ENDOCRINE SOCIETY
Hormone Science to Health

February 6, 2026

Marty Makary, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Makary:

On behalf of the Endocrine Society, the world's largest professional organization of endocrinologists, thank you for the opportunity to provide comments on your Food and Drug Administration Expert Panel on Testosterone Replacement Therapy for Men. Founded in 1916, the Endocrine Society represents approximately 18,000 physicians and scientists engaged in the treatment and research of endocrine disorders, such as diabetes, hypertension, obesity, osteoporosis, endocrine cancers (i.e., thyroid, adrenal, ovarian, pituitary) and thyroid disease. Given our members important work on men's health, we would like to offer comments on the key questions below.

Questions & Assignments
A. General

1. What are the potential impacts of TRT on: cardiovascular and thromboembolic disease, genitourinary systems, musculoskeletal health, frailty, and depression?

***Longer-term studies are still needed to determine whether testosterone therapy is safe with respect to cardiovascular, thromboembolic, and prostatic diseases.*** However, recent placebo-controlled trials (of 1-4 years) of TRT offer reassurance about the risk of cardiovascular and prostate disease (prostate cancer and lower urinary tract symptoms of benign prostatic hyperplasia, although less so for pulmonary emboli and thrombotic risk. Because the recent placebo-controlled trials of TRT excluded men at high risk of thromboembolic and prostatic disease, shorter studies (1-5 years) of typical mid- and high-normal range testosterone dosages used clinically must be performed in men with low serum testosterone and at high risk for these diseases. Placebo-controlled-studies with typical mid-range and high-range testosterone dosages for men with low serum testosterone with follow-up for up to 10, 15 and 20 years must be done to determine long-term risks of testosterone therapy for cardiovascular and prostatic disease.

***Longer-term studies are still needed to determine the potential benefit of testosterone therapy for musculoskeletal health, frailty, and mood.*** Recent, placebo-controlled trials (of 1-4 years) of TRT have

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demonstrated consistent, but modest benefit for libido and sexual function and potential benefit for muscle strength, physical function, bone density and strength, and mood for men over age 40 years and low serum testosterone. Placebo-controlled studies of 3-5 years of TRT with typical testosterone dosages that are used clinically and that produce mid-to high-normal blood testosterone concentrations must be done to determine the potential benefits for bone, muscle, and mood in specific populations: 1) men with low serum testosterone and osteoporosis based on bone densitometry; 2) men > 65 years old, low serum testosterone and moderate to severe (but not very severe) frailty; 3) and men with depressed mood (but not major depression) with endpoints of fragility fracture, improved physical function (stair climbing, walking speed, hand grip for common household products), mood (measured by validated assays).

2. How do the risks and benefits of TRT differ based on timing of hormone initiation, age of initiation of treatment, duration of use, formulation (type of testosterone replacement used), dose, and route of administration?

***The risk of erythrocytosis, infertility and dependency increases with higher dose/exposure, and longer duration of TRT***. These consequences can be irreversible. Testosterone ester injections are generally given in doses that deliver higher and more sustained blood testosterone concentrations over time than topical gels and should be used with extra care.

3. What are the biggest opportunities to improve education of providers and patients concerning the prescription of TRT?

***We need to develop fact-based guidelines and patient materials regarding TRT endorsed by all stakeholders, including patients, providers, and industry.*** Provider education should note that the benefit for TRT is high for men with hypogonadism (low testosterone and symptoms of testosterone deficiency) due to a disease affecting the hypothalamus-pituitary-testicular axis, but the benefit of TRT is small or modest in men with hypogonadism without a disease affecting the hypothalamus-pituitary-axis, such as in the case of obesity-related hypogonadism.

- Provider education should address appropriate patient selection, shared decision-making around benefits and risks, and clear guidance on monitoring and discontinuation.
- Standardized, accessible educational tools co-developed by professional societies, regulators, and patient advocates could substantially improve consistency and quality of care.

Patient education should include information that the major benefit of TRT is for men with hypogonadism (low testosterone and symptoms of testosterone deficiency) due to a disease affecting the hypothalamus-pituitary-testicular axis. For men with hypogonadism without a disease affecting the hypothalamus-pituitary-axis testosterone treatment only offers a modest improvement in libido, which needs to be balanced against the risks of the therapy. There is not good evidence to support a significant

benefit to cognition, concentration, energy, or sense of well-being for these men.

- Patient education should focus on clarifying fertility and unknown long-term cardiovascular risks and prostate cancers risk for younger men.
- Patient education should focus on distinguishing TRT for men with hypogonadism due to a disease affecting the hypothalamus-pituitary-testicular axis from testosterone therapy for appearance or performance-driven misuse.
- Both providers and patients should be educated to determine the reason for abnormal laboratory tests and to treat reversible causes first (e.g., obesity or undernutrition) before considering testosterone therapy.

4. How could interested parties—including, but not limited to, drug developers, health care providers, patients, consumers, and retailers, work together to further identify therapeutic uses of TRT and generate evidence supporting the safety and efficacy of these uses?

***It is critical for optimum public health and therapeutic use that the numerous stakeholders involved in TRT in males (industry, providers, and patients) be aligned and provide consistent messaging.*** We also need a Men's Health Initiative study analogous to the Women's Health Initiative study.

As it has for other disorders and drugs, the FDA may want to sponsor an Externally led Patient-Focused Drug Development (EL-PFDD) meeting, to ensure the patient perspective is recorded. It may also want to convene a meeting of the broad group of stakeholders including representatives from other federal partners (CDC, CMS, NIH, etc.), industry (Ascend Therapeutics, AbbVie, Lupin, Teva, Perrigo, Upsher-Smith, Pfizer, Endo Pharmaceuticals, Eugia, Xiromed, Antares Pharma, etc.), retailers (National Association of Chain Drug Stores, American Pharmacists Association, American Association of Pharmaceutical Scientists, etc.), providers and researchers (Endocrine Society, American Public Health Association, American Urologic Association, American Board of Medical Specialties, Federation of State Medical Boards, etc.), and patient representatives, with the objective of drafting uniform TRT treatment and research recommendations, which would be disseminated throughout each stakeholders respective networks and imbedded in their individual guidances. For example, partnership among stakeholders is necessary to support research investigating the long-term benefits and risks of TRT, such as a 'Men's Health Initiative'-type study analogous to the Women's Health Initiative.

B. Scientific Considerations

1. FDA seeks input on definitions and diagnostic thresholds for age-related androgen deficiency.

***The Endocrine Society guideline, as well as guidelines of most professional societies, recommend diagnosing hypogonadism in men with symptoms and signs of testosterone deficiency and consistently low serum total testosterone and/or free testosterone concentrations (when***

***indicated). This definition is agnostic of age.*** The causes of hypogonadism and co-morbidities may differ in young and older men with hypogonadism and may influence the treatment choices by the patient and his clinician. Reversable causes of hypogonadism should be treated before initiating testosterone treatment.

The 2.5$^{th}$ percentile value of serum total testosterone concentration in men, using liquid chromatography tandem mass spectrometry assay, harmonized to the Center for Disease Control and Prevention's standard, is 264 ng/dL (9.2 nmol/L). In randomized placebo-controlled trials that enrolled men with an average of two early morning, fasting testosterone levels less than 275 ng/dL or two testosterone levels <300 ng/dL, TRT improved sexual activity and sexual desire, and some other self-reported health outcomes, and corrected anemia. Therefore, two testosterone levels below 300 ng/dL or an average of two testosterone levels equal to or less than 275 ng/dL support the diagnosis of hypogonadism. Multiple low levels below the diagnostic threshold increase the confidence of accurate diagnosis.

The use of the terms that are difficult to define operationally such as “age-related hypogonadism,” “late-onset hypogonadism,” or “functional hypogonadism” should be avoided.

2. FDA seeks input on research priorities that could enhance the scientific understanding of TRT for men, including areas where additional evidence or data generation may be most valuable.

***Carefully designed, large, prospective, randomized, placebo-controlled studies of TRT are still needed***. These should investigate the efficacy and safety of TRT vs. placebo in older men with sarcopenia and frailty, subsyndromic depression, and anemia of aging and inflammation. Studies are also needed to evaluate the effects of TRT on venous thromboembolism and bone fractures. In essence, we need a Men’s Health Initiative study analogous to the Women’s Health Initiative study.

The TTrials and the TRAVERSE Trial have provided important data on the benefits and risks of testosterone replacement therapy and unveiled gaps and additional opportunities to enhance the scientific understanding of TRT for men, including areas where additional evidence or data generation may be most valuable. Some of these opportunities are listed below:

A. **The effect of TRT on bone fractures remains incompletely understood and is an issue of concern and high priority**. One of the most surprising finding of the TRAVERSE Trial was the significantly higher incidence of clinical bone fractures in the testosterone-treated men compared to the placebo-treated men. Testosterone treatment of men with hypogonadism increases areal as well as volumetric bone mineral density, and estimated bone strength in the hip and the spine. Therefore, further clarification of the effects of TRT on bone fractures in an adequately powered RCT is necessary to confirm the findings of the TRAVERSE trial, and to elucidate the potential mechanisms.

B. **In light of the widely recognized anabolic effects of anabolic effects of testosterone on the skeletal muscle, randomized trials are needed in frail older men with physical disabilities and functional limitations to evaluate whether TRT improves physician function, metabolism, and**

**wellbeing.** Numerous randomized trials have shown that testosterone treatment increases skeletal muscle mass, muscle strength and power, and some measures of physical function in men with hypogonadism. Yet, neither testosterone nor any other drug has been approved for the prevention and treatment of physical limitations or sarcopenia associated with aging or chronic wasting conditions. Given the high prevalence of sarcopenia and physical disability in older adults, large, randomized trials should evaluate the efficacy of TRT in preventing and treating sarcopenia, frailty, and mobility disability in older adults.

The mechanisms by which testosterone increases muscle mass and function, and regulates metabolism also need further investigation.

C. **Randomized trials to determine efficacy of TRT to treat subsyndromic depression in middle-aged and older men are needed.** The effects of testosterone treatment on mood, fatigue, wellbeing, and behavior are incompletely understood. The TRAVERSE Trial revealed that 50% of middle-aged and older men had depressive symptoms, and testosterone treatment improved depressive symptoms in men with mild and moderate depressive symptoms. However, testosterone treatment did not improve depressive symptoms in men with severe or clinical depression. However, the clinical significance of these findings remains incompletely understood. There is a high prevalence of subsyndromic depressive disorders in middle-aged and older men, and there is an opportunity to evaluate the efficacy of TRT in well characterized subsets of middle-aged and older men with rigorously defined subsyndromic depression.

The efficacy of TRT in improving fatigue and wellbeing also needs further research because of the high prevalence and disabling effects of fatigue.

D. **The risk of thromboembolism with TRT needs investigation.** The TRAVERSE Trial found an increased incidence of pulmonary embolism in testosterone-treated men. The relative risk of VTE was increased by about 50%. It is not clear if the increased risk of pulmonary embolism is limited to men with underlying thrombophilia or is generalized to all men. This is an important clinical problem because it is not clear whether middle-aged and older men should be pre-screened for thrombophilia and whether men with thrombophilia should receive prophylactic oral anticoagulant therapy prior to starting TRT.

Also, the increased risk of VTE was associated with absolute neutrophil and monocyte counts and increases in neutrophil and monocyte counts. Preclinical data and clinical trials data have unveiled that sex differences in myocardial infarct size and poor mortality outcomes of myocardial infarction are related to testosterone-induced increase in neutrophils. The mechanisms by which testosterone increases neutrophil and monocyte counts and how it affects myocardial infarct size and outcomes need further investigation.

E. **Because of the high prevalence of obesity, several opportunities exist for further research in this space.** Testosterone levels are lower in men with obesity partly due to lower SHBG levels, but the prevalence of true hypogonadism is also increased in men with obesity. It is important to determine

whether weight loss by obesity drugs or dietary restriction correct hypogonadism in men with moderate or severe obesity, as suggested by some uncontrolled studies? What degree of weight loss is needed to correct hypogonadism?
In the context of the increasing use of GLP-1 drugs for weight loss and the muscle and bone loss associated with incretin agonists, we need to determine whether concurrent TRT augments fat loss and preserves muscle and bone mass?
F. **Restoration of fertility of men treated with long-term testosterone is another area where research is needed.** TRT may cause long-term and seemingly irreversible suppression to men's sperm counts.

3. What scientific barriers might limit progress in increasing the availability of TRT?

***A major scientific barrier that limits the appropriate detection of men with low blood testosterone levels who might benefit from TRT is the use by most prescribers of inaccurate and non-standardized assays measuring total and free testosterone in the circulation, such that measured total testosterone values in the same blood sample can be low or normal depending on the assay used*** (Cao ZT, et al, Impact of testosterone assay standardization efforts assessed via accuracy-based proficiency testing. Clinical Biochemistry June 2019;68:37-43). The consequence of inaccurate testosterone testing is over-diagnosis or under-diagnosis of men who might benefit from TRT, so accurate and standardized testosterone blood tests are needed. Examples of the extreme variations in testosterone test values measured in the same blood samples can be found in the American College of Pathologists (CAP) Accuracy Based Performance (ABP) program results for serum total testosterone, e.g., 1036_ABS-B 2023_Survey results.
Because of the lack of standardization of total testosterone assays and the method used to develop reference ranges, the lower limit of the reference ("normal") ranges for testosterone (below which, clinicians use to define low testosterone) vary widely depending on the assay and laboratory used[#], making a specific threshold testosterone level to diagnose hypogonadism extremely difficult and contributing to over-diagnosis and under-diagnosis of who might benefit from TRT. In contrast, for total testosterone assays standardized and certified by the CDC, a harmonized reference range for non-obese young men with a standardized lower limit of 264 ng/dL can be used as a threshold for diagnosis of hypogonadism.[@]

[#]In a survey of 100 US, the lower limit of reference range for total testosterone varied from 160 to 300 ng/dL with 50% ≤ 241 ng/dL (Le M, et al, Current practices of measuring and reference range reporting of free and total testosterone in the United States, J Urol May 2016;195(5):1556-1561).
[@]Travison TG, et al, Harmonized reference ranges for circulating testosterone levels in men of cohorts of four cohort studies in the United States and Europe, J Clin Endocrinol Metab April 1, 2017;102(4):1161-

1173.

4. What additional scientific tools, technologies, or data sources could support the availability of TRT?

***Additional scientific technologies that could improve more accurate detection of men with low blood testosterone levels who might benefit from TRT are the development and routine laboratory use of automated, high-throughput mass spectrometry instruments to measure total and free testosterone accurately and reproducibly in blood samples and ongoing participation in an accuracy-based quality control program.*** Additional data that could improve more accurate detection of men with low blood testosterone levels who might benefit from TRT are more research studies that evaluate the role of free and bioavailable versus total testosterone assays in men who have symptoms compatible with testosterone deficiency.

The assays for measuring free testosterone are not standardized and have high levels of imprecision and inaccuracy. The reference ranges for free testosterone vary substantially among laboratories rendering it difficult to establish common diagnostic thresholds. Thus, there is a need to develop more advanced methods for measuring free testosterone and establish rigorously derived reference ranges.

5. Are there specific diseases or conditions that have not, traditionally, been treated with TRT for which testosterone could be safely and effectively used, and which are currently not indicated in FDA-approved product labeling? If so, please provide the data or evidence supporting these potential uses.

No, we do not believe that there are specific diseases or conditions that have not, traditionally, been treated with TRT, but for which testosterone could be safely and effectively used, and which are currently not indicated in FDA-approved product labeling. Safety over the short- to mid-term (up to 1-5 years) has been demonstrated for current indications. For men not meeting current criteria, benefits to hemoglobin, libido, and bone density are modest, and improvements in vitality are equivalent to placebo. Safety beyond 2-5 years is not known.