Joint Trust Guideline for the Adult Testosterone Replacement and Monitoring

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Version	Date	Author	Reason/Change
JCG0043 V2.5	March 2020	Clinical Lead for Endocrinology	Due to Coronavirus the document cannot be reviewed at this time but a year's review date given to allow for thorough review
JCG0043 V2.6	March 2021	Clinical Lead for Endocrinology	Just beginning to restore activity and will need time to go through Re-addition of missing hospital header for JPUH
JCG0043 V3	March 2022	Clinical Lead for Endocrinology	formulary status of products added. Additional contraindication added. Follow up section amended. Additional clinical audit standard added. Transferred to new Trust Docs template
JCG004			

3 V4			

Previous Titles for this Document:

Previous Title/Amalgamated Titles	Date Revised
None	Not applicable

Note which Trust, where applicable.

Distribution Control

Printed copies of this document should be considered out of date. The most up to date version is available from the Trust Intranet.

Consultation

The following were consulted during the development of this document:
Professor Jeremy Turner, Chief of Service
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Monitoring and Review of Procedural Document

The document owner is responsible for monitoring and reviewing the effectiveness of this Procedural Document. This review is continuous however as a minimum will be achieved at the point this procedural document requires a review e.g. changes in legislation, findings from incidents or document expiry.

Relationship of this document to other procedural documents

This document is a clinical guideline applicable to Norfolk and Norwich University Hospitals (NNUH) and The Queen Elizabeth Hospital King's Lynn (QEHKL); please refer to local Trust's procedural documents for further guidance.

Guidance Note

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

The Trust's guidelines are made publicly available as part of the collective endeavour to continuously improve the quality of healthcare through sharing medical experience and knowledge. The Trust accepts no responsibility for any misunderstanding or misapplication of this document**.**

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Testosterone investigation algorithm

* Mood or sleep disorders, changes in muscle mass or increased body fat are not specific to male hypogonadism and are less likely to improve with testosterone treatment. Testosterone should also not be routinely measured during acute intercurrent illness.

**Free testosterone should be calculated using ISSAM bioavailable testosterone calculator which can be accessed at http://www.issam.ch/freetesto.htm

Joint Trust Guideline for the Adult Testosterone Replacement and Monitoring

1. Introduction

Testosterone replacement therapy (TRT) is a long term and non-urgent therapy usually managed in primary care under secondary care guidance. As such, many testosterone products (such as the depot preparation Nebido®, and topical preparations Testogel®, Tostran® and Testim®) are not included within the hospital formulary and so prescriptions should be issued by primary care with dose adjustments recommended by secondary care.

1.1. Rationale

- Testosterone deficiency (Trust reference range 8.6-29.0 nmol/L) has a slightly higher incidence with increasing age (0.1% in 40-49 year old men to 5.1% in the 70-79 year old men) This is often in association with comorbid load. Only symptomatic patients or those with proven complications of hypogonadism require and benefit from treatment.
- TRT may improve the physical health and emotional wellbeing in symptomatic patients with biochemically confirmed testosterone deficiency
- Widespread use of testosterone supplementation for patients presenting with erectile dysfunction or non-specific symptoms without confirmed abnormal biochemistry is inappropriate, ineffective and can carry with it significant risks associated with TRT.

1.2. Objectives

The objective of the clinical guide is to:

- To produce a trust guideline to advise when and how to investigate testosterone deficiency in men.
- Guidance on how to appropriately manage testosterone deficiency in men including treatment monitoring and screening for complications associated with TRT

1.3. Scope

- Replacement is recommended in men with sexual symptoms (loss of libido, loss of early morning erections or erectile dysfunction), skeletal complications, vasomotor symptoms or haematological complications (with no alternative explanation) with confirmed low early morning testosterone on repeat testing (the repeat test should be fasting). This should be in the absence of acute inter-current illness.
- Patients should only be initiated on TRT by those with the experience and capacity to monitor testosterone therapy.
- Once the patients are established on a stable dose of TRT, monitoring intervals can be extended with consideration of discharge back to primary care in cases of isolated hypogonadism.
- TRT is contraindicated in active testicular or prostate cancer, breast cancer, elevated haematocrit (>52%), poorly controlled heart failure, untreated obstructive sleep apnoea or in patients seeking fertility (exogenous testosterone inhibits spermatogenesis).

- Screening for prostate cancer (including digital rectal examination) is not mandatory for those established on testosterone treatment but men should continue to have appropriate community screening based on their age, family history and ethnicity.
- The evidence regarding cardiovascular risk of TRT remains uncertain and some studies have even proven cardiovascular protection of treatment. This uncertainty should be communicated to patients if they have a significant cardiovascular risk profile.

1.4. Glossary

The following terms and abbreviations have been used within this document:

Term	Definition
NNUH	Norfolk and Norwich University Hospitals
QEHKL	The Queen Elizabeth Hospital King's Lynn
TRT	Testosterone replacement therapy
BMI	Body mass index
HIV	Human immunodeficiency virus
COPD	Chronic obstructive pulmonary disease
PSA	Prostate-Specific Antigen
SHBG	Sex hormone binding globulin
FSH	Follicle-stimulating hormone
LH	Luteinising hormone
MRI	Magnetic resonance imaging
DRE	Digital rectal examination
FBC	Full blood count
LFT	Liver function test
EIA	Equality Impact Assessment

2. Responsibilities

- Lead Consultant for Endocrinology – Support in producing the document and lead for the Endocrine business meeting.
- Specialist Registrar – author of the document
- Lead for Clinical Governance in Endocrine & Diabetes – For approval at speciality level.
- Clinical Director for Endocrine & Diabetes – for overall approval

3. Processes to be followed

3.1. Assessment

3.1.1. Signs and symptoms

Consider testosterone deficiency in patients presenting with signs and symptoms in table 1, but not during acute illness as non-gonadal illness can cause a temporary drop in testosterone levels which is generally reversible on recovery.

We have also included symptoms for which testing is not routinely indicated.

Table 1	
Testing indicated	**Testing not routinely indicated**
Height loss, low trauma fracture (a fracture sustained in a fall from standing height or less), or confirmed low bone mineral density (osteoporosis)	Increased body fat/BMI
Hot flushes/sweats	Diminished physical or work performance
Gynaecomastia	
Incomplete or delayed sexual development	Decreased energy, motivation, self confidence
Reduced libido	Depression, dysthymia
Decreased spontaneous erections	Poor concentration and memory
Loss of body hair, reduced shaving	Sleep disturbance
< 5mL or shrinking testes	Mild normocytic, normochromic anaemia
Low or zero sperm count	Reduced muscle bulk and strength

3.1.2. Consider screening for hypogonadism in the following group of high-risk patients

- Type 2 diabetes mellitus / obesity.
- Patients on glucocorticoids, opioids etc (interference of production or metabolism).
- HIV associated weight loss.
- End stage renal disease.
- Moderate-severe COPD.
- Known or suspected pituitary disease.
- Osteoporosis.
- Cancer treated with alkylating therapy.

3.1.3. Contraindications to testosterone replacement therapy

- Haematocrit >52% (in some cases venesection may be considered in collaboration with the haematology department).
- Patients actively seeking fertility.
- Poorly controlled heart failure.
- Untreated severe obstructive sleep apnoea.

3.1.4. Cautions with testosterone replacement therapy

- Caution is required with sex hormone dependent cancer, e.g. active prostate or breast.
- A PSA should be checked prior to starting treatment

- Patients with a high risk of prostate cancer e.g. those with a PSA measurement above the reference range for their age group, a prostate nodule, or strong family history of prostate cancer require individualised risk assessment and urological evaluation prior to the treatment decision.
- TRT may restore prostate size and unmask incidental problems associated with benign prostatic hyperplasia (BPH)
- Testosterone therapy should be temporarily discontinued if there is a significant rise in PSA, a change in urological symptoms or any changes on surveillance imaging.

3.1.5. Confirming the diagnosis of hypogonadism

Testosterone therapy should only be instituted in patients with symptoms outlined above

and

two confirmed morning total testosterone levels <8 nmol//L taken (with the confirmatory test being a fasting sample)

or

patients with total testosterone between total testosterone 8.1 -12 nmol/L, but with free testosterone* below 220 pmol/L.

*We recommend using the free testosterone calculator available at http://www.issam.ch/freetesto.htm

3.2. Investigations

3.2.1. Initial screen

- Perform a (ideally fasting) 0900 (no later than 1000) serum testosterone, whilst physiologically well for the purpose of establishing potential testosterone deficiency (<12 nmol/L).

3.2.2. Confirmatory test

- Repeat a fasting 9am serum testosterone (no later than 1000), with sex hormone binding globulin (SHBG), liver function test, LH and FSH whilst physiologically well, to confirm testosterone deficiency (<8 nmol/L), or to allow calculation of free testosterone for borderline cases (8.1 -12 nmol/L).

3.2.3. Further investigations

- On confirmation of hypogonadism, it is recommended that patients are referred to endocrinology for further assessment into the cause of their hypogonadism and ongoing management.
- High FSH and LH are consistent with primary testicular failure. Most commonly, this is due to childhood mumps or maldescent of the testes. Patients with Klinefelter's also present with this biochemistry. Endocrine evaluation is important to determine the most likely cause, arrange counselling, karyotype analysis and treatment, and to

consider abdominal imaging in the first instance for patients with undescended testes.

- Low (or inappropriately normal) FSH and LH are consistent with secondary testicular failure. Refer to endocrinology, who will arrange baseline pituitary function including prolactin. MRI imaging of the pituitary should be performed if there is severe hypogonadism (serum testosterone levels < 5.2 nmol/L), any other abnormalities of pituitary function (e.g. elevated prolactin), or symptoms of a space occupying lesion e.g. visual field defect.
- Hypogonadism must be interpreted in the context of non-gonadal illness (such as acute illness, burns, myocardial infarction, stroke, and sepsis). Hypogonadotrophic driven hypogonadism has been demonstrated during non-gonadal illness and is transient with a paucity of evidence regarding the benefit of treatment. Treatment should therefore only be considered in exceptional cases and any underlying disease should be treated as a priority.
- Endocrinology will consider baseline bone densitometry scanning in men with profound hypogonadism.
- Do not start testosterone replacement therapy in individuals actively seeking fertility.

3.3. Management

- For confirmed hypogonadism, refer to endocrinology to complete investigation and supervise treatment.
- Initiation of testosterone replacement may restore secondary sexual characteristics, improve sexual function, wellbeing, muscle mass and bone mineral density. Patients must be counselled that testosterone therapy does not improve fertility.
- Investigate and treat the underlying cause where possible e.g. medical control of hyperprolactinaemia may restore testosterone levels and fertility; opioid withdrawal or weight loss may also lead to restoration of normal testosterone levels.
- Patients with known prostate cancer should be managed jointly with the uro-oncology team.
- Routine screening for prostate cancer is not recommended and patients should undergo usual community monitoring based on their age, ethnicity and family history including a digital rectal examination if required. However, the endocrinology department will continue to monitor PSA yearly whilst on treatment.
- Treatment is currently available as daily gels, 2-4 weekly injections, or 12 weekly depot injections. Suitable adult replacement doses are 1 sachet of Testogel®, 1 tube of Testim® or 3-6 pumps of Tostran® via a metered dose applicator daily, 250mg testosterone esters 3 weekly, or 1g Nebido® every 12 weeks (with an additional dose 6 weeks after initiation of treatment). However, prepubertal patients, older patients, those with mild hypogonadism, and those with very severe long-standing hypogonadism should be started on significantly lower doses and titrated up by an experienced endocrinologist.

3.4. Follow up and monitoring

- Safety monitoring (PSA, FBC and LFT testing) should be performed at 3 months,

with clinical and biochemical review of treatment efficacy at 6 months then annually thereafter. If there is no significant improvement in symptoms at 6 months, consider withdrawal of testosterone replacement.

- Any rise in PSA should warrant further interrogation of symptoms and a DRE as required
- Lower urinary tract symptoms should be reassessed at 6-12 months as testosterone therapy can restore prostate size and unmask BPH.
- If testosterone therapy is successful, then patients should be reviewed on a yearly basis once their doses are established. If a clear cause has been identified and a management plan agreed, this follow up may be provided by the patient's GP **with their agreement.** There should be an aim to maintain:
    - Haematocrit < 50%. Higher levels may need temporary drug cessation, and then reintroduction of testosterone at a lower dose.
    - PSA <1.4 ug/L increase annually. Rapid or sustained rises require urological evaluation (Cause for concern would be a PSA increase 1ng/ml over baseline or a PSA velocity greater than 0.35 ng/ml per year).
    - No adverse effects on liver function tests.
- For transdermal applications, testosterone dose should be adjusted to achieve a mid-normal range. Levels should be 4-6 hours post transdermal application (following treatment for at least a month).
- For IM preparations, trough levels (taken prior to next injection) should be at the lower range of normal and not exceed the higher range of normal one week post dose.

4. References

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5. Audit of the service to be delivered

5.1. Clinical Audit Standards

- Appropriate investigation to confirm diagnosis prior to treatment initiation: 2x early morning testosterone levels (with one **fasting** sample) <8 nmol/Lor if 8.1 -12 nmol/L, with appropriate calculation of free testosterone.
- Appropriate clinical indications documented prior to treatment.
- Adequate annual monitoring in place.

Compliance with the process will be monitored through the following:

Key elements	Process for Monitoring	By Whom (Individual / group /committee)	Responsible Governance Committee /dept	Frequency of monitoring
As above	Notes review of 20 cases	Clinical Lead for Endocrinology	Endocrinology Governance Committee	3 years

The audit results are to be discussed at Endocrine Business Meeting. This will provide a consistent system for reviewing, actioning and monitoring changes in practice.

6. Equality Impact Assessment (EIA)

Type of function or policy	Existing

Division	Medicine	**Department**	Endocrinology
Name of person completing form	Rupa Ahluwalia	**Date**	13.6.23

Equality Area	**Potential Negative Impact**	**Impact Positive Impact**	**Which groups are affected**	**Full Impact Assessment Required YES/NO**
Race	None	None	NA	NO
Pregnancy & Maternity	None	None	NA	NO
Disability	None	None	NA	NO
Religion and beliefs	None	None	NA	NO
Sex	None	None	NA	NO
Gender reassignment	None	None	NA	NO
Sexual Orientation	None	None	NA	NO
Age	None	None	NA	NO
Marriage & Civil Partnership	None	None	NA	NO
EDS2 – How does this change impact the Equality and Diversity Strategic plan (contact HR or see EDS2 plan)?		NO		

- **A full assessment will only be required if: The impact is potentially discriminatory under the general equality duty**
- **Any groups of patients/staff/visitors or communities could be potentially disadvantaged by the policy or function/service**
- **The policy or function/service is assessed to be of high significance**

IF IN DOUBT A FULL IMPACT ASSESSMENT FORM IS REQUIRED

The review of the existing policy re-affirms the rights of all groups and clarifies the individual, managerial and organisational responsibilities in line with statutory and best practice guidance.