistent remission in CYP with Down syndrome after withdrawal of therapy (46.4% vs 26.7%; p<0.05). Antecedents of Hashimoto's thyroiditis were documented in 21.4% of CYP with Down syndrome compared with 3.7% of CYP in the control group (X^2=10.4; p<0.005). [Evidence level: low/very low]

3.3 Evidence statements: what tests should be undertaken, timing and frequency of testing

This section contains brief evidence statements for each study. These provide a succinct summary of key outcomes relating to clinical questions 1 and 2. For more detail of the reviewed studies please see the narrative summary of evidence (section 3.3) and evidence table (Appendix F).

Clinical questions:

1. What blood tests should be undertaken as part of routine surveillance to identify thyroid disorders in CYP with Down syndrome?
2. When should routine surveillance blood tests commence in CYP with Down syndrome and how often should they be repeated?

In particular, evidence statements relating to these two questions report findings from biochemical tests (TSH, fT4 and thyroid antibodies), prevalence of thyroid dysfunction, the age of CYP at testing/diagnosis and the course of thyroid dysfunction.

3.3.1 Neonatal screening

(2 studies)

A retrospective study (Erlichman et al, 2016) found that T4-based screening followed by serum TSH measurements in infants with TT4 <10th percentile improved the identification of congenital hypothyroidism compared with T4-based screening alone, however only 50% of infants deemed to require thyroxine therapy by 1 month of age were identified through this neonatal screening method. [Evidence level: low]

A second retrospective study (Myrelid et al, 2009) found that neonatal TSH dried blood spot screening results are not predictive of the development of hypothyroidism during childhood [Evidence level: very low].

This study also reported that of 22 children who developed hypothyroidism requiring thyroxine therapy before the age of 10 years, four tested positive for TPO antibodies and thyroglobulin antibodies. [Evidence level: very low]

3.3.2 Ongoing surveillance

(5 studies)

One study (Purdy et al, 2014) investigated the incidence of hypothyroidism in infants who were found to be euthyroid at birth and were then tested again before 4 months of age (n=79). Fifteen per cent were found to have compensated hypothyroidism and 17.5% were diagnosed with primary hypothyroidism and treated with thyroxine. (Evidence level: low]

Findings from a UK study (Noble et al, 2000) have shown that annual surveillance for thyroid dysfunction in pre-school and school settings is feasible using a dried blood spot test. Hypothyroidism requiring treatment was detected in 5.5% CYP tested. [Evidence level: moderate]

Of 15 CYP with a capillary TSH >10 mU/l picked up via the school-based surveillance programme, all but one was found to be positive for either microsomal antibodies or TPO antibodies consistent with Hashimoto's thyroiditis. Median age at referral 13 years. [Evidence level: low]

In a second UK study (McGowan et al, 2011) the uptake of a community-based capillary TSH screening programme was 56%, with most of these CYP being school age rather than pre-school age. The median age at referral was 9.4 years. Of those referred, 43% received immediate and 18% subsequent thyroxine therapy suggesting the surveillance is worthwhile. Referrals continued up to age 18 years. Data were insufficient to help decide the optimal frequency of screening. [Evidence level: low]

In the same study of a sample of 98 CYP referred with a capillary dried blood spot TSH ≥4 mU/l the prevalence of autoantibodies was as follows: of 22 CYP with venous TSH 6-10.9 mU/l 12 were found to be antibody positive, 11 were started on treatment. Of 25 CYP with venous TSH 11.0-20.9 mU/l four had decompensated hypothyroidism and 20 were treated; 17 of 19 tested were antibody positive. Of 24 CYP with venous TSH >21 mU/l 12 had decompensated hypothyroidism, 22 were treated and 16 of the 19 CYP tested were antibody positive. A significant correlation was found between venous TSH and TPO antibody levels. [Evidence level: low]

A third UK study (McGowan et al, 2015) found that capillary TSH concentrations above 4.0 mU/l were strongly associated with raised venous TSH concentrations but is not clinically useful for predicting fT4 concentration. Most of the CYP (77%) were aged 5 years or over. [Evidence level: very low]

An Irish feasibility study (Murphy et al, 2008) found that the dried capillary blood spot test was feasible as a screening method and was acceptable to CYP, with 4/309 declining the test. [Evidence level: moderate]

The programme in this study detected 5/305 CYP who had not been previously diagnosed, all of whom were positive for TPO antibodies. The mean age of the CYP newly diagnosed was 10.8 years (range 7.7 – 16.1 years). [Evidence level: moderate]

Of 10 CYP who had been previously diagnosed with hypothyroidism prior to the introduction of the surveillance programme, six were positive for thyroid antibodies. [Evidence level: very low]

3.3.3 Predictive value of thyroid function tests

(2 studies)

In a prospective study (Sankar et al, 2018) 25 out of 34 children diagnosed with hypothyroidism and treated with thyroxine before the age of 3 years were found to have a normalized TSH concentration at the age of 3 years. [Evidence level: low]

Findings from the study suggested a high venous TSH concentration at diagnosis may be moderately predictive of persistent hypothyroidism but data reporting is limited. [Evidence level: very low]

In the same study, of 47 children aged less than 3 years found to have a raised venous TSH and treated with thyroxine four were diagnosed with overt hypothyroidism, two of whom were positive for TPO antibodies. Of the 43 children diagnosed with subclinical hypothyroidism six were positive for TPO antibodies. Thyroglobulin antibodies were negative in all children. [Evidence level: very low]

A UK prospective study (Gibson et al, 2005) concluded that thyroid function tests performed earlier in childhood (6-14 years) have very limited usefulness for predicting later hypothyroidism during adolescence (10–20 years). [Evidence level: very low]

In this study of 103 CYP tested between the ages of 6 to 14 years, eight were found to be positive for antibodies. At second testing (age range 10 – 20 years) five remained positive for antibodies, three retained IR-TSH and one develop hypothyroidism. Two additional CYP tested positive at the second time point. There was no significant association between positive antibodies at first time point and hypothyroidism at second time point. [Evidence level: very low]

3.3.4 Prevalence and course of thyroid dysfunction, and the role of thyroid autoantibodies

(13 studies)

A summary table of the prevalence of thyroid dysfunction by age in CYP with Down syndrome is presented in Appendix J.

The observed prevalence of hypothyroidism (congenital hypothyroidism and overt hypothyroidism) in one prospective study (Iughetti et al, 2014) was found to be 9.7% in the neonatal period and 19.3% in children in their 10th year. Subclinical hypothyroidism was found to have a fluctuating course with a stable prevalence of 22-24%. Neonatal TSH concentrations were not predictive of the later development of hypothyroidism. [Evidence level: low]

The study also found that the probability of testing positive for thyroid autoantibodies increases with age. The presence of thyroid antibodies in a CYP who is euthyroid or has

subclinical hypothyroidism is associated with a higher chance of developing more severe rather than less severe hypothyroidism, with TPO antibodies being a better predictor of more severe dysfunction than thyroglobulin antibodies. [Evidence level: very low]

A study of 565 CYP (Pierce et al, 2017) reported the overall prevalence of thyroid disorder (congenital hypothyroidism, overt hypothyroidism, unknown hypothyroidism and hyperthyroidism) as 12.6%. Among those diagnosed with hypothyroidism outside of newborn screening, n=11 (7.5% of all acquired hypothyroidism) were diagnosed before 6 months of age. The estimated prevalence of thyroid dysfunction with increasing age suggested that 25% CYP with Down syndrome would have thyroid disease by the age of 7.5 years and 50% by adulthood. [Evidence level: very low]

The study also found that CYP with overt hypothyroidism were significantly more likely to be antibody positive than those with subclinical hypothyroidism and those with isolated hyperthyrotropinemia. [Evidence level: very low]

A retrospective study (Aversa et al, 2015) found that Hashimoto's thyroiditis follows a different pattern in CYP with Down syndrome compared with those without Down syndrome. The prevalence of thyroid dysfunctions in CYP with Down syndrome diagnosed with Hashimoto's thyroiditis was significantly higher in CYP with Down syndrome compared with controls. The switch from Hashimoto's thyroiditis to Graves' disease over time was confirmed by the finding of positive TSH receptor antibodies. [Evidence level: low]

In an earlier retrospective study (Popova et al, 2008) neonatal capillary TSH screening detected 76% of CYP who went on to be diagnosed with Hashimoto's thyroiditis (median age at diagnosis 12.3 years; range 2.1 to 17.7 years). The prevalence of Hashimoto's thyroiditis was 7.5%. [Evidence level: low]

Within four years of diagnosis 92% of CYP were receiving ongoing thyroxine therapy. [Evidence level: low]

In this study the majority of CYP (29/30) tested for TPO antibodies were positive, as were 4/10 tested for thyroglobulin antibodies. The six CYP who tested negative for thyroglobulin antibodies had positive microsomal antibodies. [Evidence level: low]

One prospective study (Selikowitz et al, 1993) reported a prevalence of thyroid dysfunction of 11%. Of 10 CYP identified with hypothyroidism four resolved spontaneously over five years and one developed uncompensated hypothyroidism. [Evidence level: low]

Of 10/101 CYP with compensated hypothyroidism, four CYP's disorder resolved spontaneously, none of the CYP had raised thyroid antibodies. [Evidence level: very low]

In a longitudinal study (Schmitt-Lobe, 2018) the prevalence of any thyroid disorder (including subclinical hypothyroidism, Hashimoto's thyroiditis, congenital hypothyroidism and Graves' disease) was reported as 70.4%, with prevalence increasing with age. The mean age at time of diagnosis of any thyroid dysfunction was 5.19 years, including six infants diagnosed with congenital hypothyroidism. Prevalence was found to increase with age, with 38% children

diagnosed before 4 years of age. The prevalence of Hashimoto's thyroiditis was 11.1%. [Evidence level: very low]

In another longitudinal study (Karlsson et al, 1998) the prevalence of thyroid dysfunction was 35.5% (includes subclinical hypothyroidism), with prevalence increasing with age. By 1 year of age 8% children were diagnosed with hypothyroidism, rising to 16% by 8 years of age. Of 28 children with hypothyroidism one of the 11 tested was positive for TPO antibodies, none were found to be positive for thyroglobulin antibodies. Antibody positivity was higher in CYP aged over 8 years at time of diagnosis compared with those aged less than 8 years. [Evidence level: very low]

In a retrospective study (Ivarsson et al, 1997) 11 of 17 CYP with hypothyroidism and receiving thyroxine were found to be positive for thyroglobulin antibodies and TPO antibodies. Presence of thyroid antibodies appeared to be associated with higher TSH concentrations overall. CYP over 12 years of age were significantly more likely to have thyroid autoantibodies detected than those under 12. [Evidence level: very low]

One cross-sectional study (Zori et al, 1990) has reported that 17/40 (42.5%) individuals with hypothyroidism were positive for TPO antibodies, including 12 CYP aged 20 years or younger. In individuals with thyroid dysfunction 12/25 (48%) over the age of 10 years had thyroid autoantibodies compared with 3/15 (20%) of those aged under 10 years (p=0.06). [Evidence level: very low]

3.3.4.1 Subclinical hypothyroidism

The prevalence of thyroid dysfunction (subclinical hypothyroidism and hypothyroidism receiving thyroxine) was reported as 36.6% in one study (Tenenbaum et al, 2012). CYP with subclinical hypothyroidism were found to be significantly younger (4.7 vs 8.9 years) than those without hypothyroidism and have a significantly higher level of hypotonia. [Evidence level: very low]

In a study of children diagnosed before 5 years of age the prevalence of thyroid dysfunction was found to be 7.8% (includes subclinical hypothyroidism, overt hypothyroidism and hyperthyroidism) (Claret et al, 2013). Most of the children (74%) diagnosed with subclinical hypothyroidism went into remission during the follow up period (mean age at most recent visit 6.7 ± 1.4 years). Children diagnosed with subclinical hypothyroidism before the age of 5 years the absence of thyroid antibodies was associated with an increased likelihood of remission. [Evidence level: low]

Thyroid antibodies were detected in 12 CYP (22.6%) at a median age of 2.8 years (range 1.6 to 4.9 years). [Evidence level: very low]

In the same study the absence of a goitre was found to be associated with spontaneous remission. [Evidence level: very low]

One study (van Trotsenburg et al, 2006) reported that at the age of 2 years four out of 92 infants with a normal congenital hypothyroidism neonatal screening result were found to be

TPO antibody positive. TSH concentration did not appear to be associated with TPO antibody positivity. [Evidence level: moderate]

3.3.4.2 Overactive thyroid gland (Graves' disease)

One study (DeLuca et al, 2010) found that CYP with Down syndrome are likely to be younger at the age of diagnosis of Graves' disease compared with CYP without Down syndrome (9.9 years vs 11.5 years), and the course of the disease is less severe. Antecedents of Hashimoto's thyroiditis are seen more commonly in CYP with Down syndrome and Graves' disease compared to those without Down syndrome. The study found no significant difference in TSH receptor antibodies between CYP with Down syndrome and a group of CYP without Down syndrome. [Evidence level: moderate]

3.4 Consideration of evidence: what tests should be undertaken, timing and frequency of testing

The following section summarises the GDG's consideration of the evidence and notes key points of discussion and decision-making when making recommendations for practice.

3.4.1 Overall quality of evidence and strength of recommendations

This section includes consideration of the evidence findings, including their applicability to clinical practice, benefits and risks associated with interventions, the experiences of CYP and their families/carers and resource implications. Where the evidence reviewed is linked directly to a recommendation it is cross-referenced. In some instances recommendations have been drafted based upon an overall consideration of a body of evidence rather than on a particular finding, again this association is cross-referenced. Some recommendations were drafted following the GDG's discussion of the evidence in order to encourage good practice. These recommendations are based upon the clinical experience and expertise of professionals in the group and the views and experiences of care expressed by CYP's representatives and do not link specifically to the evidence reviewed.

The strength of recommendations is reflected in their wording, as used in NICE clinical guidelines. The term "offer" is used to represent a strong recommendation and "consider" represents a less strong recommendation. The body of evidence for this guideline is predominantly of low and very low certainty as defined using the GRADE methodology. This is usual for evidence based upon observational studies, many of which rely upon the retrospective examination of medical records, and so the strength of recommendations for this guideline is not based solely upon the level of certainty of findings as there is a clear floor effect in this instance. Where there were two or more studies providing evidence for a recommendation supported by GDG consensus a strong recommendation was made. Additionally, where good practice recommendations regarding provision of information and how to minimize the distress associated with blood tests were made with the full agreement of all GDG members, including CYP's representatives, these were also worded as strong recommendations. Where there was very limited supporting evidence or some disagreement

amongst GDG members (but with overall consensus) a less strong recommendation was made.

3.4.2 Q.1. What blood tests should be undertaken?

3.4.2.1 UK and Ireland newborn screening (Recommendations section 3.5.5)

The two studies reviewed (Erlichman et al, 2016; Myrelid, 2009) did not investigate the type of test that should be carried out for newborn screening. The UK national screening for congenital thyroid dysfunction is conducted using a dried blood spot test for all infants in the first week of life. The vast majority of children born in the UK and Ireland with primary congenital hypothyroidism will be detected and referred through this programme. The guideline group commented that in some hospitals additional thyroid function tests are carried out for newborn infants with Down syndrome. It was agreed that this practice was unnecessary unless there was a clinical indication suggesting thyroid dysfunction in the newborn baby and a recommendation drafted to discourage this. Infants who develop thyroid dysfunction after the first week of life, including the very small proportion that go on to develop central congenital hypothyroidism, will not be detected through this screening programme and this document summarises the evidence for ongoing surveillance.

3.4.2.2 Dried blood spot vs venous blood testing (Recommendations section 3.5.3)

Evidence from four UK studies (Noble et al 2000; Murphy et al, 2008; McGowan et al 2011 and McGowan et al 2015) have shown that a TSH dried blood spot testing (by finger-prick) surveillance programme is feasible and will detect a clinically significant number of CYP with Down syndrome with thyroid dysfunction. Findings from two of these studies suggest that the uptake of surveillance is higher in school age CYP than in pre-school children. The guideline group felt this was possibly due to the logistics of the surveillance, as uptake is likely to be higher with school-based testing. There was some concern expressed amongst the guideline group that the uptake of pre-school surveillance appeared low, although it was felt this could be partly explained by the fact that these children may have been receiving regular blood tests for other medical reasons with their own paediatric team outside of the surveillance programme.

The guideline group agreed that dried blood spot testing by finger prick was easier to undertake and less distressing for CYP than venous blood testing as supported by findings from feasibility studies (Noble et al, 2000; Murphy et al, 2008), although they noted that the detection of an abnormal TSH result on a dried blood spot test would necessitate a follow up venous blood test for TSH, fT4 and TPO antibodies in order to make a diagnosis. It was also noted that dried blood spot testing can only detect suspected hypothyroidism and not hyperthyroidism. The evidence shows this method to be sensitive for detecting a raised TSH at appropriate thresholds (see later for discussion of thresholds). In addition, the young people involved in the focus group conducted for this guideline also expressed a preference for this type of blood sampling. Given this, and that hypothyroidism is more likely in children aged under one year than hyperthyroidism, the guideline group felt this surveillance method by finger prick testing , where available, is the most appropriate for ongoing surveillance. The group were aware that in some areas of the UK, TSH testing using the dried blood spot method

before the age of one year is established and local laboratories are able to process the additional blood spot cards. However, there are health authorities that do not have facilities for dried blood spot testing meaning only venous testing can be offered, thus in making the recommendation the GDG felt unable to be prescriptive regarding type of blood test for surveillance. The group felt that where venous blood testing is being performed TSH, fT4 and TPO antibodies should be tested rather than just a TSH measurement as this can provide more information about thyroid function and thus better guide clinical decision-making.

The group recognised that in some instances a capillary sample might be obtained by finger prick and blood collected in a test tube for laboratory testing. In this case, as the sample tested would be plasma and not whole dried blood, the blood test results would be treated in the same way as venous blood tests as both samples will have been spun and testing performed on the blood plasma (rather than whole blood as is the case with a dried blood spot test). The GDG noted, however, that when a finger-prick is used to obtain blood other than for a dried blood spot test the blood test result may be inaccurate as squeezing the area to obtain an adequate sample increases the concentration of the haemoglobin and hence results in a falsely low TSH measurement (Butler, 2017). Thus when taking a sample for plasma testing (i.e. a sample taken into a test tube rather than a dried blood spot) a venous sample is recommended not a capillary sample.

The guideline group recommended that in the presence of clinical symptoms and/or signs a venous sample for thyroid function tests should be undertaken and not a capillarydried blood spot test as the latter has poor sensitivity and specificity at low TSH concentrations (seen in hyperthyroidism) and increased variability (Butler et al, 2017). The group also agreed that an abnormal dried blood blood spot test must be confirmed by follow up venous blood tests prior to making a diagnosis and initiating treatment.

The group felt that the advantages and disadvantages associated with both types of blood testing were evenly balanced and so it was appropriate to recommend that either can be used for surveillance depending upon local arrangements. It was also emphasised that clinicians should take into account the preferences of the CYP and their parents/carers, offering a choice where this is possible. The guideline group agreed that it is important to explain to parents/carers that if a dried blood spot sample test was abnormal; it is likely that the CYP would need two further venous blood test samples to confirm the diagnosis and formulate a management plan.

3.4.2.3 Types of test (TSH, fT4 and antibody testing) (Recommendations sections 3.5.3)

Dried blood spot tests are used to measure whole blood TSH concentrations. This concentration is approximately half that of an equivalent serum sample (Pokrovska et al, 2016).

TSH and fT4 are required for an accurate diagnosis of thyroid dysfunction in an individual and this is current UK practice when taking venous samples in CYP. Studies often report using TSH, fT4 and TPO antibodies for assessing thyroid function and the guideline group agreed it was appropriate to endorse this approach.

There is low level evidence from five studies that thyroid antibodies are less prevalent in younger children (Iughetti et al, 2014; Karlsson et al, 1998; Ivarsson et al, 1997; Zori et al, 1990; van Trotsenburg et al, 2006) and hence testing for antibody levels each time a venous blood test is taken in a young child under the age of two years may not be clinically useful immediately. The guideline group felt, however, that a baseline TPO antibody level would be useful, even in younger children. The group advised that fT4 is preferred over TT4 as the latter is influenced by the presence of binding proteins. In addition, the group advised that there is no evidence to measure fT3 levels or TSH receptor antibodies (TRAB), unless there is a definite clinical indication and following discussion with an endocrinologist.

Reviewed evidence from seven studies suggests that antibody testing for TG antibodies and/or TPO antibodies may be useful in determining the likelihood of developing of thyroid dysfunction and the severity of disease. Thyroid autoimmunity is associated with higher concentrations of TSH and more severe dysfunction (Ivarsson 1997; McGowan et al 2011; Claret et al, 2013; Iughetti et al, 2014; Pierce et al, 2017). An absence of antibodies is associated with an increased likelihood of remission (Claret et al, 2013; Selikowitz et al, 1993). The guideline group recognized that TPO antibodies are non-specific and may also be associated with low TSH in Graves' disease. The reviewed evidence suggests that the presence of thyroid antibodies increases with age, becoming more common after the age of eight and being rare in children under the age of two years (Ivarsson 1997; Karlsson et al, 1998; Van Trotsenburg et al, 2006; McGowan et al, 2011; Iughetti et al, 2014). There was some evidence that TPO antibodies may be a better indicator of severity of thyroid dysfunction than TG antibodies (Iughetti et al, 2014; Pierce, 2017), which the GDG confirmed was in line with current practice. The guideline group agreed that antibody testing can be useful in determining the likelihood of developing thyroid dysfunction and deciding appropriate clinical management. For this reason, they decided to recommend that TPO antibody testing be conducted where surveillance is carried out using a venous sample, and whenever there are borderline abnormal thyroid function blood test results or when clinical signs and/or symptoms of thyroid dysfunction are noted. In practice this is likely to mean that antibody testing is carried out whenever venous blood testing is done. The types of antibodies tested for will depend partly upon local laboratory practices but should include TPO antibodies where hypothyroidism is suspected. Where hyperthyroidism is indicated TSH receptor antibodies (TRAB) and TPO antibodies should be tested for (DeLuca et al, 2010; Aversa et al, 2015).

3.4.2.4 Hyperthyroidism (Recommendations sections 3.5.4)

There is some evidence to suggest that the conversion from Hashimoto's disease to Graves' disease was more common and occurred at an earlier age in CYP with Down syndrome compared with CYP without Down syndrome (Claret 2013). A venous blood sample is needed to test for hyperthyroidism as this is not possible using a dried blood spot test, as the dried blood spot test is not sensitive to detect low levels of TSH. Blood test findings may be misleading as in some cases only fT3 is elevated whilst other test results may be within the

normal range. Thus, whenever hyperthyroidism is suspected fT3 should be tested along with TSH, fT4, TPO antibodies and TSH receptor antibodies.

3.4.3 Q.2. When should testing commence and how frequently should it be repeated?

3.4.3.1 UK and Ireland newborn screening (Recommendations section 3.5.5)

The two studies investigating neonatal screening (Erlichman et al, 2016; Myrelid et al, 2009) did not add to current knowledge about neonatal screening and supported a continuation of the current national screening programme. The GDG thus recommended that newborn babies with Down syndrome, including premature infants and twins, should follow the national newborn bloodspot screening programme for the detection and management of congenital hypothyroidism.

3.4.3.2 Ongoing surveillance (Recommendations section 3.5.6)

See summary table of prevalence of thyroid dysfunction by age in Appendix J.

The evidence reviewed shows that the prevalence of thyroid dysfunction in the first year of life ranges between approximately 10% and 18% in infants with Down syndrome (Iughetti et al, 2014; Erlichman et al, 2016; Purdy et al, 2014) with the upper end of the range being recorded in infants aged 3-120 days (Purdy et al, 2014). Given this high prevalence and the importance of thyroid hormone actions on myelination of the developing brain, the guideline group felt that there are potential advantages of initiating the surveillance programme for thyroid dysfunction during the first year of life. They noted that guidelines in Australia (van Cleve et al, 2006) and the USA (American Academy of Pediatrics Committee on Genetics, 2011) recommend thyroid function testing at the age of 6 months and agreed that testing around this age reflected best practice.

The guideline group noted that the evidence shows that the course of thyroid dysfunction, including subclinical hypothyroidism, fluctuates over time and is unpredictable (Sankar et al, 2018; Iughetti et al, 2014; Claret et al, 2013; Gibson et al, 2005; Selikowitz, 1993). The group acknowledged that transient congenital hypothyroidism is well documented in the general population of CYP and felt it was likely this would also be true of CYP with Down syndrome. Of note was that hypothyroidism detected in infants who have Down syndrome, can resolve by the age of 3 years (Sankar et al, 2018). There was also some evidence that Hashimoto's thyroiditis is more prevalent in CYP with Down syndrome and may go on to develop into Graves' disease (Aversa et al, 2015). The evidence indicates that prevalence of thyroid dysfunction increases with age (Pierce et al, 2017; Schmidt-Lobe et al, 2018; Karlsson et al, 1998). The guideline group also noted that some symptoms of thyroid dysfunction such as dry skin and constipation are commonly seen in CYP with Down syndrome resulting in diagnostic overshadowing (Claret et al, 2013). For these reasons the group felt that it is important to offer annual thyroid function tests from the age of one year until care is transitioned to adult services. The GDG were aware that this represents an increase in surveillance compared to the current DSMIG guidance which recommends venous sampling biochemical testing at least once every two years from the age of one year (DSMIG, 2001). The GDG agreed that the

potential health and developmental gain outweighed the additional financial cost of the tests which is relatively small. The guideline group felt that given the variation in the course of thyroid dysfunction, diagnostic overshadowing of symptoms and the increasing prevalence with age, that two years was too long to wait between surveillance testing.

Findings from the evidence show that the presence of antibodies is associated with more severe thyroid dysfunction and the guideline group agreed that testing should be carried out more frequently than annually if previous blood tests suggest a degree of thyroid dysfunction, including a rise in antibody levels (McGowan et a, 2001; Popova et al, 2008; Claret et al, 2013; Iughetti et al, 2014). This additional testing should be performed using a venous sample. The frequency and timing of additional blood tests should be made on an individual basis and take into account blood test results, clinical signs and symptoms as well as the concerns of the parents/carers. The CYP's age should also be taken into consideration with more frequent surveillance required for children under the age of three years, although a clinical judgement must always prevail to prevent unnecessary blood tests in a young child. The guideline group recognised however, that some CYP with Down syndrome may have persistently raised thyroid antibodies without necessarily developing thyroid disease. Therefore, the guideline group concluded that if results from three consecutive repeat tests of TSH and fT4 concentrations remained stable, and no symptoms developed suggestive of thyroid dysfunction, surveillance should be annual, unless there was a change in clinical symptoms.

The group agreed that a flowchart detailing the timing and frequency of testing would be very useful for clinicians and that the guideline should be accompanied by a flowchart summarising the recommendations to aid clinical decision-making and practice.

The group felt strongly that annual testing should continue beyond the age of 18 but acknowledged that young people aged over 18 are outside the scope of this guideline.

3.4.3.3 The experience of blood tests for the child or young person and their parents/carers (Recommendations section 3.5.2)

The guideline group acknowledged that it is vital to take into consideration the CYP's experience of having blood tests, as well as the experience of the parent/carer. For some CYP blood tests can be very distressing and some families may choose not to have them for this reason. The group noted that the CYP and their parents/carers should be prepared for what to expect during the blood tests and that signposting to YouTube children's phlebotomy sites can be useful in this regard, see for example http://www.lchtv.com/blood-taking and https://www.downs-syndrome.org.uk/for-families-and-carers/health-and-well-being/giving-blood-samples/ (last accessed 22.11.19)

For CYP who find blood tests particularly difficult encouraging doctor/nurse play with dolls or teddies or looking at picture book including hospital treatments and blood tests can be helpful in reducing their anxiety. It is also important that the parent/carers are fully informed about the purpose of the tests, the options available and the advantages and disadvantages associated with each. This should include the need for repeat venous testing should an abnormal result be reported following a dried blood spot test. The potential benefits of

identifying a disorder early and its effective treatment should also be explained. It was emphasized that measures should be put in place to minimize any distress associated with blood tests, for example that appropriate distraction is used during the procedure involving either the CYP's parent/carer or a second health care practitioner or assistant. It is also important that blood tests are performed by a skilled, experienced practitioner. The presence of a play therapist or other health care staff skilled at engaging CYP, if available, can also be very helpful. Minimising any distress associated with blood tests is especially important given the ongoing nature of surveillance and the possible need for repeat testing. The group also noted that additional blood tests for thyroid function should be timed to coincide with other blood tests or clinic visits in order to minimize disruption to the family and the trauma associated with blood testing.

3.4.3.4 Predictive value of testing (Recommendations section 3.5.1)

The evidence reviewed supports the clinical understanding that thyroid function tests for TSH and T4 can only indicate thyroid function at the time of testing and are not useful as predictive indicators of future risk of thyroid dysfunction (Sankar et al 2018; Gibson et al 2015; Iughetti 2014). Furthermore, the course of thyroid dysfunction may fluctuate over time, further necessitating regular surveillance (Iughetti 2014; Claret 2013; Selikowitz 1993). The guideline group felt it important that health care practitioners inform parents/carers of this and ensure they understand that ongoing surveillance of thyroid function is recommended for CYP with Down syndrome.

3.4.3.5 Signs and symptoms of thyroid dysfunction (Recommendations section 3.5.4)

Evidence from five studies suggests there is little or no predictive association between signs and symptoms of hypothyroidism and thyroid function as determined on biochemical testing in CYP with Down syndrome (Selikowitz et al, 1993; Gibson et al, 2005; Tenenbaum et al, 2012; McGowan et al, 2011; McGowan et al, 2015) However, the guideline group felt it was important to acknowledge that signs and/or symptoms do continue to have a role to play in helping accurate diagnosis. The group also noted that the signs and symptoms of hypothyroidism, for example constipation and dry skin, are difficult to detect in CYP with Down syndrome as these are often present in this group. Where growth was investigated findings suggested that there was no association between growth and TSH values (Selikowitz et al, 1993; Gibson et al, 2005; McGowan et al, 2015) or BMI and TSH concentrations (Iughetti et al, 2014). However, the detection and subsequent treatment of thyroid dysfunction has been shown to improve growth velocity (Karlsson et al. 1998). The guideline group noted that growth should be monitored in CYP with Down syndrome using Down syndrome specific growth charts. Whilst acknowledging the importance of recognizing and working to alleviate symptoms of, for example, constipation and dry skin, the guideline group agreed that that all CYP with Down syndrome should be offered regular thyroid function blood tests as part of ongoing surveillance for thyroid dysfunction and treated where indicated in a timely manner.

Subclinical hypothyroidism

There was evidence from one study that the absence of a goitre was associated with remission of subclinical hypothyroidism (Claret et al, 2013) and from another study that CYP with subclinical hypothyroidism have significantly higher levels of hypotonia than those without subclinical hypothyroidism (Tenenbaum et al, 2012). Whilst some other studies did report findings associated with signs and symptoms of hypothyroidism these were often inconsistent. However, the guideline group recognized the role played by signs and symptoms in diagnosing thyroid dysfunction, especially where these are severe or reported by parents/carers as being significant. The group recommended that signs and symptoms suggestive of thyroid dysfunction, although not always associated with the disorder, should be taken into account when deciding frequency of ongoing surveillance.

Hyperthyroidism

Hyperthyroidism is less common in CYP with Down syndrome than hypothyroidism (Karlsson et al, 1998; Iughetti et al, 2014; Pierce et al, 2017) although it is more prevalent than in CYP without Down syndrome (DeLuca et al, 2010). A dried blood spot test is not specific or sensitive to detect a low TSH concentration associated with hyperthyroidism. Testing should be undertaken to measure TSH, fT4, TPO antibodies and TSH receptor antibody (TRAB) levels. Free T3 should also be measured, in particular in the presence of normal fT4 and where there is a high clinical suspicion of disease.

3.4.3.6 Resource implications

The GDG recognised that this updated guidance for CYP with Down syndrome represents additional testing compared to the previous DSMIG guidance and usual current UK and Ireland practice. This additional testing includes closer surveillance as well as testing for TPO antibodies when venous sampling is undertaken. The GDG felt, however, that the potential health and developmental gains of identifying thyroid dysfunction early and treating appropriately outweighed the additional financial cost of the tests, which is relatively small. There are no national tariffs for thyroid function blood tests, however local figures obtained are as follows: TSH £0.50, fT4 £0.59 and TRO antibodies £2.68 per test (Leeds Teaching Hospitals NHS Trust, personal communication).

3.5 Recommendations for what tests to perform and timing of tests

The recommendations below have been based upon the evidence reviewed for clinical questions 1 and 2. They are ordered to reflect the priority the GDG give to ensuring CYP and their families/carers are appropriately informed and that measures are taken to minimise any distress associated with blood tests.

3.5.1 Information for children and young people, parents/carers

Offer information at each contact to parents/carers and children and young people with Down syndrome on thyroid disorders in order to explain the offer and importance of ongoing surveillance, for example using the following resources:

https://www.btf-thyroid.org/parents-and-carers Last accessed 22.11.19
https://www.btf-thyroid.org/hypothyroidism-leaflet Last accessed 22.11.19
https://www.btf-thyroid.org/hyperthyroidism-leaflet Last accessed 22.11.19
https://www.btf-thyroid.org/thyroid-nodules-and-swellingsleaflet Last accessed 22.11.19
https://www.downs-syndrome.org.uk/download-package/thyroid/ Last accessed 22.11.19

Inform parents/carers that blood test results will show what the child's or young person's thyroid function is at the time of testing and that thyroid function can change over time so further tests will be offered throughout life or if the child or young person develops signs or symptoms.

3.5.2 General recommendations on performing blood tests

Take measures to minimize any potential associated distress when performing blood tests. These measures should include:

- Informing the child or young person (where appropriate) and their parents/carers of the purpose of the test and the possible outcome of the tests including the need for repeat or follow up testing. Explain when and how (by phone or letter) to expect the results of the tests.
- before the blood test is taken explain the process of taking a blood test and inform parents/carers where to find child-friendly online resources showing what happens during a blood test
- providing support and comfort as needed, if the child or young person is anxious
- making any reasonable additional adjustments needed to support the blood-taking process
- ensuring that the blood test being performed by a skilled, experienced practitioner

Also consider:

- the use of distraction techniques e.g. pictures, bubbles, the presence of a play therapist
- the use of topical local anaesthetic (cream or spray) to numb the area and the application of a plaster afterwards
- the use of rewards

See, for example: http://www.lchtv.com/blood-taking
https://www.downs-syndrome.org.uk/for-families-and-carers/health-and-well-being/giving-blood-samples/ (last accessed 22.11.19)

Time blood tests for routine surveillance to coincide with other blood tests or appointments wherever possible, for example at the annual health review, to minimize any disruption and distress to the child or young person and family. However, it is important to remember an illness can affect the concentration of TSH, free T4 and free T3.

3.5.3 Dried blood spot versus venous testing

Decide whether testing will be venous (TSH, free T4 and thyroid peroxidase (TPO) antibodies) or a dried blood spot test (TSH) in accordance with the clinical presentation, local arrangements and taking into account the preferences of the child or young person and their parents/carers.

3.5.4 Signs and symptoms of thyroid disorder

Offer venous blood tests for TSH, free T4 and thyroid peroxidase (TPO) antibodies if a child/young person has any signs/symptoms suggestive of hypothyroidism. Do not perform a dried blood spot test in this instance.

Offer venous blood tests for TSH, free T4, thyroid peroxidase (TPO) antibodies and thyroid stimulating hormone receptor antibodies (TRABs) if there is a clinical suspicion of hyperthyroidism.

3.5.5 Neonatal screening

Follow the current national newborn screening blood spot programme for screening for congenital hypothyroidism.
https://www.gov.uk/government/publications/health-professional-handbook-newborn-blood-spot-screening/7-conditions#congenital-hypothyroidism (last accessed 22.11.19)

Do not undertake additional blood tests for thyroid dysfunction in the neonatal period in babies with Down syndrome unless there are signs and/or symptoms of thyroid dysfunction or where additional testing is recommended by the national newborn screening programme, such as for premature or sick neonates.

3.5.6 Ongoing surveillance (from 4-6 months of age)

Offer all infants with Down syndrome thyroid function testing at 4-6 months of age, at 12 months of age and annually thereafter, unless they are already receiving treatment for thyroid disorder or develop signs and symptoms of thyroid dysfunction when earlier testing would be indicated.

Decide the frequency of any follow-up blood tests on an individual basis taking into account initial blood test findings and any signs/symptoms of thyroid dysfunction, including presence or absence of a goitre.

3.6 Evidence statements: Thresholds for initiating treatment

Clinical questions:

3. At what thresholds should treatment be initiated when hypothyroidism has been detected, including clinical symptoms and biochemical thresholds?

4. At what thresholds should treatment be initiated when hyperthyroidism has been detected?

Evidence statements relating to these two questions report findings relating to average TSH and fT4 concentrations in study samples and sub-groups as well as the thresholds used in the studies.

For narrative summary see section 3.2.

For table summarising thresholds reported in included studies see Appendix K.

3.6.1 Neonatal screening

(2 studies)

A retrospective study (Erlichman et al, 2016) found that TT4 concentrations measured as part of a neonatal screening programme were similar in babies who were treated for congenital hypothyroidism and those who were not treated, with mean values of 11.2 and 11.3 mcg/dL respectively. TSH concentrations were significantly higher in the treated group at 18.2 $\pm$ 18.1 mU/L compared with 9.2 $\pm$ 12.0 mU/L in the untreated group. [Evidence level: low]

In a second retrospective study (Myrelid et al, 2009) the TSH threshold used for a neonatal dried blood spot screening programme was ≥40mU/l. [Evidence level: very low]

3.6.2 Ongoing surveillance

(4 studies)

In an annual school-based surveillance programme a dried blood spot TSH threshold of >10mU/l was confirmed on venous blood testing for all 15 CYP referred (Noble et al, 2000). [Evidence level: moderate]

Seven of 15 CYP who were referred following dried blood spot screening were commenced on treatment immediately, three of whom showed symptoms of hypothyroidism and one who was <5th centile for height for CYP with Down syndrome. [Evidence level: low]

In a UK surveillance programme (McGowan et al, 2011) the dried blood spot threshold for TSH was ≥4 mU/l in whole blood. The reference ranges for venous blood tests were: TSH 0.55-5.8 mU/l and fT4 9-26 pmol/l (2002 onwards). [Evidence level: low]

Two of the 13 pre-school children referred following surveillance testing were symptomatic. [Evidence level: very low]

In a similar UK study (McGowan et al, 2015) dried blood spot TSH concentrations above 4.0 mU/l were found to be accurate in identifying raised venous TSH at values, however this was

at the expense of a high false positive rate. Twenty-nine per cent of CYP had symptoms that could have been thyroid related. The height and weight of CYP with symptoms were not significantly different from those without symptoms. [Evidence level: low]

In an Irish feasibility study (Murphy et al, 2008) the dried blood spot threshold for TSH was >10 mU/l in whole blood. [Evidence level: moderate]

In the same study of the five newly diagnosed CYP, three had clinical signs and/or symptoms of hypothyroidism. Of the two CYP previously diagnosed with hyperthyroidism, one had presented with clinical signs. [Evidence level: very low]

3.6.3 Predictive value of thyroid function tests

(2 studies)

In a study of children aged under 3 years a venous TSH >11.6 5mU/l was moderately predictive of persistent hypothyroidism but data reporting is limited (Sankar et al, 2018). The normal range for TT4 in this study was defined as 4.5 – 12.5 µg/dl. [Evidence level: very low]

A UK study used a TSH threshold of ≥6 mu/ml in a venous blood sample along with low thyroxine concentrations to define hypothyroidism (Gibson et al, 2005). [Evidence level: very low]

Symptoms associated with hair growth, skin, appetite, bowel function, height and weight were found not to be related to thyroid function. [Evidence level: very low]

3.6.4 Prevalence and course of thyroid dysfunction, and the role of thyroid autoantibodies

(13 studies)

The following fT4 and TSH concentrations have been used in one study (Iughetti et al, 2014) to define thyroid function:

- Euthyroidism: normal fT4 and TSH ≤5 µIU/ml
- Hypothyroidism: low fT4 and TSH ≥10 µIU/ml
- Subclinical hypothyroidism: normal fT4 and TSH >5 µIU/ml
- Hyperthyroidism: high fT4 and low TSH

[Evidence level: low]

One study (Pierce et al, 2017) reported the mean TSH for CYP diagnosed with subclinical hypothyroidism as 11.6 µIU/ml (range 5.31 to 72.7) and mean fT4 as 1.03 ng/dl (range 0.6 to 1.8) (13.26 pmol/l (range 7.72 to 23.17)) at time of diagnosis. For CYP with overt hypothyroidism these values were reported as TSH 52.1 µIU/ml (range 21.6 to 150) and fT4 0.43 ng/dl (range 0.1 to 0.75) (5.53 pmol/l (range 1.287 to 9.65)). For CYP diagnosed with hyperthyroidism the mean TSH was 0.02 µIU/ml (range 0.008 to 0.1) and the mean fT4 3.64 ng/dl (range 1.0 to 6.5) (46.85 pmol/l (range 12.87 to 83.66)). The study reported reference ranges after one month of age as TSH 0.5 to 5.0 µIU/ml and fT4 0.8 to 1.8 ng/dl (10.30 to

23.17 pmol/l), whilst also acknowledging local laboratory variations in definitions of "high" and "low" concentrations. [Evidence level: very low]

Serum thresholds for normal thyroid function have been defined in one study as fT4 10.3 to 24.4 pmol/l and TSH 0.3 to 4.5 mU/l (Aversa et al, 2015). In CYP who developed Graves' disease following an initial diagnosis of Hashimoto's thyroiditis this was confirmed by finding positive TSH receptor antibodies at the time of reassessment. (Evidence level: low]

In one study (Popova et al, 2018) TSH and fT4 concentrations in CYP diagnosed with Hashimoto's thyroiditis and identified as having compensated hypothyroidism were as follows: asymptomatic: median TSH 10.8 mU/l (range 7.3 to 29.3) and fT4 10.4 pmol/l (range 9.1 to 18.0); symptomatic: median TSH 14.2 mU/l (range 7.8 to 29.3) and fT4 11.3 pmol/l (range 9.3 to 15.0). In CYP with compensated hypothyroidism who were asymptomatic: TSH 66.9 mU/l (range 19.3 to 122.4) and fT4 8.0 pmol/l (range 4.2 to 8.1); symptomatic: median TSH 92.1 mU/l (range 18.2 to 1100) and fT4 7.1 pmol/l (range 5.0 to 8.9). [Evidence level: low]

One study (Selikowitz et al, 1993) has defined the normal threshold for TSH in venous blood as <3.8 (units not reported). [Evidence level: low]

Hashimoto's thyroiditis has been defined in one study as TSH >6 µUI/mL and low fT4 with TPO antibody and/or thyroglobulin antibody positive (Schmitt-Lobe et al, 2018). [Evidence level: very low]

The normal range for serum TSH has been defined in one study as 0.3 – 4 mU/l (Karlsson et al, 1998). [Evidence level: very low]

In a retrospective study of 17 CYP with Down syndrome receiving thyroxine therapy, nine had thyroglobulin antibodies and TPO antibodies detected and TSH concentrations ranging from 5.8 – 197 mU/l (normal range: 0.4 – 4.0 mU/l); six CYP had no antibodies detected and TSH concentrations ranging from 4.6 – 23.0 mU/l when treatment was started (2 missing values) (Ivarsson et al, 1997). [Evidence level: very low]

One cross-sectional study (Zori et al, 1990) used a definition of thyroid dysfunction of venous TSH ≥5 µIU/ml or previously diagnosed Hashimoto's thyroiditis or Graves' disease and reported the prevalence in children aged less than 10 years was 68% and in CYP aged 10-20 years was 72%. [Evidence level: very low]

3.6.4.1 Subclinical hypothyroidism (compensated hypothyroidism)

One study (Tenenbaum et al, 2012) found the mean TSH in a group of CYP (mean age 5.9 years) with subclinical hypothyroidism (n=20) to be 9.0 mU/l (SD 2.2) compared with a mean TSH of 3.6 mU/l (SD 1.5) in a group without subclinical hypothyroidism (n=85) (p=0.0001). CYP with subclinical hypothyroidism were found to have a significantly higher degree of hypotonia compared to those without subclinical hypothyroidism. No significant differences were found between the groups for BMI or the occurrence of constipation, dry skin, bradycardia or anaemia. [Evidence level: low]

A second study of children diagnosed with hypothyroidism before age 5 years the following definitions were used (Claret et al, 2013):

- Subclinical hypothyroidism: TSH 5.5-25 mU/l (6 months - 4 years) or 4.13-25 mU/l (4 - 7 years), with fT4 11.45 – 24.07 pmol/l (6 months - 4 years) or 12.35 – 23.94 pmol/l (4 - 7 years).
- Overt hypothyroidism: TSH elevation with low fT4 and/or TT3.

For CYP with subclinical hypothyroidism the presence of signs and/or symptoms was similar between the groups of CYP who experienced remission compared with those who did not experience remission. [Evidence level: low]

For CYP with subclinical hypothyroidism the absence of goitre was significantly higher in those who experienced remission compared with those who did not experience remission. [Evidence level: very low]

One further study (van Trotsenberg et al, 2006) found the mean plasma TSH concentrations of the infants with Down syndrome decreased from 5.45 mIU/l at age 0.8 months to 4.53 mIU/l at 6 months and stabilized between 4.24 and 4.52 mIU/l after 6 months. Only 9.3% CYP with Down syndrome had all TSH measurements within the laboratory's reference interval. From age 0.8 month to age 6 months the mean plasma fT4 concentrations decreased approximately 20%. After six months values stabilized around 14.2 pmol/l. TSH concentration did not appear to be associated with TPO antibody positivity. [Evidence level: moderate]

3.6.4.2 Hyperthyroidism

One study (DeLuca et al, 2010) comparing the course of Graves' disease in CYP with Down syndrome with a control group of CYP without Down syndrome found a mean fT4 concentration of 43.3 pmol/l (SD 17.3) in CYP with Down syndrome compared with 41.2 pmol/l (SD 15.1) in the control group. TSH receptor antibodies level was 28 IU/l (range 9-205) in CYP with Down syndrome and 20 IU/l (range 2-369) in CYP without Down syndrome. Normal values for antibody levels were defined as: TPO antibodies <20 IU/l, thyroglobulin antibodies <20 IU/l and TSH receptor antibodies < 1.5 IU/l. [Evidence level: low]

The prevalence of clinical signs and symptoms in CYP with Down syndrome with Graves' disease compared with CYP without Down syndrome with Graves' disease showed no significant difference between the two groups. [Evidence level: very low]

3.7 Consideration of evidence for thresholds for initiating treatment

3.7.1 Overall quality of evidence

This section includes consideration of the evidence findings for thresholds for initiating treatment and/or further investigations. Where the evidence reviewed linked directly to a recommendation the recommendation is cross-referenced. In some instances recommendations have been drafted based upon an overall consideration of a body of evidence rather than on a particular finding, again this association is cross-referenced. Some

recommendations have been drafted following the GDG's discussion of the evidence in order to encourage good practice. These recommendations are based upon the clinical experience and expertise of professionals in the group and the views and experiences of care expressed by CYP's representatives.

The strength of recommendations is reflected in their wording, as used in NICE clinical guidelines. The term "offer" is used to represent a strong recommendation and "consider" represents a less strong recommendation. The body of evidence for this guideline is predominantly of low and very low certainty as defined using the GRADE methodology. This is usual for evidence based upon observational studies, many of which rely upon the retrospective examination of medical records, and so the strength of recommendations for this guideline is not based solely upon the level of certainty of findings as there is a clear floor effect in this instance. Where there were two or more studies providing evidence for a recommendation supported by GDG consensus a strong recommendation was made. Where there was very limited supporting evidence or some disagreement amongst GDG members (but with overall consensus) a less strong recommendation was made.

3.7.2 Q.3. At what thresholds should treatment be initiated when hypothyroidism has been detected, including clinical symptoms and biochemical thresholds?

3.7.2.1 Newborn period

The guideline development group emphasized that the national blood spot screening programme for congenital hypothyroidism suspected all infants, including thresholds for repeat testing and treatment, should be followed for newborn babies with Down syndrome (including those born preterm, twins, sick neonates etc).

3.7.2.2 Ongoing surveillance and repeat testing (Recommendations section 3.8.1)

For summary table of thresholds used in included studies see Appendix K.

The guideline group noted that test thresholds for TSH, fT4, TT4 and fT3 are assay specific and recommending specific thresholds could therefore be very misleading (Barth et al, 2017). This is underlined by the range of thresholds reported in the reviewed evidence (n=19 studies; see thresholds summary table in Appendix K). The group were aware that normal reference ranges would vary from area to area and over time and thus refer instead to local assay-specific laboratory-defined normal reference ranges in the recommendations. They also felt clinicians may need to discuss findings with their local laboratory in order to gain a full understanding of blood test results and their implications (Recommendations section 3.8.1).

The GDG made recommendations for seven of the more common abnormal blood test findings relating to hypothyroidism (Recommendations 3.8.1.1 to 3.8.1.7) plus a recommendation for blood test results suggesting hyperthyroidism (3.8.1.8). These recommendations are made to improve the clinical applicability of the guideline and provide more detailed guidance for specific scenarios. The recommendations draw upon evidence reviewed for thresholds and the GDG's personal clinical experience and expertise as well as building on findings from evidence reviewed regarding what tests to perform and when to carry them out (questions 1 and 2) which provides information on the prevalence and nature

of thyroid disorder and underlines the unpredictable and varying course that thyroid disorder can take. These findings highlight the value of discussing abnormal and borderline abnormal findings with a more experienced clinician and recommendations include this advice throughout the section on abnormal findings (Recommendations sections 3.8.1 and 3.8.2).

The group felt that it was appropriate to mention the more consistent cut-off concentration for TSH measurement in order to guide practice around borderline measurements. A venous TSH threshold concentration of >10 mU/l is recommended as reported in three of the reviewed studies as an upper limit above which further testing should be considered (Zori et al, 1990; Iughetti et al, 2014; McGowan et al, 2015) (Recommendations 3.8.1.2, 3.8.1.3, 3.8.1.4, 3.8.1.5). A capillary dried blood spot TSH threshold of 10 mU/l is also recommended as reported in three UK studies (Noble et al, 2000; Murphy et al, 2008; McGowan et al, 2015) (Recommendation 3.8.1.1). Both thresholds are in line with current UK practice.

The guideline group recognised that a TSH level above the local laboratory-defined reference range and below 10mU/l with a normal or low fT4 should raise concern of central hypothyroidism and should be investigated further as soon as possible. In this instance an individualised management plan, including further investigations, should be developed in discussion with a paediatrician with expertise in endocrinology (or equivalent level of relevant expertise depending upon local availability). Possible implications of blood test findings can also be discussed with local laboratory clinical biochemists. The timing of follow up blood tests will vary depending upon individual circumstances including signs and/or symptoms and the CYP's age (Noble et al, 2000; Murphy et al, 2008; Tenenbaum et al, 2012; McGowan et al, 2015). Due to the higher than anticipated prevalence of thyroid disorder in young children (see prevalence table in Appendix K) and the vulnerability of the developing brain the group recommended that in children under the age of 3 years follow up should be done in 1 – 3 months. For CYP aged 3 and over the follow up period is recommended as 3 – 6 months (Recommendation 3.8.1.5). The guideline group were aware that this age cut-off of 3 years for differentiating management is a year older than the age cut-off of 2 years recommended in the NICE (2019) guideline on thyroid disease, but all members of the group felt strongly that additional caution was appropriate for young children who have Down syndrome (Recommendation 3.8.1.5).

3.7.2.3 Signs and symptoms of thyroid dysfunction

In addition to blood test results the guideline group also considered the role of signs and symptoms in decision-making regarding thresholds for repeat blood testing and/or treatment. The group felt that whilst signs and symptoms of thyroid dysfunction can be difficult to recognize in children and young people with Down syndrome they do play a part in deciding the presence and potential severity of thyroid dysfunction as illustrated in some of the reviewed studies (Noble et al, 2000; Murphy et al, 2008; Tenenbaum et al, 2012; McGowan et al, 2015) although the evidence is mixed (Recommendation 3.8.1.1, 3.8.1.2, 3.8.1.5). When asking parents/carers to look out for these symptoms the group felt it important to provide accurate sources of information in an easy to read form, preferably with photographs/illustrations to aid accessibility and recommended the Down's Syndrome

Association/Down Syndrome Medical Interest Group leaflet https://www.downs-syndrome.org.uk/download-package/thyroid/ last accessed 23.11.19.

When considering the threshold for repeat testing or treatment the role played by the CYP's age was also acknowledged, and the group agreed clinicians would repeat tests sooner if there was any cause for concern in a child aged less than three years compared with an older CYP. For this reason, and to take into account differences in severity of symptoms, a time range is given when recommending repeat blood tests (Recommendation 3.8.1.5). The group also noted that it is not necessarily the number or severity of symptoms that might prompt a repeat blood test but that a change in symptoms can also be clinically important e.g. the onset of constipation in a CYP with previously normal bowel habit. The importance of noting information provided by parents or carers in this regard was highlighted. Psychological symptoms such as low mood, anxiety and mood swings can also be associated with thyroid dysfunction. These changes are most likely to be noticed by parents, carers, or teachers. Family history should also be taken into account when deciding whether repeat blood tests are indicated (Claret et al, 2013).

The guideline development group considered it is important to investigate the presence of goitre in an infant or CYP using ultrasound scanning, as it is not always possible to discern asymmetrical enlargement or the presence of nodules using clinical examination alone. This should be carried out even if blood test results are normal and expert advice sought if any abnormalities are present or suspected. In the presence of goitre there should be continued careful clinical evaluation for the presence of lymph nodes, the texture and symmetry of the goitre.

It was also noted that it was not necessary to perform routine ultrasound scans as part of ongoing surveillance for thyroid dysfunction and made a recommendation to reflect this. (Recommendations section 3.8.2)

3.7.3 Q.4 At what thresholds should treatment be initiated when hyperthyroidism has been detected, including clinical symptoms and biochemical thresholds?

The guideline group agreed that there should be a low threshold for suspicion when hyperthyroidism is suggested, either due to abnormal blood test findings or clinical signs and/or symptoms as a thyrotoxicosis crisis is more common and severe in CYP as compared to myxoedema (hypothyroid crisis). (Recommendation 3.8.1.8)

3.7.4 Audit and future research

The guideline group recognized that thyroid function surveillance and repeat testing varies across different regions of the UK and Ireland and that uptake of previous guidance has been inconsistent. Thyroid dysfunction is easy to treat, and treatment improves the health and development of CYP who have Down syndrome. Therefore, the guideline group recommended that clinicians caring for CYP who have Down syndrome undertake an annual local audit of surveillance for thyroid dysfunction (Recommendations section 3.8.3). It is also

hoped that this local audit will support implementation and monitoring of the uptake of this of this new guidance.

Furthermore, although there is some evidence describing the natural history of thyroid function and thyroid dysfunction in CYP with Down syndrome this evidence is usually of low quality and some of the findings are inconsistent. There remain areas where our understanding is still limited, particularly thyroid disease in the first 3 years of life, transient disease and the role of thyroid antibodies which current evidence suggest may be a marker for more severe disease. Thus, the group felt it important to highlight the need for further research to address this uncertainty and drafted research recommendations to that effect (Recommendations section 3.8.4).

3.1. Recommendations for thresholds

3.8.1 Abnormal blood test findings

Discuss reference ranges for thyroid hormones with the local laboratory as this will vary depending upon the assay method employed and the child or young person's age.

The timing of repeat blood tests following an initial abnormal finding for TSH and free T4 should be made according to clinical judgement regarding urgency and bearing in mind that in some instances an abnormal finding may be transient.

3.8.1.1 Dried blood spot test TSH concentration above local laboratory-defined normal reference range on surveillance sample:

- Offer a venous blood test for TSH, free T4 and thyroid peroxidase (TPO) antibodies within 5 working days of the initial blood test.

- Consider initiating treatment whilst awaiting blood test results if TSH is very high and there is clinical suspicion of hypothyroidism.

3.8.1.2 Initial venous TSH concentration above 10mU/l, and low free T4:

- Offer immediate repeat venous blood test to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies.

- Consider initiating treatment whilst awaiting blood test results if TSH is very high and there is clinical suspicion of hypothyroidism.

Formulate an individualised management plan for the child or young person if blood test results confirm a diagnosis of hypothyroidism and consider discussing the plan with a clinician with expertise in paediatric endocrinology.

3.8.1.3 Initial venous TSH concentration above 10mU/l with normal free T4

- Offer a repeat venous blood test to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies as a TSH concentration above 10mU/l with normal free T4 is likely to be a form of hypothyroidism, and discuss with a clinician with expertise in paediatric endocrinology.

3.8.1.4 Initial venous TSH concentration above local laboratory-defined reference range but below 10 mu/l, and low free T4:

- Offer a repeat blood test as soon as possible, to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies.

- Formulate an individualised management plan for the child or young person if blood tests confirm a diagnosis of hypothyroidism and consider discussing the plan with a clinician with expertise in paediatric endocrinology.

3.8.1.5 Initial venous TSH concentration above local laboratory-defined reference range, but below 10 mu/l and normal free T4:

- Offer an infant/child under the age of 3 years a repeat TSH and free T4 test in 1-3 months. Include thyroid peroxidase (TPO) antibodies in order to ascertain a baseline.

- In a child or young person aged 3 years and over offer:
    - a repeat venous blood test in 6 months to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies if there are no clinical signs and/or symptoms suggestive of thyroid dysfunction and thyroid antibodies are negative.
    - a repeat blood test sooner than 6 months to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies if clinical signs and/or symptoms develop.

Return to annual surveillance if three consecutive repeat tests show TSH and free T4 remain stable and there are no signs and symptoms suggestive of thyroid dysfunction.

3.8.1.6 Initial venous TSH within or below the local laboratory-defined reference range, and free T4 below the reference range:

- Offer repeat venous blood tests as soon as possible for TSH, free T4 and thyroid peroxidase (TPO) antibodies.

Seek advice promptly from a paediatric endocrinologist if repeat blood test findings show that the abnormality persists as this may be indicative of a more unusual form of hypothyroidism or central hypothyroidism and further specialized investigations are likely to be needed.

3.8.1.7 Blood test shows a normal TSH and normal free T4 but raised thyroid peroxidase (TPO) antibodies:

- Offer a venous blood test to measure TSH, free T4 and thyroid peroxidase (TPO) antibodies.
- The timing of these repeat tests should be:
    - in 6 months for children and young people aged 3 years and over
    - in 1 – 3 months in children aged under 3 years.

Offer a repeat blood test sooner if there are clinical concerns.

Return to annual surveillance if there are no signs and/or symptoms suggestive of thyroid dysfunction.

Hyperthyroidism

3.8.1.8 Venous TSH below local laboratory-defined reference range and high free T4, or clinical symptoms of hyperthyroidism:

- Seek advice from a paediatric endocrinologist
- Offer a venous blood test for TSH, free T4, free T3, thyroid peroxidase (TPO) antibodies and TSH receptor antibody (TRAB) levels and seek advice from a paediatric endocrinologist if there are any clinical signs and/or symptoms of hyperthyroidism.

Do not routinely test for free T3 as part of ongoing surveillance.

3.8.2 Presence of a goitre

If there is clinical evidence of a goitre:

- Offer venous blood testing for TSH, free T4 and thyroid peroxidase antibodies.
- Offer an ultrasound scan.
- Monitor closely for cervical lymphadenopathy.

Seek advice from a paediatric endocrinologist if there are any abnormal findings or clinical concerns.

Do not routinely perform ultrasound surveillance of the thyroid gland in the absence of goitre.

3.8.3 Audit

Staff responsible for commissioning or providing surveillance services for children with Down syndrome should conduct a yearly audit to include the timing, frequency, types of blood tests and test results carried out for children and young people with Down syndrome, and children's and young people's and parents experience of care The test result should also be correlated to clinical signs, symptoms and outcomes. This is usually within the remit of the local secondary paediatric services.

Audit should include pooling of individual patient data regarding antibody levels, and reporting how they relate to other blood test findings and clinical signs and symptoms of thyroid dysfunction.

3.8.4 Research recommendations

What is the incidence of thyroid dysfunction in children and young people who have Down syndrome and is thyroid dysfunction more common in the first year of life?

What is the natural history of thyroid dysfunction in children and young people who have Down syndrome?

What is the natural history of thyroid autoimmunity in children and young people with Down syndrome? How often should thyroid antibodies be evaluated?

4. Barriers and facilitators to guideline implementation

Potential barriers and how they may be overcome:

1. Change to current practice involving increased surveillance, starting at an earlier age and continuing annually (compared to bi-annually as previously recommended, DSMIG 2004): In order to overcome this barrier extensive dissemination of the guideline is proposed in order to raise awareness of this change and explain the rationale behind it. This includes a proposed launch at the RCPCH annual conference 2020, and publication of the full guideline on the DSMIG website. In addition the DSMIG have made a submission for presentation at the European Academy of Childhood Disability 2020 and submission for presentation at the World Down Syndrome Congress in Dubai 2020. It is also hoped that the guidelines will be published in a peer reviewed journal, e.g. Archives of Disease in Childhood. The full guideline will be freely available on the DSMIG website. The guideline will be accompanied by a summary flowchart for ease of reference which will help to support decision-making following the new recommendations. The flowchart will be free to use and published on the DSMIG website. In addition, the DSMIG intends to co-ordinate a national audit through participation of its members. This will include the collection of data on thyroid function tests, including antibody testing and ongoing blood tests following initiation of treatment, where appropriate, to gather information on the natural history of thyroid disease in children and young people who have Down syndrome. To facilitate this work, and to assist guideline implementation, the guideline will be accompanied by an audit tool which will be free to use and published on the DSMIG website.

2. Increased resource needed for blood testing associated with surveillance and repeat testing. It is anticipated that the dissemination of the guideline and associated education will help to overcome this barrier, in particular a recognition of the relatively low additional resource needed to undertake additional testing (locally costed at £0.50 for TSH; £0.59 for fT4 and £2.68 for TPO antibodies) compared with the potentially large gains to be made in terms of earlier identification and treatment of thyroid disorder and the associated improvement in cognition, behavior and symptoms this will bring. Implementation will be further supported by endorsement of the guideline by national bodies, recognising the robustness of the guideline and its clinical applicability. This endorsement has been sought from the RCPCH, RCN, RCGP and NICE.
3. Inconsistency between other published health care documents and the guideline recommendations: The DSMIG have been in contact with other partners working in this field to ensure the guideline recommendations are represented in other health care documents, for example the Down syndrome specific inserts for the parent held child health record (PCHR, "Red Book") has been updated simultaneously with the development of the guideline to reflect the recommendations within the guideline. It is hoped that the Down's syndrome Association, Early Support Information on Down syndrome, disseminated by the Council of Disabled Children will also be updated.
4. Possible reluctance from CYP and their families/carers to agree to adopt proposed changes: The GDG recognise that CYP and their families/carers often state a preference for finger prick blood spot testing over venous sampling but as this is not available in all sites, the guideline recommends that either method may be used. It is hoped that the uptake of the increased surveillance will be facilitated by offering a choice that takes into consideration the preferences of CYP and their parents/carers as well as local arrangements and usual practices. Good practice recommendations and hyperlinks to a range of resources for CYP and families have been provided to minimize any distress associated with blood tests and to facilitate an understanding of thyroid disorder and the benefit of regular surveillance.
5. Complexity brought about by the nature of biochemical testing involved in thyroid function tests and the varied presentation and course of thyroid disorder in CYP who have Down syndrome: During the consultation period stakeholders enquired regarding specific laboratory values for thyroid function tests. The guideline highlights that as each local area has their own unique specific laboratory assay it is not possible to provide a specific cut off value for thyroid disorders, although a widely used and accepted value of 10 mU/l is used to guide practice where possible. By acknowledging these local differences it is hoped that the guideline recommendations will be more readily implemented. The guideline describes and provides recommendations for many biochemical scenarios to aid clinical management on when to carry out repeat testing and initiate treatment, as well as underlining the importance of decision-making based upon individual clinical presentation. It is intended that the provision of

useful specific guidance plus a degree of flexibility will facilitate the implementation of the guideline.

The recently published NICE guideline on thyroid disorder (November 2019) does not specifically include guidance on surveillance in CYP with Down syndrome. The current guideline developed specifically for CYP with Down syndrome can be considered as an adjunct to the NICE guideline, thus facilitating specific appropriate care for this group of CYP. In addition, NICE endorsement is being sought for the DSMIG guideline to be considered as an adjunct to the NICE guideline on thyroid disease. Endorsement is also being sought from the RCPCH, RCN and RCGP to further support implementation of the guideline through recognition of its methodological rigour.

The scope of this guideline is for surveillance and when to initiate treatment. The treatment and on-going management of thyroid disorders in CYP who have Down syndrome is not included in the scope of this guideline as it would be the same as for the general population. On-going treatment and management of thyroid disorders is covered in the NICE guideline on Thyroid Disease (NG145, NICE 2019).

5. Online Resources

5.1 DSA resources - guidance for supporters/families/carers

Giving blood samples - https://www.downs-syndrome.org.uk/for-families-and-carers/health-and-well-being/giving-blood-samples/

Thyroid function - https://www.downs-syndrome.org.uk/for-families-and-carers/health-and-well-being/thyroid/

Thyroid booklet download - https://www.downs-syndrome.org.uk/download-package/thyroid-disorder/

Children with Down's syndrome giving blood samples (blog) - https://www.downs-syndrome.org.uk/news/children-with-downs-syndrome-giving-blood-samples/?highlight=finger%20prick

Where is the thyroid gland and what does it do? (Blog) - https://www.downs-syndrome.org.uk/news/where-is-the-thyroid-gland-and-what-does-it-do/?highlight=finger%20prick

5.2 DSA resources – guidance for GPs

Thyroid dysfunction – https://www.downs-syndrome.org.uk/for-professionals/health-medical/annual-health-check-information-for-gps/ last accessed 23.11.19

5.3 DSA resources – PWDS – easy read

Kate Powell blog piece – What does my Thyroid gland do? https://www.downs-syndrome.org.uk/news/thyroid-2/?highlight=thyroid

5.4 Non-DSA resources

British Thyroid Foundation resources – http://www.btf-thyroid.org/

https://www.btf-thyroid.org/parents-and-carers last accessed 22.11.19
https://www.btf-thyroid.org/hypothyroidism-leaflet Last accessed 22.11.19
https://www.btf-thyroid.org/hyperthyroidism-leaflet Last accessed 22.11.19
https://www.btf-thyroid.org/thyroid-nodules-and-swellingsleaflet Last accessed 22.11.19
https://www.downs-syndrome.org.uk/download-package/thyroid/ last accessed 22.11.19

6. References

American Academy of Pediatrics Committee on Genetics (2011) Health supervision for children with Down syndrome *Pediatrics* 128: 393-406

Aversa T, Salerno M, Radetti G, Faienza M, Iughetti L, Corrias A, Predieri B, Mussa A, Mirabelli S, De Luca F and Wasniewska M (2015) Peculiarities of presentation of Hashimoto's thyroiditis in children and adolescents with Down's syndrome *Hormones* 14(3): 410-416

Balsham H, Helfand M, Schunemann H, Oxman A, Kunz R, Brozek et al (2011) GRADE guidelines: 3. Rating the quality of evidence *Journal of Clinical Epidemiology* 64: 401-406

Barth J, Luvai A, Jassam N, Mbagaya W, Kilpatrick E, Narayanan D and Spoors S (2018) Comparison of method-related reference intervals for thyroid hormones: studies from a prospective reference population and a literature review *Annals of Clinical Biochemistry* 55(1): 107-112

Butler A, Charoensiriwatana W, Krasao P, Pankanjanato R, Thong-Ngao P et al (2017) Newborn thyroid screening: Influence of pre-analytic variables on dried blood spot thyrotropin measurement *Thyroid* 27(9): 1128-1134

Claret C, Goday A, Benaiges D, Chillarón J.J, Flores J. A, Elisa Hernandez E, Corretger J.M and Cano J.F (2013) Subclinical hypothyroidism in the first years of life in patients with Down syndrome *Pediatric Research* Vol. 73, No. 5: 674-678

De Luca F, Corrias A, Salerno M, Wasniewska M, Gastaldi R, Cassio A, Mussa A, Aversa T, Radetti G and Arrigo T (2010) Peculiarities of Graves' disease in children and adolescents with Down syndrome *European Journal of Endocrinology* 162: 591-595

Down Syndrome Medical Interest Group (2001) Basic medical surveillance essentials for people with Down's syndrome. Thyroid disorder. DSMIG UK

Down's Syndrome Association website

https://www.downs-syndrome.org.uk/about/general/ (accessed 20.01.20)

Erlichman I, Mimouni F.B, Erlichman M, and Schimmel M.S (2016) Thyroxine-based screening for congenital hypothyroidism in neonates with Down syndrome *The Journal of Pediatrics* 173: 165-8

Gibson P, Newton R, Selby K et al (2005) Longitudinal study of thyroid function in Down's syndrome in the first two decades *Archives of Diseases in Childhood* 90:574-578

Goday-Arno A, Cerda-Esteva M, Flores-Le-Roux JA et al (2008) Hyperthyroidism in a population with Down syndrome Clinical Endocrinology (Oxford) 71(1):110-114

Guyatt G, Oxman A, Akl E, Kunz R, Vist G, Brozek J, Norris S et al (2011) GRADE guidelines: Introduction – GRADE evidence profiles and summary of findings tables *Journal of Clinical Epidemiology* 64: 383-394

Iughetti L, Predieria B, Bruzzia P, Predieria F, Vellania G, Madeoa S M, Garavellib L, Biagionic O, Bedognid G and Bozzolae M (2014) Ten-year longitudinal study of thyroid function in children with Down's syndrome

Ivarsson S-A, Ericsson U-B, Gustafsson J, Forslund M, Vegfors P and Anneren G (1997) The impact of thyroid immunity in children and adolescents with Down syndrome *Acta Paediatricia* 86: 1065-1067

Karlsson B, Gustafsson J, Hedov G, Ivarsson S-A and Anneren G (1998) Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity *Archives Diseases in Childhood* 79: 242-245

King K, O'Gorman C and Gallagher S (2014) Thyroid dysfunction in children with Down Syndrome: a literature review *Irish Journal of Medical Science* 183: 1-6

McGowan S, Jones J, Brown A, Reynolds L, Leyland K, Charleton P, Rahim M, Mansor M, Ritha S, Donaldson M on behalf of the Scottish Down Syndrome Thyroid Screening Group (2011) Capillary TSH screening programme for Down's syndrome in Scotland, 1997-2009 *Archives Diseases in Childhood* 96: 1113-1117

McGowan S, Jones J, McMillan D, McLaughlin K, Smith S, Leyland K, Charleton P and Donaldson M (2015) Screening for hypothyroidism in Down syndrome using the capillary thyroid stimulating hormone method *The Journal of Pediatrics* 166: 1013-1017

Murphy J, Philip M,Macken J, Roche E, Mayne P, O'Regan M and Hoey H (2008) Thyroid dysfunction in Down's syndrome and screening for hypothyroidism in children and adolescents using capillary TSH measurement *Journal of Pediatric Endocrinology and Metabolism* 21: 155-163

Myrelid A, Jonsson B, Guthenberg C, U von Dobeln, Anneren G, Gustafsson J (2009) Increased neonatal thyrotropin in Down syndrome *Acta Pædiatrica* pp. 1010-1013

Noble S, Leyland K, Findlay C, Clark C, Redfern J, Mackenzie J, Girdwood R and Donaldson M (2000) School based screening for hypothyroidism in Down's syndrome by dried blood spot TSH measurement *Archives Diseases in Childhood* 82: 27-31

Pierce M, LaFranchi S and Pinter J (2017) Characterization of thyroid abnormalities in a large cohort of children with Down syndrome *Hormone Research in Pediatrics* 87: 170-178

Pokrovska T, Jones J, Gufta Shaikh A, Smight S and Donaldson M (2016) How well does the capillary thyroid-stimulating hormone test for newborn thyroid screening predict the venous free thyroxine level? *Archives of Diseases in Childhood* 101: 539-545

Popova G, Paterson W, Brown A and Donaldson M (2008) Hashimoto's thyroiditis in Down's syndrome: clinical presentation and evolution *Hormone Research* 70: 278-284

Purdy, I.B, Singh N, Brown W.L, Vangala S, & Devaskar U.P (2014) Revisiting early hypothyroidism screening in infants with Down syndrome. *Journal of Perinatology* 34: 936-940

Sankar H, Anjukrishna K and Riaz I (2018) Thyroid stimulating hormone level at diagnosis as a predictor of persistent subclinical hypothyroidism in children with Down syndrome *Indian Pediatrics* 55: 576-579

Schmitt-Lobe M, Scheidemantel A, Correa Nepomuceno M, Fogaca H (2018) thyroid disease in children and adolescents with Down syndrome – 16 years of follow up in a single service *57th ESPE 2018 Meeting Athens, Greece* (conference poster)

Selikowitz M (1993) A five-year longitudinal study of thyroid function in children with Down syndrome *Developmental Medicine and Child Neurology* 35: 396-401

Tenenbaum A, Lebel E, Malkiel S, Kastiel Y, Abulibdeh A and Haim Zangen D (2012) Euthyroid submedian free T4 and subclinical hypothyroidism may have a detrimental effect in Down syndrome *Hormone Research in Paediatrics* 78: 113-118

Van Cleve S and Cohen W (2006) Part 1: Clinical practice guidelines for children with Down syndrome from birth to 12 years *Journal of Pediatric Health Care* 20(1): 47-54

Van Cleve S and Cohen W (2006) Part 2: Clinical practice guidelines for adolescents and young adults with Down syndrome: 12 – 21 years *Journal of Pediatric Health Care* 20: 198-205

van Trotsenburg A, Kempers M, Endert E, Tijssen J, de Vijlder J and Vulsma T (2006) Trisomy 21 causes persistent congenital hypothyroidism presumably of thyroidal origin *Thyroid* 16(7): 671-680

Zori R, Schatz D, Ostrer H, Williams C, Spillar R and Riley W (1990) Relationship of autoimmunity to thyroid dysfunction in children and adults with Down syndrome *American Journal of Medical Genetics Supplement* 7: 238-241