

Supplementary Online Content:

Elliott et al. Testosterone replacement therapies in hypogonadal men: a systematic review and network meta-analysis

Appendix 1: Search strategy

The search was originally executed on June 3, 2014 and updated May 25, 2017.

Testosterone Replacement Therapy
Primary Studies - Final Strategies
2014 Jun 3

Database: Embase Classic+Embase <1947 to 2014 June 02>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

- 1 exp Testosterone/aa, ad, ae, tu (9143)
- 2 Testosterone Congeners/ad, ae, tu (391)
- 3 exp Testosterone/ and Hormone Replacement Therapy/ (4361)
- 4 exp Androgens/ and Hormone Replacement Therapy/ (5792)
- 5 (testosteron* adj3 (replac* or substitut* or supplement* or therap* or treatment* or buccal or cream\$1 or gel or gels or implant* or inject* or oral* or patch* or transdermal*)).tw. (20369)
- 6 (androgen* adj (replac* or substitut* or supplement* or therap* or treatment* or cream\$1 or gel or gels or implant* or inject* or patch*)).tw. (6312)
- 7 (androgen* adj3 (buccal* or oral* or transdermal*)).tw. (632)
- 8 TRT.tw. (2125)
- 9 (testosterone adj (beta cyclopentylpropionate or cyclopentylpropionate or cipionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")).tw. (2636)
- 10 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron).tw. (1095)
- 11 ("Bio-T-Gel" or Ciclosterone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatestryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Delatestryl or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate).tw. (492)
- 12 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Ofterone or Oreton or "Oreton-F" or Orquisteron).tw. (292)
- 13 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primoteston or Relibra or Restandol or Sterotate or Striant or Sustanon\$1 or "Sustason 250" or Synandrol).tw. (674)
- 14 (Teslen or "Testa-C" or Testamone or Testandron or Testaqua or Testerone or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropon or Testosteroid).tw. (691)
- 15 (Testostosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or Trans-Testosterone).tw. (604)
- 16 (UNII-3XMK78S470 or Undestor or Virilon or Virormone or Virosterone or Vogelxo).tw. (61)
- 17 or/1-16 (39453)
- 18 exp Animals/ not (exp Animals/ and Humans/) (8702141)
- 19 17 not 18 (25517)
- 20 (controlled clinical trial or randomized controlled trial).pt. (457659)
- 21 clinical trials as topic.sh. (169995)
- 22 (randomi#ed or randomly or RCT\$1 or placebo*).tw. (1423548)
- 23 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (296647)
- 24 trial.ti. (292735)
- 25 or/20-24 (1829141)
- 26 19 and 25 (3594)
- 27 (comment or editorial or interview or letter or news).pt. (2802584)
- 28 26 not 27 (3546)
- 29 (control* adj2 trial*).tw. (323672)
- 30 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73609)
- 31 (nRCT or nRCTs or non-RCT\$1).tw. (647)
- 32 (control* adj3 ("before and after" or "before after")).tw. (6046)
- 33 time series.tw. (33994)
- 34 (pre- adj3 post-).tw. (110642)
- 35 (pretest adj3 posttest).tw. (6260)

36 (control* adj2 stud\$3).tw. (346641)
 37 Control Groups/ (74764)
 38 (control\$ adj2 group\$1).tw. (752277)
 39 or/29-38 (1509227)
 40 19 and 39 (2115)
 41 40 not 27 (2097)
 42 exp Cohort Studies/ (1517558)
 43 cohort\$1.tw. (675350)
 44 Retrospective Studies/ (837256)
 45 (longitudinal or prospective or retrospective).tw. (1721897)
 46 ((followup or follow-up) adj (study or studies)).tw. (89267)
 47 Observational study.pt. (2469)
 48 (observation\$2 adj (study or studies)).tw. (111012)
 49 ((population or population-based) adj (study or studies or analys#s)).tw. (26131)
 50 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (187)
 51 Comparative Study.pt. (1676994)
 52 ((comparative or comparison) adj (study or studies)).tw. (185742)
 53 or/42-52 (4729450)
 54 19 and 53 (3389)
 55 54 not 27 (3352)
 56 28 or 41 or 55 (6587)
 57 56 use prmz (3219) [ALL MEDLINE RECORDS]
 58 28 use prmz (1720) [MEDLINE RCTS]
 59 41 use prmz (845) [MEDLINE NON-RCTS]
 60 55 use prmz (1837) [MEDLINE OBSERV]
 61 androgen therapy/ (3539)
 62 androgen deficiency/dt (507)
 63 testosterone undecanoate/ (1591)
 64 testosterone cipionate/ (871)
 65 testosterone enantate/ (2439)
 66 (testosteron* adj3 (replac* or substitut* or supplement* or therap* or treatment* or buccal or cream\$1 or gel or gels or implant* or inject* or oral* or patch* or transdermal*)).tw. (20369)
 67 (androgen* adj (replac* or substitut* or supplement* or therap* or treatment* or cream\$1 or gel or gels or implant* or inject* or patch*)).tw. (6312)
 68 (androgen* adj3 (buccal* or oral* or transdermal*)).tw. (632)
 69 TRT.tw. (2125)
 70 (testosterone adj (beta cyclopentylpropionate or cyclopentylpropionate or cipionate or cypionate or enanthate or enanthane or ethanate or heptonate or heptylate or oenanthate or undecanoate or undecylate or "17 undecylate")).tw. (2636)
 71 ("8-Isotestosterone" or andriol or "andro 100" or "androgyn LA" or androderm or androfort or androgel or androlin or andronaq or andropatch or androsorb or androstenolone or androtardyl or androtest or androtop or andrusol or axiron).tw. (1095)
 72 ("Bio-T-Gel" or Ciclosterone or "Cristerona T" or "Cristerone T" or CompleoTRT or "CP 601B" or Delatestryl or Depandro or Deposteron or Depostomead or Depo-Testosterone or Depotest or Depovirin or Depoviron or Delatestryl or Duratest or Durathate or Everone or "first-testosterone" or Fortesta or Rortigel or Hexanecarboxylate or Histerone or Homosteron* or Intrinsa or Jenasteron or LibiGel or Livensa or Malerone or Malogen or Malogex or Mertestate).tw. (492)
 73 (Nasobol or Nebido or "Neo-Hombreol F" or "Neo-testis" or Neotestis or "NSC 9700" or Ofterone or Oreton or "Oreton-F" or Orquisteron).tw. (292)
 74 (Pantestone or Perandren or Percutacrine androgenique or Percutacrine androgine or Pertestis or Primotest or Primoteston or Relibra or Restandol or Sterotate or Striant or Sustanon\$1 or "Sustason 250" or Synandrol).tw. (674)
 75 (Teslen or "Testa-C" or Testamone or Testandrone or Testaqua or Testeron or Testex or Testiculosterone or Testim or Testo Enant or Testobase or Testoderm or Testogel or Testoject-50 or Testolin or Testoluton or Testopel or Testopropon or Testosteroid).tw. (691)
 76 (Testostosterone or Testoviron or Testrin or Testro or Testrone or Theramex or Tostrelle or Testryl or Tostrex or Trans-Testosterone).tw. (604)
 77 (UNII-3XMK78S470 or Undestor or Virilon or Virormone or Viosterone or Vogelxo).tw. (61)
 78 or/61-77 (33099)
 79 randomized controlled trial/ or controlled clinical trial/ (936519)
 80 exp "clinical trial (topic)"/ (104828)
 81 (randomi#ed or randomly or RCT\$1 or placebo*).tw. (1423548)
 82 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (296647)
 83 trial.ti. (292735)
 84 or/79-83 (1962147)
 85 78 and 84 (4042)
 86 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37422531)
 87 exp humans/ or exp human experimentation/ or exp human experiment/ (28425359)
 88 86 not 87 (8998814)
 89 85 not 88 (3544)
 90 (letter or editorial).pt. (2492646)
 91 89 not 90 (3515)

92 (control* adj2 trial*).tw. (323672)
 93 (nonrandom* or non-random* or quasi-random* or quasi-experiment*).tw. (73609)
 94 (nRCT or nRCTs or non-RCT\$1).tw. (647)
 95 (control* adj3 ("before and after" or "before after")).tw. (6046)
 96 time series analysis/ (13996)
 97 time series.tw. (33994)
 98 pretest posttest control group design/ (202)
 99 (pre- adj3 post-).tw. (110642)
 100 (pretest adj3 posttest).tw. (6260)
 101 controlled study/ (4336835)
 102 (control* adj2 stud\$3).tw. (346641)
 103 control group/ (74764)
 104 (control* adj2 group\$1).tw. (752277)
 105 or/92-104 (5430128)
 106 78 and 105 (7057)
 107 106 not 88 (3849)
 108 107 not 90 (3833)
 109 cohort analysis/ (334727)
 110 cohort\$1.tw. (675350)
 111 retrospective study/ (837256)
 112 longitudinal study/ (153245)
 113 prospective study/ (618128)
 114 (longitudinal or prospective or retrospective).tw. (1721897)
 115 follow up/ (824941)
 116 ((followup or follow-up) adj (study or studies)).tw. (89267)
 117 observational study/ (58475)
 118 (observation\$2 adj (study or studies)).tw. (111012)
 119 population research/ (68859)
 120 ((population or population-based) adj (study or studies or analys#s)).tw. (26131)
 121 ((multidimensional or multi-dimensional) adj (study or studies)).tw. (187)
 122 exp comparative study/ (2694962)
 123 ((comparative or comparison) adj (study or studies)).tw. (185742)
 124 or/109-123 (5973302)
 125 78 and 124 (4650)
 126 125 not 88 (3667)
 127 126 not 90 (3625)
 128 91 or 108 or 127 (7409)
 129 128 use emczd (5052) [ALL EMBASE RECORDS]
 130 91 use emczd (2221) [EMBASE RCTS]
 131 108 use emczd (3091) [EMBASE NON-RCTS]
 132 127 use emczd (2341) [EMBASE OBSERV]
 133 58 or 130 (3941) [MEDLINE/EMBASE RCTS]
 134 remove duplicates from 133 (2771) [UNIQUE RCTS]
 135 134 use prmz (1666) [MEDLINE UNIQUE RCTS]
 136 134 use emczd (1105) [EMBASE UNIQUE RCTS]
 137 59 or 131 (3936) [MEDLINE/EMBASE NON-RCTS]
 138 137 not 133 (1817) [OVERLAP REMOVED]
 139 remove duplicates from 138 (1633) [UNIQUE NON-RCTS]
 140 139 use prmz (264) [MEDLINE UNIQUE NON-RCTS]
 141 139 use emczd (1369) [EMBASE UNIQUE NON-RCTS]
 142 60 or 132 (4178) [MEDLINE/EMBASE OBSERV]
 143 142 not (133 or 137) (2513) [OVERLAP REMOVED]
 144 remove duplicates from 143 (2170) [UNIQUE OBSERV]
 145 144 use prmz (1216) [MEDLINE UNIQUE OBSERV STUDIES]
 146 144 use emczd (954) [EMBASE UNIQUE OBSERV STUDIES]
 147 134 or 139 or 144 (6574) [UNIQUE RECORDS – ALL STUDY TYPES]

Appendix 2: Scales represented in the analysis of data for each outcome

Quality of life	Aging Males' Symptoms
	Minnesota Living with Heart Failure Questionnaire
	Quality of Life Specific to Male Erection Difficulties
	International Prostate Symptoms Score Quality of Life
	Quality of Life Enjoyment and Satisfaction Questionnaire
	Questions on Life Satisfaction, health subscale
	Health Related Quality of Life, sexual function domainSF-36 (total score)
Depression	Hospital Anxiety and Depression Scale
	Beck's Depression Inventory
	General Well-Being Index, depressed mood dimension
	Geriatric Depression Scale
	Hamilton Depression Scale
Libido	International Index of Erectile Function (sexual desire domain)
	Men's Sexual Health Questionnaire (sexual desire domain)
	Partial Androgen Deficiency in Aging Men (PADAM) Questionnaire
	Psychosexual Daily Questionnaire
Erectile function	International Index of Erectile Function (IIEF-5 or erectile function domain of IIEF-15)

eAppendix 3: Included studies*

*The list of excluded studies is available from the authors on request.

Note: studies were not evaluated for inclusion on the basis reported outcomes.

1. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol*. 2005; 173: 533–6.
2. Agledahl I, Brodin E, Svartberg J, et al. Impact of long-term testosterone treatment on plasma levels of free TFPI and TF-induced thrombin generation ex vivo in elderly men with low testosterone levels. *Thrombo Haemostasis*. 2009; 102: 945.
3. Agledahl I, Hansen JB, Svartberg J. Impact of testosterone treatment on postprandial triglyceride metabolism in elderly men with subnormal testosterone levels. *Scand J Clin Lab Invest* 2008; 68: 641.
4. Alamir MA, Ellenberg SS, Swerdloff RS, et al. The Cardiovascular Trial of the Testosterone Trials: Rationale, design, and baseline data of a clinical trial using computed tomographic imaging to assess the progression of coronary atherosclerosis. *Coronary Artery Disease*. 2016;27:95.
5. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 2004; 89: 503–10.
6. Andrade ES, Jr., Clapauch R, Buksman S. Short term testosterone replacement therapy improves libido and body composition. *Arq Bras Endocrinol Metabol* 2009;53:996–1004.
7. Arafa M, Zohdy W, Aboulsoud S, et al. Prevalence of late-onset hypogonadism in men with type 2 diabetes mellitus. *Andrologia* 2012; 44: 756.
8. Arver S, Sinha-Hikim I, Beall G, Guerrero M, Shen R, Bhasin S. Serum dihydrotestosterone and testosterone concentrations in human immunodeficiency virus-infected men with and without weight loss. *J Androl* 1999; 20: 611–8.
9. Atkinson RA, Srinivas-Shankar U, Roberts SA, et al. Effects of testosterone on skeletal muscle architecture in intermediate-frail and frail elderly men. *J Gerontol A Biol Sci Med Sci* 2010; 65: 1215.
10. Aversa A, Bruzziches R, Francomano D, et al. Effects of testosterone undecanoate on cardiovascular risk factors and atherosclerosis in middle-aged men with late-onset hypogonadism and metabolic syndrome: results from a 24-month, randomized, double-blind, placebo-controlled study. *J Sex Med* 2010; 7: 3495.
11. Aversa A, Bruzziches R, Francomano D, Spera G, Lenzi A. Efficacy and safety of two different testosterone undecanoate formulations in hypogonadal men with metabolic syndrome. *J Endocrinol Invest* 2010; 33: 776–3.
12. Aversa A, Bruzziches R, Francomano D, et al. Effects of long-acting testosterone undecanoate on bone mineral density in middle-aged men with late-onset hypogonadism and metabolic syndrome: Results from a 36 months controlled study. *Aging Male* 2012; 15: 96.
13. Aydogdu A, Bolu E, Sonmez A, et al. Effects of three different medications on metabolic parameters and testicular volume in patients with hypogonadotropic hypogonadism: 3-year experience. *Clin Endocrinol* 2013; 79: 243–51.
14. Bachman E, Travison TG, Basaria S, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. *J Gerontol A Biol Sci Med Sci* 2014; 69: 725–735.
15. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010; 363: 109–22.
16. Basaria S, Davda MN, Travison TG, Ulloor J, Singh R, Bhasin S. Risk factors associated with cardiovascular events during testosterone administration in older men with mobility limitation. *J Gerontol A Biol Sci Med Sci* 2013; 68: 153–160.
17. Basaria S, Harman SM, Travison TG, et al. Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial. *JAMA : the journal of the American Medical Association*. 2015;314:570.
18. Basaria S, Travison TG, Alford D, et al. Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. *Pain*. 2015;156:280.

19. Basurto L, Zarate A, Gomez R, Vargas C, Saucedo R, Galvan R. Effect of testosterone therapy on lumbar spine and hip mineral density in elderly men. *Aging Male* 2008; 11: 140–5.
20. Beggs LA, Yarrow JF, Conover CF, et al. Testosterone alters iron metabolism and stimulates red blood cell production independently of dihydrotestosterone. *Am J Physiol Endocrinol Metab* 2014; 307: E456–E461.
21. Behre HM, Tammela TL, Arver S., et al. A randomized, double-blind, placebo-controlled trial of testosterone gel on body composition and health-related quality-of-life in men with hypogonadal to low-normal levels of serum testosterone and symptoms of androgen deficiency over 6 months with 12 months open-label follow-up. *Aging Male* 2012; 15: 198.
22. Bhasin S, Storer TW, Asbel-Sethi N, et al. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *J Clin Endocrinol Metab* 1998; 83: 3155–62.
23. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA* 2000; 283: 763–70.
24. Black AM, Day AG, Morales A. The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: Can a case be made for a 3-month therapeutic trial? *BJU International* 2004; 94: 1066–70.
25. Blick G. Optimal diagnostic measures and thresholds for hypogonadism in men with HIV/AIDS: comparison between 2 transdermal testosterone replacement therapy gels. *Postgrad.Med* 2013; 125: 30–9.
26. Borst SE, Yarrow JF, Conover CF, et al. Musculoskeletal and prostate effects of combined testosterone and finasteride administration in older hypogonadal men: a randomized, controlled trial. *Am J Physiol Endocrinol Metab* 2014; 306: E433–E442.
27. Borst SE, Yarrow JF, Fernandez C, et al. Cognitive effects of testosterone and finasteride administration in older Hypogonadal men. *Clin Interv Aging*. 2014; 9: 1327–33.
28. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male* 2003; 6: 1–7.
29. Brock G, Heiselman D, Maggi M, Kim SW, Rodr JM. Effect of Testosterone Solution 2% on Testosterone Concentration, Sex Drive and Energy in Hypogonadal Men: Results of a Placebo Controlled Study. *J Urol*. 2016;195:699.
30. Brockenbrough AT, Dittrich MO, Page ST, Smith T, Stivelman JC, Bremner WJ. Transdermal androgen therapy to augment EPO in the treatment of anemia of chronic renal disease. *Am J Kidney Dis* 2006; 47: 251–62.
31. Budoff MJ, Ellenberg SS, Lewis CE, et al. Testosterone Treatment and Coronary Artery Plaque Volume in Older Men With Low Testosterone. *JAMA : the journal of the American Medical Association*. 2017;317:708.
32. Buisson J. Effects of testosterone supplementation on sexual function in elderly men: Results of a six month randomised, placebo controlled study. *Cahiers de l'Annee Gerontologique* 2010; 2: 144–6.
33. Burnett AL, Kan-Dobrosky N, Miller MG. Testosterone replacement with 1% testosterone gel and priapism: no definite risk relationship. *J Sex Med* 2013; 10: 1151–61.
34. Caminiti G, Volterrani M, Iellamo F, et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am College Cardiol* 2009; 54: 919.
35. Cavallini G, Biagiotti G, Giudice C. Association between Peyronie disease and low serum testosterone levels: detection and therapeutic considerations. *J Androl* 2012; 33: 381.
36. Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. *Urology* 2004; 63: 641–6.
37. Cheetham TC, An JJ, Jacobsen SJ, et al. Association of testosterone replacement with cardiovascular outcomes among men with androgen deficiency. *JAMA Internal Medicine*. 2017;177:491.
38. Cherrier MM, Anderson K, Shofer J, Millard S, Matsumoto AM. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. *Am J Alzheimers Dis Other Demen*. 2015;30:421.
39. Chiang HS, Cho SL, Lin YC, Hwang TI. Testosterone gel monotherapy improves sexual function of hypogonadal men mainly through restoring erection: evaluation by IIEF score. *Urology* 2009; 73(4): 762-6.
40. Chiang HS, Hwang TI, Hsui YS, et al. Transdermal testosterone gel increases serum testosterone levels in hypogonadal men in Taiwan with improvements in sexual function. *Int J Impot Res* 2007; 19(4): 411–7.

41. Chillar JJ. Testosterone undecanoate improves lipid profile in patients with type 1 diabetes and hypogonadotropic hypogonadism. *Endocrine journal*. 2017;63:849.
42. Clague JE, Wu FC, Horan MA. Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. *Int J Androl* 1999; 22(4): 261-265.
43. Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. Association of sex hormones with sexual function, vitality, and physical function of symptomatic older men with low testosterone levels at baseline in the testosterone trials. *Journal of Clinical Endocrinology and Metabolism*. 2015;100:1146.
44. Cunningham GR, Stephens-Shields AJ, Rosen RC, et al. Testosterone treatment and sexual function in older men with low testosterone levels. *Journal of Clinical Endocrinology and Metabolism*. 2016;101:3096.
45. Dean JD, Carnegie C, Rodzvilla J, Smith T. Long-term effects of Testim 1% testosterone gel in hypogonadal men. *Rev Urol* 2005; 7(2): 87–94.
46. Debruynne FMJ, Behre HM, Roehrborn CG, et al. Testosterone treatment is not associated with increased risk of prostate cancer or worsening of lower urinary tract symptoms: prostate health outcomes in the Registry of Hypogonadism in Men. *BJU International*. 2017;119:216.
47. Dhindsa S, Ghanim H, Batra M, et al. Insulin Resistance and Inflammation in Hypogonadotropic Hypogonadism and Their Reduction After Testosterone Replacement in Men With Type 2 Diabetes. *Diabetes Care*. 2016;39:82.
48. Dias JP, Melvin D, Shardell M, et al. Effects of transdermal testosterone gel or an aromatase inhibitor on prostate volume in older men. *Journal of Clinical Endocrinology and Metabolism*. 2016;101:1865.
49. Dias JP, Melvin D, Simonsick EM, et al. Effects of aromatase inhibition vs. testosterone in older men with low testosterone: randomized-controlled trial. *Andrology*. 2016;4:33.
50. Dias JP, Shardell MD, Carlson OD, et al. Testosterone vs. aromatase inhibitor in older men with low testosterone: effects on cardiometabolic parameters. *Andrology*. 2017;5:31.
51. Dias JP, Veldhuis JD, Carlson O, et al. Effects of transdermal testosterone gel or an aromatase inhibitor on serum concentration and pulsatility of growth hormone in older men with age-related low testosterone. *Metabolism*. 2017;69:143-147, 2017 Apr.
52. Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab* 1999; 84(10): 3469–78.
53. Drinka PJ, Jochen AL, Cuisinier M, Bloom R, Rudman I, Rudman D. Polycythemia as a complication of testosterone replacement therapy in nursing home men with low testosterone levels. *J Am Geriatr Soc* 1995; 43(8): 899–901.
54. Eisenberg ML, Li S, Herder D, Lamb DJ, Lipshultz LI. Testosterone therapy and mortality risk. *Int J Impot Res* 2014; 27:46–8.
55. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. *JAMA* 2008; 299(1): 39–52.
56. Emmelot-Vonk MH, Verhaar HJ, Nakhai-Pour HR, Grobbee DE, van der Schouw YT. Effect of testosterone supplementation on sexual functioning in aging men: a 6-month randomized controlled trial. *Int J Impot Res* 2009; 21: 129-38.
57. Fennell C, Sartorius G, Ly LP, et al. Randomized cross-over clinical trial of injectable vs. implantable depot testosterone for maintenance of testosterone replacement therapy in androgen deficient men. *Clin Endocrinol* 2010; 73: 102.
58. Ferrando AA, Sheffield-Moore M, Paddon-Jones D, Wolfe RR, Urban RJ. Differential anabolic effects of testosterone and amino acid feeding in older men. *J Clin Endocrinol Metab* 2003; 88:358–62.
59. Ferrando AA, Sheffield-Moore M, Yeckel CW, et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. *Am J Physiol Endocrinol Metab* 2002; 282: E601–E607.
60. Fitts RH, Peters JR, Dillon EL, Durham WJ, Sheffield-Moore M, Urban RJ. Weekly versus monthly testosterone administration on fast and slow skeletal muscle fibers in older adult males. *Journal of Clinical Endocrinology and Metabolism*. 2015;100:E223.
61. Francomano D, Bruzziches R, Barbaro G, et al. Effects of testosterone undecanoate replacement and withdrawal on cardio-metabolic, hormonal and body composition outcomes in severely obese hypogonadal men: A pilot study. *J Endocrinol Invest* 2014; 37: 401–11.

62. Francomano D, Ilacqua A, Bruzziches R, et al. Effects of 5-year treatment with testosterone undecanoate on lower urinary tract symptoms in obese men with hypogonadism and metabolic syndrome. *Urology* 2014; 83: 167.
63. Francomano D, Lenzi A, Aversa A. Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. *Int J Endocrinol* 2014; 2014: 527470.
64. Fui MNT, Hoermann R, Prendergast LA, Zajac JD, Grossmann M. Symptomatic response to testosterone treatment in dieting obese men with low testosterone levels in a randomized, placebo-controlled clinical trial. *Int J Obes (Lond)*. 2017;41:420.
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eAppendix 4: Characteristics of the included RCTs and NRS

eTable 1: Characteristics of included RCTs that reported at least 1 outcome of interest

Author, year, page (companion publications)	Population*	Duration	Groups (no. randomized)	Age, yr, mean (SD);	Baseline Total T, mean (SD), nmol/L	Industry funding
Dias 2016, p. 1865 (Dias 2017 p.143; Dias 2016, p. 33; Dias 2017, p. 31)	Older men with low testosterone	12 mo	1% Gel, 50 mg/d (16) Placebo (13)	72 (SEM 1) 72 (SEM 1)	10.4 (1.9) 10.5 (2.1)	No
Chillaron 2016, p. 849	T1D	22 wk	IM TU 1000 mg/10 wk (6) Placebo (7)	47.9 (7.3) 45.2 (11.7)	12.4 (3.5) 9.9 (4.5)	Yes
Brock 2016, p. 699 (Maggi 2017, p. 1220)	≥ 1 symptom of testosterone deficiency	12 wk	2% solution, 60 mg/d (358) Placebo (357)	54.7 (10.6) 55.9 (11.4)	7.0 (2.3) 7.0 (2.3)	Yes
Dhindsa 2016, p. 82	T2DM	24 wk	IM TC, 250 mg/2wk (22) Placebo (22)	54.6 (7.9) (NR by group)	8.7 (2.8) (NR by group)	No
Konaka 2016, p. 25 (Shigehara 2017, p. 1; Shigehara 2015, p. 169)	Late onset hypogonadism	52 wk	IM TE, 250 mg/4 wk (169) No treatment (165)	65.7 (9) 67.6 (9.4)	Free T 7.1 (3.2) 6.7 (3.5) pg/ml	No
Magnussen 2016, p. 980	T2DM	24 wk	1% gel, 50 mg/d (22) Placebo (21)	61 (6) 59 (6)	7.1 (95%CI 6.6-11.9) 9.4 (95%CI 8.1-12.5)	Yes
Ng Tang Fui 2016, p. 153 (Ng Tang Fui 2017, p. 420)	BMI ≥ 30	56 wk	IM TU, 1000 mg/10 wk (49) Placebo (51)	54.3 (IQR 47.3-59.8) 52.8 (IQR47.6-60.1)	8.2 (2.5) 8.4 (2.3)	Yes
Sinclair 2016, p. 906	Cirrhosis	54 wk	IM TU, 1000 mg/12 wk (50) Placebo (51)	55.5 (IQR 52-60) 54.0 (IQR 50-59)	9.3 (IQR 3.9-17) 9.1 (IQR 2.7-12.7)	Yes
Snyder 2016 p. 611† (Cunningham 2016, p. 3096; Snyder 2017, p. 471; Roy 2017, p. 480; Resnick 2017, p. 717; Cunningham 2015, p. 1146; Abd Alamir 2016, p. 95; Swerdloff 2015, p. 3280; Budoff 2017,	Older men with decreased libido or sexual function (Sexual function trial); limited mobility (Physical function trial); low vitality (Vitality trial)	12 mo	1% gel, 50 mg/d (395) Placebo (395)	72.1 (5.7) 72.3 (5.8)	8.0 (2.2) 8.2 (2.3)	Mix

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p. 708)						
Basaria 2015, p. 570 (Storer 2017, p. 583)	Older men	3 yr	1% gel, 75 mg/d (156) Placebo (152)	66.9 (5.0) 68.3 (5.3)	10.7 (2.2) 10.7 (2.3)	Yes
Basaria 2015, p. 280 (Huang 2016, p. 232)	Opioid-induced hypogonadism	12 wk	1% gel, 50 mg/d (43) Placebo (41)	48 (9) 50 (6)	8.2 (3.4) 7.7 (3.0)	Yes
Cherrier 2015, p. 421	Mild cognitive impairment	6 mo	Gel, 50-100 mg/d (10) Placebo (12)	70.5 (8.2)	10.7 (3.2) 9.8 (2.7)	Mix
Paduch 2015, p.2956	Ejaculatory dysfunction	16 wk	2% solution, 60 mg/d (36) Placebo (40)	48.4 (9.8) 52.7 (9.3)	7.4 (1.9) 7.7 (1.8)	Yes
Borst 2014, p. E433	Hypogonadal	12 mo	Placebo (16) IM TE, 125 mg/wk (14)	70.8 (9.7) 69.2 (8.0)	8.5 (10.1) 9.2 (11.9)	Mix
Gianatti 2014, p. 2098 (Gianatti 2014, p. 3821; Gianatti 2016, p. 55)	Type 2 diabetes	40 wk	Placebo (43) IM TU, 1000 mg/12 wk (45)	62 (7.4) 62 (8.1)	8.5 (2.8) 8.7 (3.0)	Yes
Hackett 2013, p.1891 (Hackett 2013, p. 1612, Hackett 2014)	T2DM and symptoms of hypogonadism	30 wk	Placebo (102) IM TU, 1000 mg/12 wk (97)	62.0 (9.3) 61.2 (10.5)	8.9 (3.8) 9.2 (3.1)	Yes
Wang 2013, p. 1	Osteoporosis	24 mo	Placebo (62) Oral TU, 20 mg/d (62) Oral TU, 40 mg/d (62)	68.0 (4.8) 68.4 (5.5) 68.1 (5.4)	7.6 (0.7) 7.6 (0.9) 7.4 (0.8)	No
Behre 2012, p. 198	AMS score >36	6 mo	Placebo (179) 1% gel, 50 mg/d (183)	62.1 (6.3) 61.9 (6.6)	10.6 (2.6) 10.4 (2.6)	Yes
Spitzer 2012, p. 681 (Spitzer 2013)	Erectile dysfunction	14 wk	Placebo (70) 1% gel, 100 mg/d (70)	54.6 (8.5) 55.1 (8.3)	8.8 (2.4) 8.6 (2.2)	No
Stout 2012, p. 893	Chronic heart failure	12 wk	Placebo (20) Sustanon, 100 mg/2 wk (20)	65.9 (8.8) 68.3 (5.3)	11.2 (2.6) 10.4 (2.7)	No
Zhang 2012, p. 3806	Positive score on ADAM questionnaire	6 mo	Vitamin E/C (80) Oral TU, 120 or 160 mg/d (based on T level at baseline)(80)	61.1 (7.1) 59.4 (6.3)	7.7 (0.8) 8.0 (0.7)	No
Ho 2011, p. 260 (Tan 2013, Tong 2012)	At least mild AMS symptoms	42 wk	Placebo (60) IM TU, 1000 mg/12 wk (60)	53.0 (8.2) 53.4 (7.4)	8.9 (2) 9.1 (1.8)	Yes
Jones 2011, p. 828	MetS or T2DM	12 mo	Placebo (112)	59.9 (9.4)	9.5 (3.3)	Yes

(Stanworth 2014)	with at least 2 symptoms of hypogonadism		2% gel, 60 mg/d (108)	59.9 (9.1)	9.2 (2.6)	
Kaufman 2011, p. 2079	“otherwise healthy”	6 mo	Placebo (40) 1.62% gel, 40.5 mg/d (234)	55.5 (10.3) 53.6 (9.5)	10.2 (NR) 9.8 (NR)	Yes
Sheffield-Moore 2011, p. E1831 (Fitts 2015, p. E223)	Community-dwelling men	5 mo	Placebo (8) IM TE, 100 mg/wk (8)	65 (3) 73 (8)	11.8 (2.9) 11.9(2.9)	No
Shigehara 2011, p. 53	Benign prostate hypertrophy	12 mo	No treatment (26) IM TE, 250 mg/4 wk (26)	68.9 (9.1) 72 (6.5)	Free T 6.7 (1.9) pg/ml 7.0 (1.7) pg/ml	NR
Aversa 2010, p. 776	MetS or T2DM	6 mo	Placebo (10) Oral TU 160 mg/d (10) IM TU 1000 mg/12 wk (32)	55 (5) 57 (8) 58 (10)	11.1 (NR by group)	NR
Aversa 2010, p. 3495	MetS or T2DM	12 mo	Placebo (10) IM TU, 1000 mg/12wk (40)	57 (8) 58 (10)	9.0 (1.7) 8.33 (2.4)	NR
Basaria 2010, p. 109 (Bachman 2014, Huang 2013, Basaria 2013, Travison 2011; Storer 2016)	Limited mobility	6 mo	Placebo (103) 1% gel, 100 mg/d (106)	74 (5) 74 (6)	8.2 (2.3) 8.7 (2.0)	No
Kalinenko 2010, p. 602 (Giltay 2010)	MetS	30 wk	Placebo (71) IM TU, 1000 mg/12wk (113)	52.8 (9.67) 51.6 (9.76)	7.5 (5.2) 6.7 (3.0)	Yes
Kenny 2010, p. 1134	Low bone mass and frailty	12–24 mo	Placebo (62) 1% gel, 5 mg/d (69)	76.3 (8.0) 77.9 (7.3)	14.5 (6.7) 13.2 (6.2)	Mix
Srinivas-Shankar 2010, p. 639 (O’Connell 2010, Atkinson 2010)	Intermediate-frail and frail	6 mo	Placebo (136) 1% gel, 50 mg/d (138)	73.9 (6.4) 73.7 (5.7)	10.9 (3.1) 11 (3.2)	Yes
Caminiti 2009, p. 919 (Schwartz 2011)	Chronic heart failure	12 wk	Placebo (35) IM TU, 1000 mg/6 wk (35)	69 (66–74) 71 (67–76)	7.3 (7.3) 8.0 (6.2)	No
Chiang 2009, p. 467	Hypogonadal	3 mo	Placebo (20) 1% gel, 50 mg/d (20)	NR	NR	NR
Emmelot-Vonk, 2009, p. 129 (Emmelot-Vonk 2008, Nakhai-Pour 2007, Buisson 2010)	Moderately low T levels	26 wk	Placebo (117) Oral TU, 160 mg/d (120)	67.4 (4.9) 67.1 (5.0)	10.4 (1.9) 11.0 (1.9)	No

Heufelder 2009, p. 726	MetS and T2DM	52 wk	Placebo (16) 1% gel, 50 mg/d (16)	55.9 (6) 57.3 (5.6)	10.4 (0.8) 10.5 (0.8)	Yes
Hohl 2009, p. 989	High AMS score	12 or 14 wk	IM TU, 1000 mg/6 wk (10) IM TC, 200 mg/4wk (11) Durateston, IM, 250 mg/4wk (11)	59.6 (8.9) 59.6 (7.1) 60.4 (8.8)	9.9 (1.1) 10.1 (1.1) 9.9 (1.5)	No
Mathur 2009, p. 443	Chronic angina pectoris	12 mo	Placebo (7) IM TU, 1000 mg/12 wk (8)	67.8 (7.9) 62.1 (5.2)	10.1 (2.8) 9.8 (1.9)	Yes
Morales 2009, p. 104	Sexual dysfunction	4 mo	Placebo (29) Oral TU, 160 mg/d (29)	60.2 (9.6) 59.0 (10.6)	10.0 (5.5) 10.2 (4.9)	Yes
Shores 2009, p. 1009	Dysthymia or minor depression	12 wk	Placebo (16) 1% gel, 75 mg/d (17)	61.7 (7.0) 57.1 (5.7)	9.3 (3.4) 10.1 (3.7)	Mix
Agledahl 2008, p. 641	Subnormal total T	52 wk	Placebo (13) IM TU, 1000 mg/12 wk (14)	69.3 (5.0) 68.9 (5.4)	8.2 (2.4) 8.5 (1.7)	Mix
Basurto 2008, p. 140	Low total T	12 mo	Placebo (23) IM TE, 250 mg/3wk (25)	63.1 (7.7) 63.2 (8.5)	10.8 (1.3) 10.4 (1.1)	No
Raynaud 2008, p. 168	Hypogonadal	6 mo	Patch, 4.8 mg/d(188) IM TE, 250 mg/3 wk (36)	42.0 (12.7) 40.7 (10.5)	4.6 (3.2) 5.1 (3.3)	Yes
Svartberg 2008, p. 378	NR	12 mo	Placebo (19) IM TU, 1000 mg/12 wk (19)	69 (5) 69 (5)	8.2 (2.1) 8.4 (1.7)	Mix
Chiang 2007, p. 411	Hypogonadal	3 mo	Placebo (20) 1% gel, 50 mg/d (20)	56.1 (14.6) 47.9 (17.0)	9.1 (6.9) 7.4 (5.6)	Yes
Brockenbrough 2006, p. 251	Hemodialysis-dependent end-stage renal disease	6 mo	Placebo (21) 1% gel, 100 mg/d (19)	53.0 (17.2) 58.9 (14.9)	7.0 (3.0) 7.6 (2.2)	Yes
Marks 2006, p. 2351	Symptoms of LOH	6 mo	Placebo (22) IM TE, 150 mg/2wk (22)	68 (NR) 70 (NR)	8.7 (1.6) 7.7 (1.4)	Mix
Merza 2006, p. 381	Sexual dysfunction	6 mo	Placebo (19) Patch, 5 mg/d (20)	59.7 (10.2) 63.0 (9.0)	7.5 (2.5) 8.4 (3.3)	Yes
Kuhnert 2005, p. 317	Primary, secondary, LOH and symptoms of T deficiency	24 wk	Patch, 5 mg/d (52) 2.5%, gel, 125 mg/d (56) 2.5%, scrotal gel, 25 mg/d (54)	53 (IQR 16) 52.2 (IQR 22.5) 50 (IQR 21)	NR	Yes
Orengo 2005, p. 20	Treatment-	12 wk	Placebo (5)	63 (8.5) (NR by	8.9 (1.7)	No

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	resistant depression		1% gel, 50 mg/d (7)	group)	10.2 (2.3)	
Amory 2004, p. 503 (Page 2005, Vaughan 2007)	T below the range of normal for young adult men	36 mo	Placebo (24) IM TE 200 mg/2wk (24)	71 (4) 71 (4)	10.1 (2.1) 9.9 (1.6)	No
Cavallini 2004, p. 641	Symptoms of androgen decline	6 mo	Placebo (45) Oral TU, 160 mg/d (40)	63 (NR) 64 (NR)	10.5 (2.1) 9.9 (1.8)	No
Schubert 2004, p. 5429 (Jockenhovel 2009, Jockenhovel 2009, Minnemann 2008)	Primary or secondary hypogonadism	30 wk	IM TU, 1000 mg/9 wk (20) IM TE, 250 mg/3 wk (20)	41.1 (13.4) 36.3 (12.3)	3.9 (4.4) 2.7 (2.3)	Mix
Shabsigh 2004, p. 658 (Burnett 2013, Wang 2001, Swerdloff 2000)	Erectile dysfunction not responsive to sildenafil	12 wk	Placebo (36) 1% gel, 50 mg/d (39)	59.1 (9.4) 56.8 (10.2)	65% had T < 10.4 (NR by group)	Yes
Boyanov 2003, p. 1	T2DM, obesity, and "symptoms of andropause or erectile dysfunction"	3 mo	No treatment (24) Oral TU, 120 mg/d (24)	All: 57.5 (4.8) (NR by group)	10.76 (11.20) 9.56 (2.33)	NR
McNicholas 2003, p. 69	≥ 1 symptoms of "low T"	90 d	Patch, 5 mg/d (68) 1% gel, 50 mg/d (68) 1% gel, 100 mg/d (72)	57.9 (10.2) 59.0 (9.5) 56.7 (10.3)	7.90 (2.2) 7.95 (2.2) 7.92 (2.4)	Yes
Steidle 2003, p. 2673 (Seftel 2004)	≥ 1 symptoms of "low T"	90 d	Placebo (99) Patch, 5 mg/d (102) 1% gel, 50 mg/d (99) 1% gel, 100 mg/d (106)	56.8 (10.8) 60.5 (9.7) 58.1 (9.7) 56.8 (10.6)	7.9 (2.8) 8.3 (2.4) 8.1 (2.0) 8.1 (2.1)	Yes
Tan 2003, p. 13	Alzheimer's disease	12 mo	Placebo (5) IM TE, 200mg/2wk (5)	68.9 (NR) 72.4 (NR)	NR 3.6 (NR)	No
Ferrando 2002, p. 358 (Ferrando 2003)	"Healthy older men"	6 mo	Placebo (5) IM TE 50–400 mg/wk (7)	67 (6.7) 68 (7.9)	9.8 (4.3) 12.4 (4.4)	No
Kang 2002, p. 862	Coronary artery disease	12 wk	Placebo (17) Oral TU, 160 mg/d (18)	58 (9) 57 (7)	Free T, 13.8 (1.8) pg/ml 9.9 (3.1) pg/ml	NR
Simon 2001, p. 2149	Healthy adult	3 mo	Placebo (6)	55.4 (3.6)	9.4 (1.0)	NR

	men		Gel, 125 mg/d (6)	52.8 (4.2)	8.3 (0.3)	
Bhasin 2000, p. 763	HIV-infected with weight loss	16 wk	Placebo (14) IM TE, 100 mg/wk (17)	41.8 (9.4) 40.8 (4.9)	6.1 (2.9) 7.1 (3.0)	No
Wang 2000, p. 2839	Primary, secondary or LOH	90 d	Patch, 5 mg/d (76) 1% gel, 50 mg/d (76) 1% gel, 100 mg/d (78)	51.1 (NR) 51.3 (NR) 51.0 (NR)	8.2 (4.8) 8.2 (4.6) 8.6 (4.8)	Mix
Clague 1999, p. 261	Community-living	3 mo	Placebo (7) IM TE, 200 mg/2wk (7)	65.3 (1.8) 68.1 (6.6)	11.6 (0.9) 11.3 (1.7)	No
Dobs 1999, p. 3469	Receiving TRT for at least 3 mo	24 wk	Patch, 5 mg/d (33) IM TE, 200 mg/2wk (33)	44.3 (11.1) 44.9 (11.6)	5.8 (2.7) 6.3 (3.3)	Mix
Bhasin 1998, p. 3155 (Arver 1999)	HIV	12 wk	Placebo (21) Patch, 5 mg/d (20)	NR	7.3 (2.9) 9.0 (1.7)	Mix
Grinspoon 1998, p. 18 (Grinspoon 2000)	AIDS wasting syndrome	6 mo	Placebo (26) IM TE, 300 mg/3wk (26)	44 (9) 40 (7)	10.1 (6.4) 11.3 (5.4)	No
Jockenhovel 1997, p. 2510	Primary or secondary androgen deficiency	12 wk	IM TE, 250 mg/3 wk (10) Pellets, 1200 mg (12)	30.0 (7.3) 36.3 (11.1)	1.6 (1.3) 1.9 (1.1)	NR
Jockenhovel 1997, p. 293 (Jockenhovel 1999, Schubert 2001)	Primary or secondary androgen deficiency	210 d	Oral TU, 160 mg/d (13) IM TE, 250 mg/3wk (15) Pellets, 1200 mg (15)	34.5 (14.1) 31.8 (10.1) 35.8 (10.4)	2.9 (1.4) 2.3 (2.3) 2.7 (1.5)	NR
Sih 1997, p. 1661	Community-dwelling healthy men	12 mo	Placebo (15) IM TC, 200 mg/2wk (17)	68 (6) 65 (7)	8.1 (0.7) 10.2 (0.9)	NR

Note: ADAM = Androgen Deficiency of the Aging Male, AMS = Aging Males' Symptoms [scale], CI = confidence interval, IM = intramuscular, IQR = interquartile range, LOH = late onset hypogonadism, MetS = metabolic syndrome, NR = not reported, SD = standard deviation, T = testosterone, T1D = type 1 diabetes, T2DM = type 2 diabetes mellitus, TC = testosterone cypionate, TE = testosterone enanthate, TRT = testosterone replacement therapy, TU = testosterone undecanoate.

*All RCTs involved men that were either described as hypogonadal and met the cut-off for hypogonadism (total T < 12 nmol/L or free T < 225 pmol/L) or reported total or free T below these cut-off points.

†The Testosterone Trials were a coordinated set of seven trials. In order to enroll, participants had to qualify for at least one of the Sexual Function Trial, Physical Function Trial, or the Vitality Trial (NCT00799617).

‡Blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

eTable 2: Characteristics of included non-randomized studies that reported at least one outcome of interest

Study	Population*	Duration	Group (no. in group)	Age, yr, mean (SD)	Baseline total T, mean (SD), nmol/L†	Industry funding
Retrospective cohort						
Cheetham 2017, p. 491	≥ 40 yr with documented androgen deficiency	Follow-up: 4.4 years (mean)	TRT (injection, oral, topical), dose NR (8,808) Never TRT (35,527)	58.4 (NR) 59.8 (NR)	TRT group: 7.4 (IQR 5.5-8.8)**	No
Layton 2015, p. 1187	New users of TRT‡		Gel (114,918) Injection (111,354) Patch (9,906)	Range: 52.4 (15.1) to 72.7 (6.7)§	NR††	No
Pastuszak 2015, p. 165	New TRT users or had been off TRT for ≥ 3 or mo	26.2 (10.6) 29.8 (8.8) 28.2 (8.6) mo	Gel (1% 50–100 mg/d and 1.62% 20.25–80.1 mg/d) (47) IM TE or TC, 100–200mg/wk (57) Pellets, 75 mg/3–6 mo (74)	54.1 (9.8) 42.5 (12.3) 53.8 (13.0)	10.4 (3.1) 10.6 (5.7) 9.3 (5.8)	No
Ramasamy 2016	≥ 65 yr and ≥3 hypogonadal symptoms	3.4-3.8 yr	TRT, dose NR (153) No treatment (64)	74 (6.3) 75(6)	NR	NR
Aydogdu 2013, p. 243	IHH	24 wk	Sustanon, ¶ IM 250 mg/3wk (28) 1% gel, 50 mg/d (24)	20.9 (1.4) 21.3 (1.6)	0.9 (0.6) 1.4 (1.3)	No
Vigen 2013, p. 1829	Men who underwent coronary angiography at a VA medical centre	Follow-up: 840 d (mean)	TRT, dose NR (1223) No treatment (7486)	60.6 (7.6) 63.8 (9.0 yr)	6.1 (2.2) 7.2 (2.6)	NR
Shores 2012, p. 2050	> 40 yr treated at a VA medical center	20.2 (16.7) mo	TRT, dose NR (398) No treatment (633)	62.1 (10.6)	5.6 (2.2) 6.7 (1.9)	No
Rhoden 2006, p. 201	Hypogonadal men with negative prostate biopsy prior to initiation of TRT	12 mo	IM TRT, dose NR (33) 1% gel, dose NR (25)	58.3	10.3 (5.4) 10.2 (3.1)	No
Guay 2000, p. 132	Men with ED and primary or secondary hypogonadism	2-3 mo	IM TE, 200–300 mg/2-3 wk (25) Patch, 5 mg/d (16)	40–80	Free T: 8.1–9.7 pg/ml	NR
Hajjar 1997, p. 3793	Elderly men	24 mo	IM TE or TC, IM 200 mg/2 wk (45) No treatment (27)	71.8 (SE 1.7) 69.9 (SE 1.9)	10.8 (4.7) 9.6 (3.8)	NR
Prospective cohort						
Debruyne	≥18 years with a	36 mo	TRT, dose NR (750)	58.9 (10.3)	8.3 (3.9)	Yes

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2017, p. 216	diagnosis of hypogonadism		No TRT (249)	59.7 (11.1)	9.4 (3.7)	
Traish 2016, p. 1	Symptoms of hypogonadism	Up to 8 yr	IM TU, 1000 mg/12wk (360) No TRT (296)	57.4 (7.3) 64.8 (4.3)	9.8 (1.3) 9.6 (1.2)	Yes
Yassin 2017, p. 1	Treated or untreated hypogonadal men	6 yr	TRT, dose NR (42) No treatment (162)	61.3 (4.7)	≤ 12.1 7.1 (2.3)	NR
Jung 2016, p. 194	Symptoms of hypogonadism	8 mo	TU, 1000 mg/3 mo + lifestyle modification (54) Lifestyle modification (52)	56.7 (12.6) 57.8 (11.4)	8.7 (2.1) 9 (2.4)	No
Francomano 2014, p. 401	Severely obese men (mean BMI 42) with ≥ symptoms of hypogonadism	54 wk	DPE (12) DPE + IM TU, 1000 mg/12 wk (12)	53 (8) 56 (9)	8.2 (1.8) 8.5 (1.8)	NR
Blick 2013, p. 30	HIV/AIDS	12 mo	1% gel (Androgel), 50 mg/d (92) 1% gel (Testim), 50 mg/d (75)	49.5 (8.1)	13.9 (5.5)†† 13.7 (7.2)	Yes
Aversa 2012, p. 96	Middle-aged men with LOH and MetS	36 mo	IM TU, 1000 mg/12 wk (40) No treatment (20)	58 (10) 57 (8)	8.3 (2.4)	NR
Dean 2005, p. 87	21–81 yr	Up to 12 mo	1% gel, 50 mg/d (NR) 1% gel, 100 mg/d (NR)	58.5 (10.0)	8.1 (2.1)	NR
Wang 2004, p. 2085 (Swerdloff 2003 p.207)	19–68 yr	36 mo	1% gel, 50 mg/d (NR) 1% gel, 75 mg/d (NR) 1% gel, 100 mg/d (NR)	51.5 (0.9)	14.1 (1.3) ¶¶ 22.4 (2.7) 25.6 (2.4)	No

Note: DPE = diet plus exercise, ED = erectile dysfunction, IHH = idiopathic hypogonadotropic hypogonadism, IM = intramuscular, IQR = interquartile range, LOH = late-onset hypogonadism, MetS = metabolic syndrome, NR = not reported, SE = standard error, SD = standard deviation, T = testosterone, TC = testosterone cypionate, TE = testosterone enanthate, TRT = testosterone replacement therapy, VA = Veterans Affairs.

*All studies involved men that were either described as hypogonadal and met the cut-off for hypogonadism (total T < 12 nmol/L or free T < 225 pmol/L) or reported total or free T below these cut-off points.

†Unless otherwise stated.

‡Full cohort includes patients with testosterone levels in the normal range; data extracted only for patients with total testosterone < 300 ng/dl (10.4 nmol/L).

¶Blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

§Data provided separately for 3 databases. Range represents the high and low ages (SD) across the three databases.

**Baseline testosterone level not reported for the never-TRT group. In both the TRT group and the no TRT group, 98%–99% of patients were reported to have total T < 10.4 nmol/L at baseline.

††Mean total testosterone level not provide among patients with a “low” testosterone level (< 10.4 nmol/L).

‡‡Study eligibility was total T < 300 ng/dl or free T < 50 pg/ml.

¶¶Long term extension of an included RCT (Wang 2000). Total testosterone levels reported here are after 6 months of TRT treatment in the RCT.

eTable 3: Risk of bias of included randomized controlled trials that reported at least one outcome of interest

Author, year	Adequate sequence generation	Allocation concealment	Blinding of outcome assessment (objective outcomes)	Blinding of outcome assessment (subjective outcomes)	Incomplete outcome data addressed (efficacy outcomes)	Incomplete outcome data addressed (harm outcomes)
Dias 2016	Low	Unclear	Low	Low	High	Unclear
Chillarón 2016	Unclear	Low	Low	Unclear	Low	Low
Brock 2016	Low	Low	Low	Low	Low	Low
Dhindsa 2016	Unclear	Unclear	Low	Unclear	High	Unclear
Konaka 2016	Low	Unclear	Low	High	High	Unclear
Magnussen 2016	Low	Low	Low	Low	Low	Low
Ng Tang Fui 2016	Low	Low	Low	Low	High	Unclear
Sinclair 2016	Unclear	Low	Low	Low	High	High
Snyder 2016	Low	Low	Low	Low	Low	Low
Basaria 2015, p. 570	Unclear	Unclear	Low	Low	High	Unclear
Basaria 2015, p. 280	Low	Unclear	Low	Low	High	Unclear
Cherrier 2015	Unclear	Unclear	Low	Unclear	Low	Low
Paduch 2015	Low	Low	Low	Unclear	Low	Low
Gianatti 2014	Unclear	Low	Low	Low	Low	Low
Borst 2014	Low	Unclear	Low	High	High	High
Hackett 2013	Unclear	Low	Low	Low	Low	Low
Wang 2013	Unclear	Unclear	Low	NA	Low	High
Behre 2012	Low	Low	Low	Low	Low	High
Spitzer 2012	Unclear	Low	Low	Low	Low	Low
Stout 2012	Unclear	Unclear	NA	Low	High	High
Zhang 2012	Unclear	Low	Low	High	Low	Low
Ho 2011	Unclear	Low	Low	Low	Low	Low
Jones 2011	Unclear	Unclear	Low	Low	High	High
Kaufman 2011	Unclear	Low	Low	Low	High	Low
Sheffield-Moore 2011	Unclear	Low	Low	NA	Low	High
Shigehara 2011	Unclear	Unclear	Low	High	Low	Low
Aversa 2010, p. 776	Unclear	Unclear	Low	Low	Unclear	Unclear
Aversa 2010, p. 3495	Unclear	Unclear	Low	Low	Low	Low
Basaria 2010	Low	Low	Low	Low	Low	Unclear
Kalinchenko 2010	Unclear	Low	Low	Low	Low	Low
Kenny 2010	Unclear	Low	Low	Low	High	Unclear
Srinivas-Shankar 2010	Low	Low	Low	Low	Low	Unclear
Caminiti 2009	Unclear	Low	Low	Low	Low	Low
Chiang 2009	Unclear	Unclear	Low	Low	High	High

Emmelot-Vonk 2009	Low	Low	Low	Low	Low	Low
Heufelder 2009	Low	Unclear	Low	High	Low	Low
Hohl 2009	High	High	Low	High	Low	Low
Mathur 2009	Low	Unclear	Low	Low	Low	High
Morales 2009	Low	Low	Low	Low	Low	Low
Shores 2009	Low	Low	Low	Low	High	Unclear
Agledahl 2008	Unclear	Unclear	Low	NA	Low	Low
Basurto 2008	Low	Low	Low	Low	Low	Unclear
Raynaud 2008	Unclear	Unclear	Low	High	High	High
Svartberg 2008	Unclear	Unclear	Low	Low	Low	Unclear
Chiang 2007	Unclear	Unclear	Low	Unclear	High	Low
Brockenbrough 2006	Unclear	Low	Low	Unclear	High	Low
Marks 2006	Unclear	Unclear	Low	Low	Low	Low
Merza 2005	Unclear	Unclear	Low	Unclear	Low	Low
Kuhnert 2005	Unclear	Low	Low	High	High	High
Orengo 2005	Low	Unclear	Low	Unclear	High	High
Amory 2004	Low	Low	Low	Low	Unclear	Unclear
Cavallini 2004	Unclear	Unclear	Low	Unclear	Unclear	High
Schubert 2004	Low	Unclear	Low	High	Unclear	Low
Shabsigh 2004	Low	Unclear	Low	Low	Low	Unclear
Boyanov 2003	Unclear	Unclear	Low	High	Low	Low
McNicholas 2003	Unclear	Unclear	Low	High	High	High
Steidle 2003	Unclear	Unclear	Low	High	High	High
Tan 2003	Unclear	Unclear	Unclear	High	Low	Low
Ferrando 2002	Unclear	Unclear	Low	NA	Low	Low
Kang 2002	Unclear	Unclear	Low	NA	Low	Low
Simon 2001	Unclear	Unclear	Low	Low	NA	Low
Bhasin 2000	Low	Unclear	Low	Unclear	Low	Unclear
Wang 2000	Unclear	Unclear	Low	High	High	High
Clague 1999	Unclear	Unclear	Low	NA	Low	Low
Dobs 1999	Unclear	Low	Low	High	High	Unclear
Bhasin 1998	Unclear	Unclear	Low	Unclear	High	Unclear
Grinspoon 1998	Low	Low	Low	Low	High	Unclear
Jockenhovel 1997, p. 2510	Unclear	Unclear	Low	NA	Unclear	Unclear
Jockenhovel 1997, p. 293	Unclear	Unclear	Low	NA	Low	Unclear
Sih 1997	Low	Unclear	Low	Unclear	High	Unclear
Note: Risk of bias was not assessed for the studies that reported no outcomes of interest or that did not provide usable data (e.g., cross-over studies without first period data reported separately).						

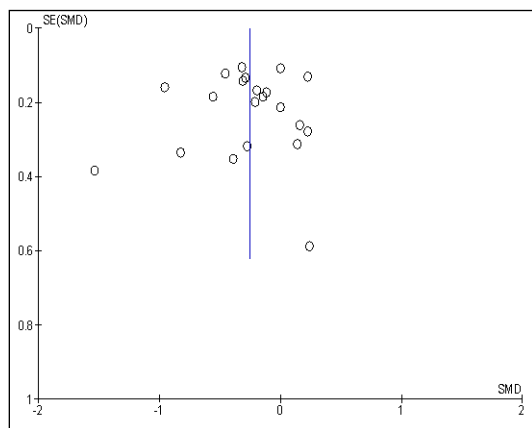
eTable 4: SIGN50 assessment of included non-randomized studies that reported at least one outcome of interest. Overall assessment was based on consideration of all domains of the SIGN50 Methodology checklist for cohort studies.

Study*	Overall assessment†	Comments
Traish 2017	Unacceptable (–)	Prospective cohort. Study “not designed or powered to address the effects of [TRT] on mortality in men with hypogonadism.” Control group comprised men who opted against TRT. Did not adjust for previous CV events, and groups were not balanced at baseline for some factors. Unclear from where participants were recruited and whether outcome assessment was blinded to exposure status. Outcomes assessed for up to 8 years.
Jung 2016	Unacceptable (–)	Prospective cohort. Did not report how study participants were assigned to treatment groups. Unblinded, with 8 month treatment and follow-up
Debruyne 2017	Acceptable (+)	Prospective cohort. Multinational registry of treated or untreated newly diagnosed hypogonadal men. Follow-up on 93% of cohort over 3-yr period. Included a wide age range and multiple comorbidities but groups were not well balanced across all baseline characteristics. Men with a history of prostate cancer were excluded. Outcome assessment blinded to exposure status.
Layton 2015	Acceptable (+)	Retrospective cohort. Comparative safety of TRT products grouped by route of administration (no comparison to non-users). Data unavailable for some patient characteristics. Study included a “large diverse patient sample representing men across age groups, populations, treatment and practice patterns, and health care systems.” Unclear whether outcome assessment was blinded to exposure status. Mean treatment duration between 96 and 122 days.
Cheetham 2017	Acceptable (+)	Retrospective cohort. Cohort entry determined by dispensation of a TRT product. Over 50% of cohort prescribed an intramuscular TRT. Possible confounding by indication, analysis could not adjust for all CV risk factors, and dose and duration of TRT were not considered. Unclear whether outcome assessment was blinded to exposure status. Length of follow up about 1 year longer for no TRT group.
Yassin 2017	Unacceptable (–)	Prospective registry. Investigation and biopsy frequency equal in both groups. Outcome assessment not blinded to exposure status. Percentage of cohort for whom data were available not reported. Confounding not considered.
Pastuszak 2015	Unacceptable (–)	Retrospective cohort. Considerable variation in baseline characteristics between groups, and confounding not considered. Outcome assessment not blinded to exposure status. 36 month follow-up.
Ramasay 2015	Unacceptable (–)	Retrospective cohort. “All major adverse cardiovascular events were verified by telephone with the patient (or family members if patient died).” Authors did not provide clear description and measurement about the outcomes. Median follow-up 3.8 (TRT) or 3.4 (no TRT) yr. Confounding not considered, and outcome assessment not blinded to exposure status.
Francomano 2014	Unacceptable (–)	Prospective cohort. Obese men with low testosterone. Baseline characteristics were well matched on reported characteristics, but control group had contraindications to TRT. 33% dropout in treatment group, zero in control group; no comparison between those who dropped out or remained in study.
Aydogdu	Acceptable (+)	Retrospective cohort. Men with IHH. SAE not defined as an outcome but

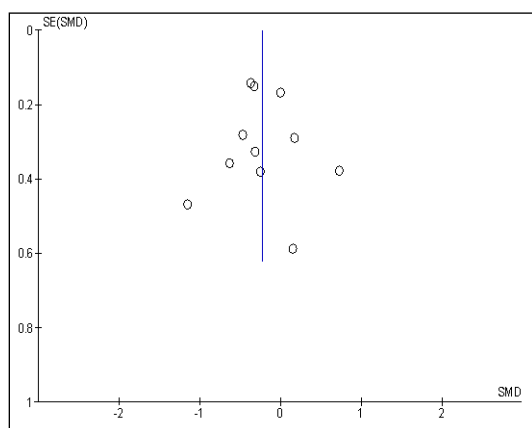
2013		reported that no SAEs were detected for any treatment group.
Blick 2013	Acceptable (+)	Prospective cohort. Groups were generally well matched on baseline characteristics with no statistically significant differences (except for study site). Patients in the 2 treatment groups were not followed for an equal length of time (AndroGel: mean 6.1 yr; Testim: mean 1.9 yr). Skin reactions assessed but not reported. Outcome assessment was not blinded to exposure status.
Vigen 2013	Acceptable (+)	Retrospective cohort. All-cause mortality was assessed via the Veterans Affairs vital status file. Myocardial infarction and ischemic stroke was assessed via ICD-9 codes from Veterans Affairs inpatient treatment files. Conclusions based on a composite outcome. Sufficient data not reported to allow analysis of stroke or MI separately at each time point. Outcome assessment was not blinded to exposure status.
Aversa 2012	Unacceptable (-)	Prospective cohort. Men with multiple sclerosis and late onset hypogonadism. Baseline characteristics were well matched; however, control group was comprised of men who had refused or had contraindications to testosterone. Adherence to treatment over 3 years was 50% in TU group.
Shores 2012	Acceptable (+)	Retrospective cohort. Hazard ratio for mortality took person-years of observation into account. Adjusted HR and CIs provided. Outcome assessment not blinded to exposure status. Exposure determined via Veterans Affairs pharmacy records and outcomes ascertained from 2 mortality databases.
Rhoden 2006	Acceptable (+)	Retrospective cohort. Patients had to have negative prostate biopsy before initiation of TRT, thus excluding any men with pre-existing large volume disease. Type and dose of IM testosterone not reported. Dose of gel not reported (data NR by type). Outcome assessment not blinded to exposure status.
Dean 2005	Unacceptable (-)	Prospective cohort. Poor reporting of the number of patients in each group and which group the safety events occurred in. Number of and reasons for withdrawals not reported. Safety data reported overall but not by treatment group. Outcome assessment not blinded to exposure status.
Wang 2004	Unacceptable (-)	Prospective cohort (open-label extension of an RCT). The number of men assigned to each group NR. Safety data poorly reported: 3 cases of prostate cancer reported but number of people in each group not reported. Outcome assessment not blinded to exposure status.
Guay 2000	Unacceptable (-)	Retrospective cohort. Safety data not reported by treatment group. Outcome assessment not blinded to exposure status.
Hajjar 1997	Unacceptable (-)	Retrospective cohort. Data not clearly provided. Safety outcomes were reported based on a subset of people assigned to each group, and it is not clear why the other patients were omitted. Outcome assessment not blinded to exposure status.
<p>Note: CI = confidence interval, ICD-9 = International Classification of Diseases, Ninth Revision, IHH = idiopathic hypogonadotropic hypogonadism, HR = hazard ratio, MI = myocardial infarction, NR = not reported, RCT = randomized controlled trial, SAE = serious adverse events, TRT = testosterone replacement therapy, TU = testosterone undecanoate.</p> <p>*Non-randomized studies that reported at least 1 outcome of interest.</p> <p>†Assessed by use of SIGN50 for cohort studies (www.sign.ac.uk/checklists-and-notes.html).</p>		

eAppendix 5: Funnel plots for assessment of publication bias

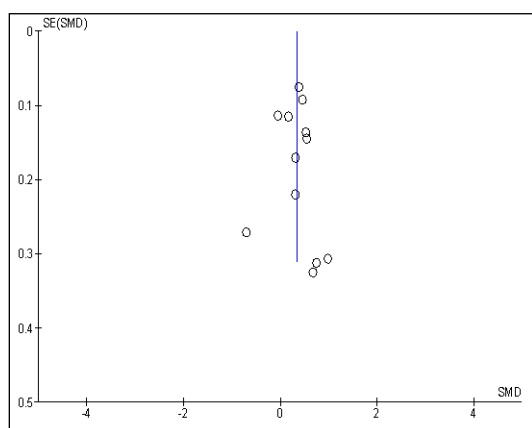
A) Quality of life



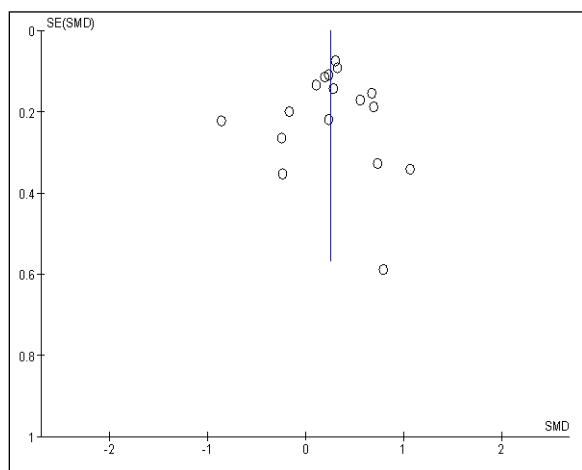
B) Depression



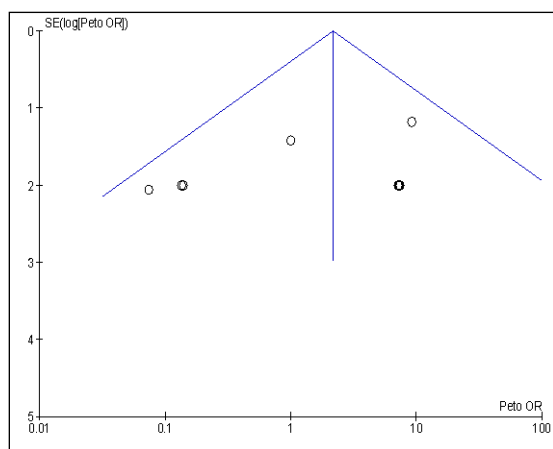
C) Libido



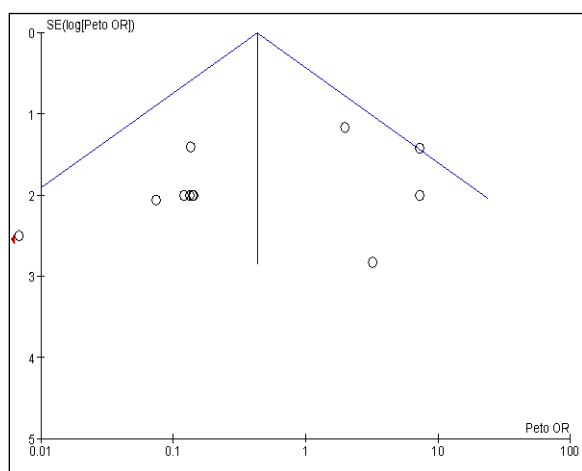
D) Erectile function



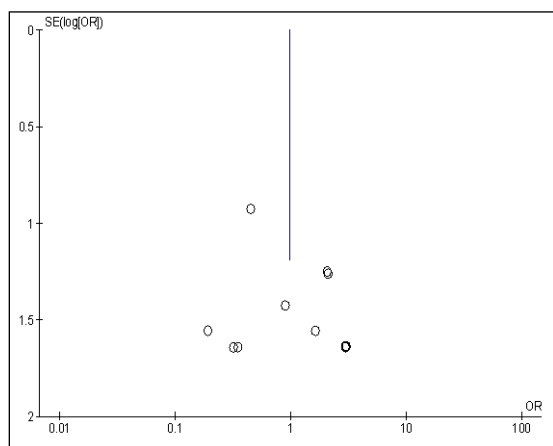
E) Cardiovascular death



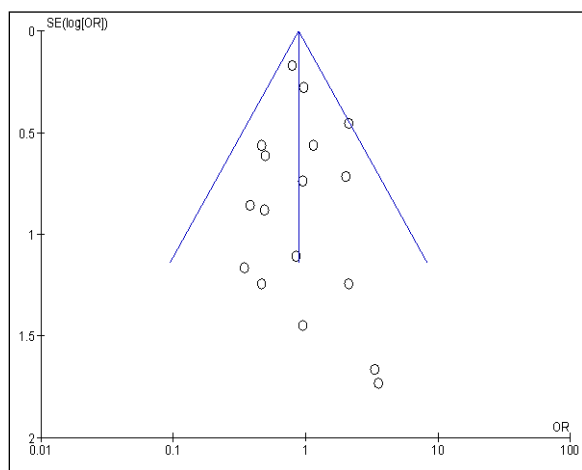
F) Myocardial infarction



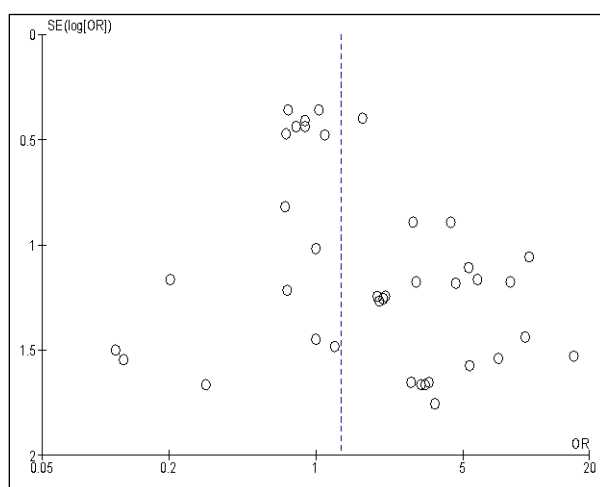
G) Prostate cancer



H) Serious adverse events



I) Withdrawals due to adverse events



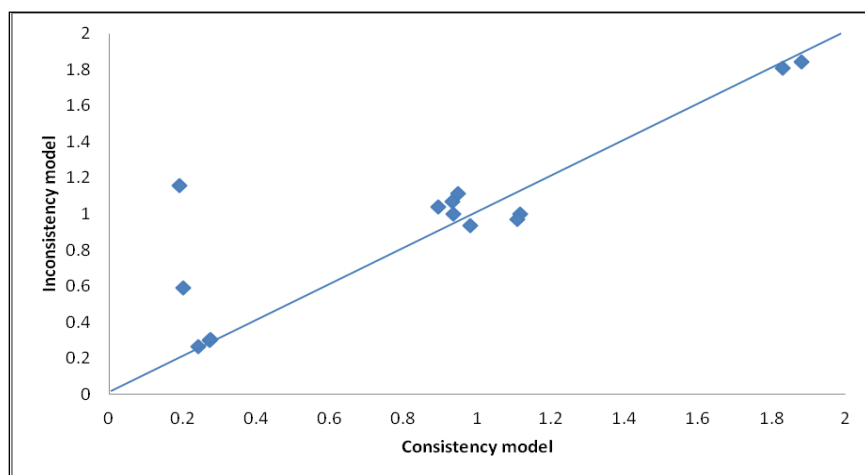
eAppendix 6: Evaluation of network consistency

We evaluated the consistency of networks with closed loops. To be classified as a “closed loop,” at least 2 nodes had to be connected by more than one trial (e.g., not connected solely by a multi-arm trial).

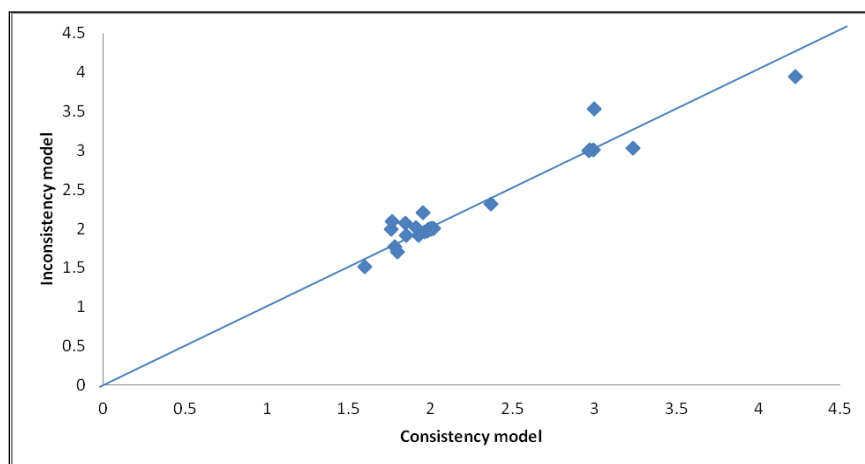
To evaluate the consistency of networks with closed loops, two analyses were performed. One was conducted using the standard consistency model, which assumes that the data in the network are consistent. A second analysis was performed using an inconsistency model, which assumes that the data in the network are not consistent. The posterior mean deviance of the individual data points derived from the inconsistency model was plotted against the posterior mean deviance derived from the consistency model. If inconsistency is present, data points will lie under the diagonal line, indicating deviation from the consistency model. Data points above the diagonal line indicate deviation from the inconsistency model and are not indicative of inconsistency.

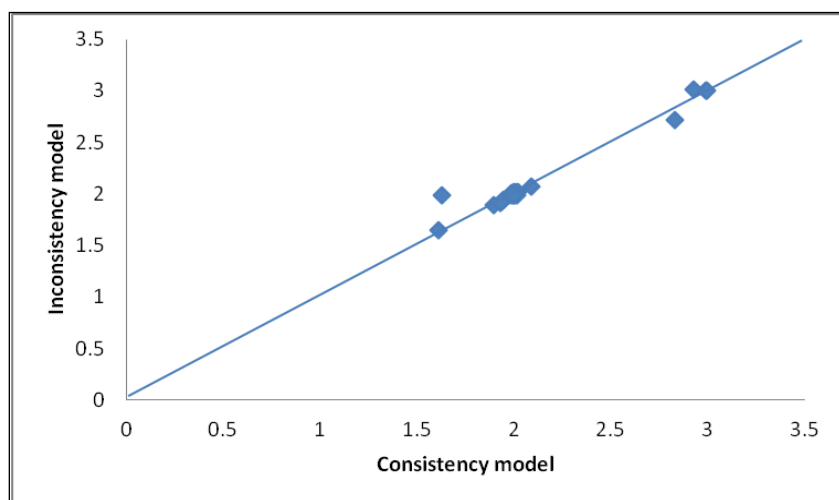
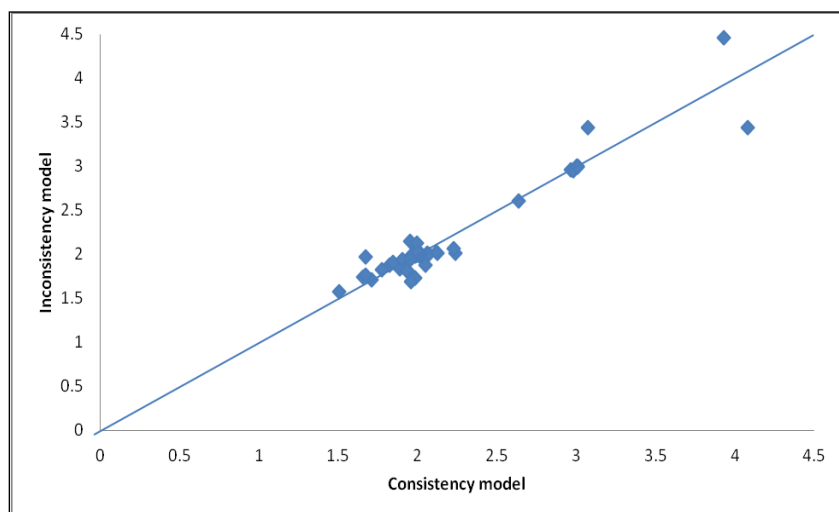
Model fit was also evaluated by considering the residual deviance and deviance information criterion (DIC) of the inconsistency and consistency models, with the model that has the lower residual deviance and DIC representing the better fit for the data. For each network, the consistency model had a lower residual deviance and DIC for each outcome, representing better model fit.

LIBIDO: BASE CASE (ALL STUDIES)



TOTAL TESTOSTERONE LEVEL, 3 MO



TOTAL TESTOSTERONE LEVEL, 6 MO**TOTAL TESTOSTERONE LEVEL, END OF STUDY**

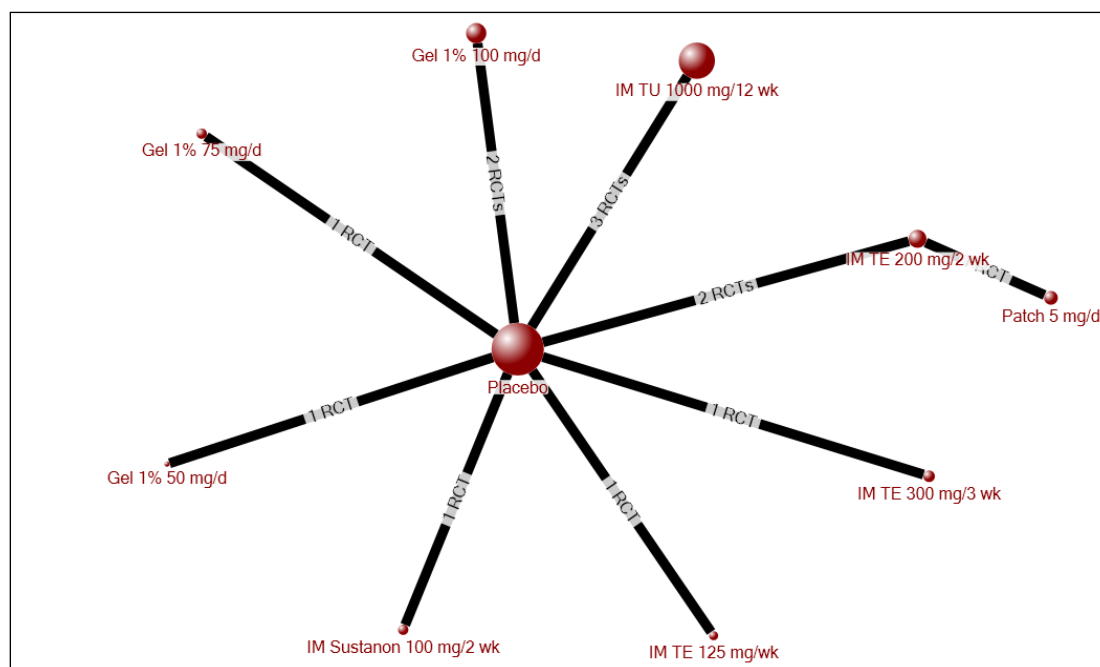
eAppendix 7: Evidence networks

Summary of network characteristics

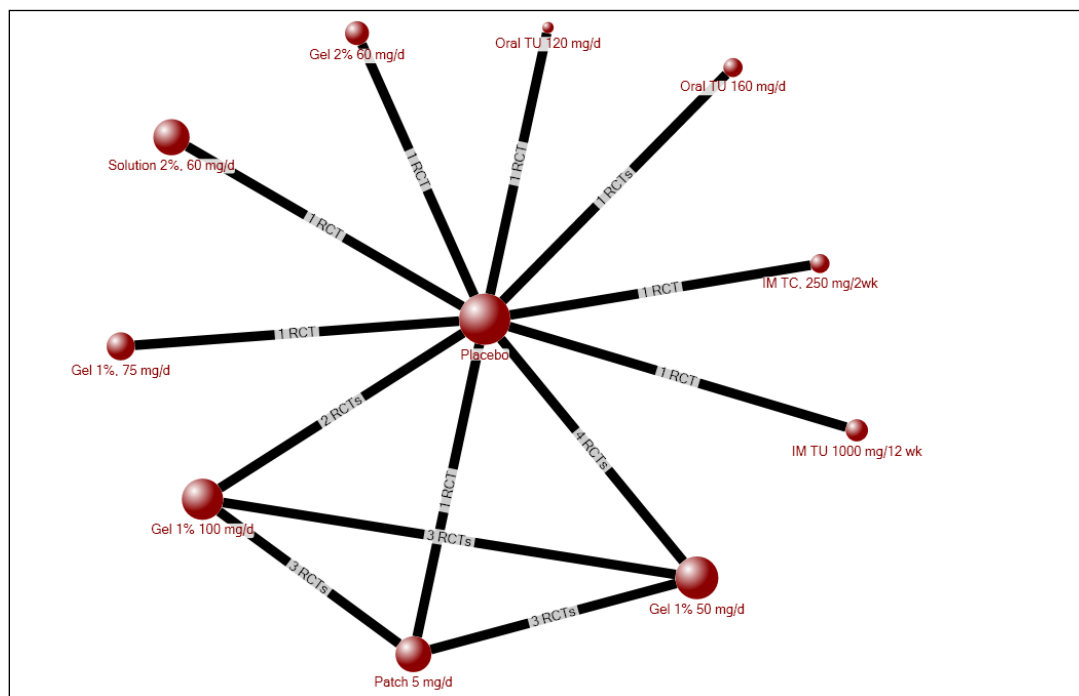
Outcome	No. of trials	No. of treatments*	No. of comparisons†	No. of participants	Treatment duration
Quality of life	23	14	27	3090	12 wk to 3 yr
Depression	12	9	12	852	12 wk to 3 yr
Libido	14	10	23	3167	12 wk to 3 yr
Erectile function	17	9	19	3165	12 wk to 3 yr
Total testosterone, 3 mo	26	15	39	2739	NA
Total testosterone, 6 mo	23	18	29	2908	NA
Total testosterone, end of study	57	28	74	5538	12 wk to 3 yr
Serious AEs	15	7	15	1860	12 to 3 yr
Withdrawals due to AEs	27	16	29	4165	12 wk to 3 yr

Note: AE = adverse event.
 *In addition to placebo
 †Direct comparisons based on the number of 2-, 3-, and 4-arm trials.

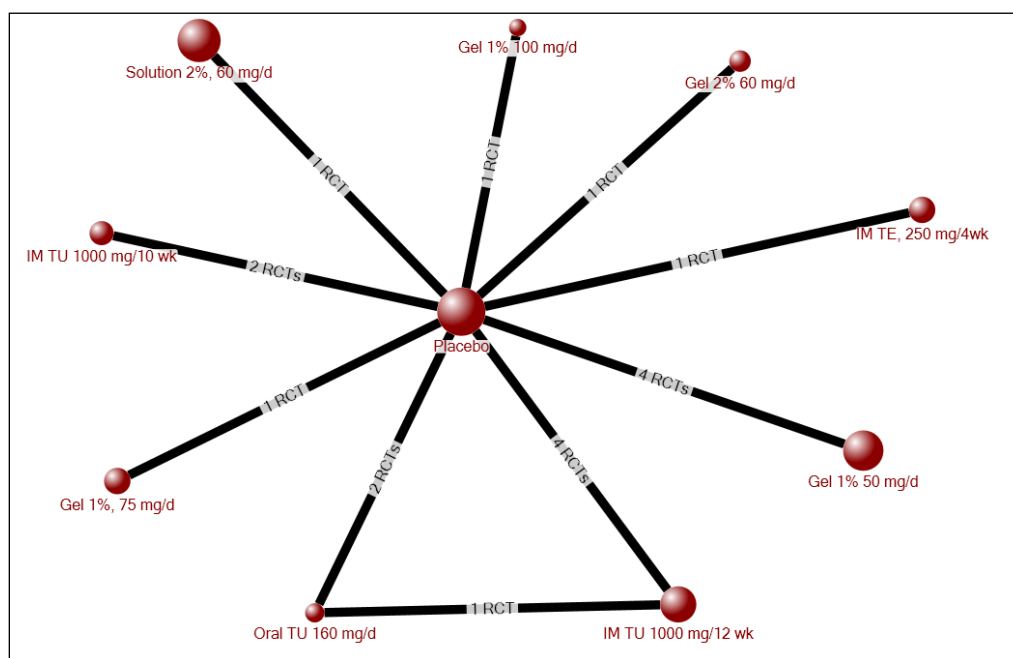
eFigure 1A) Depression



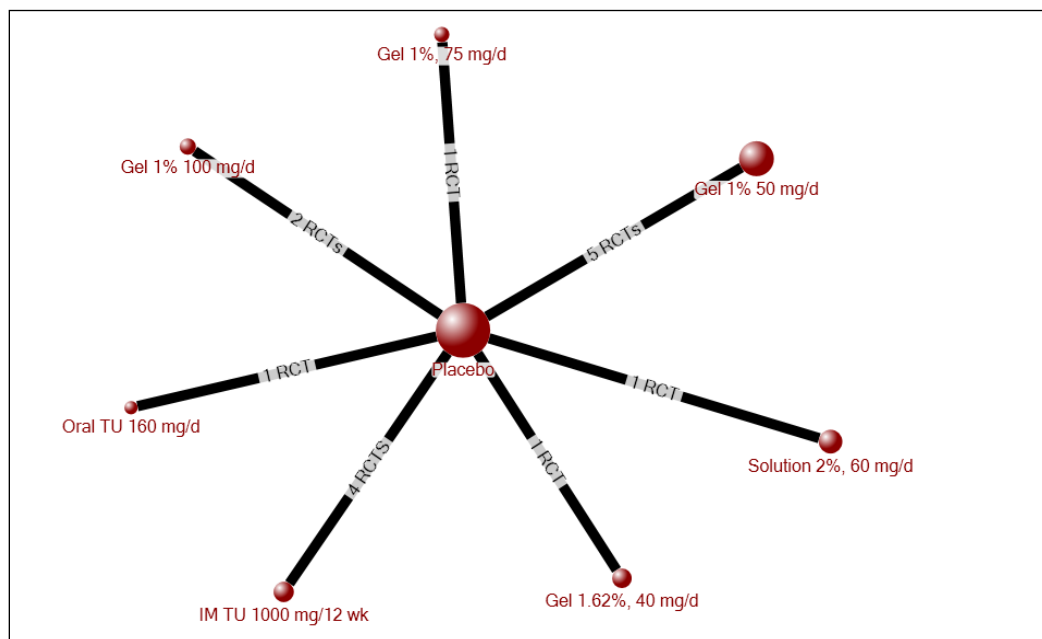
B) Libido



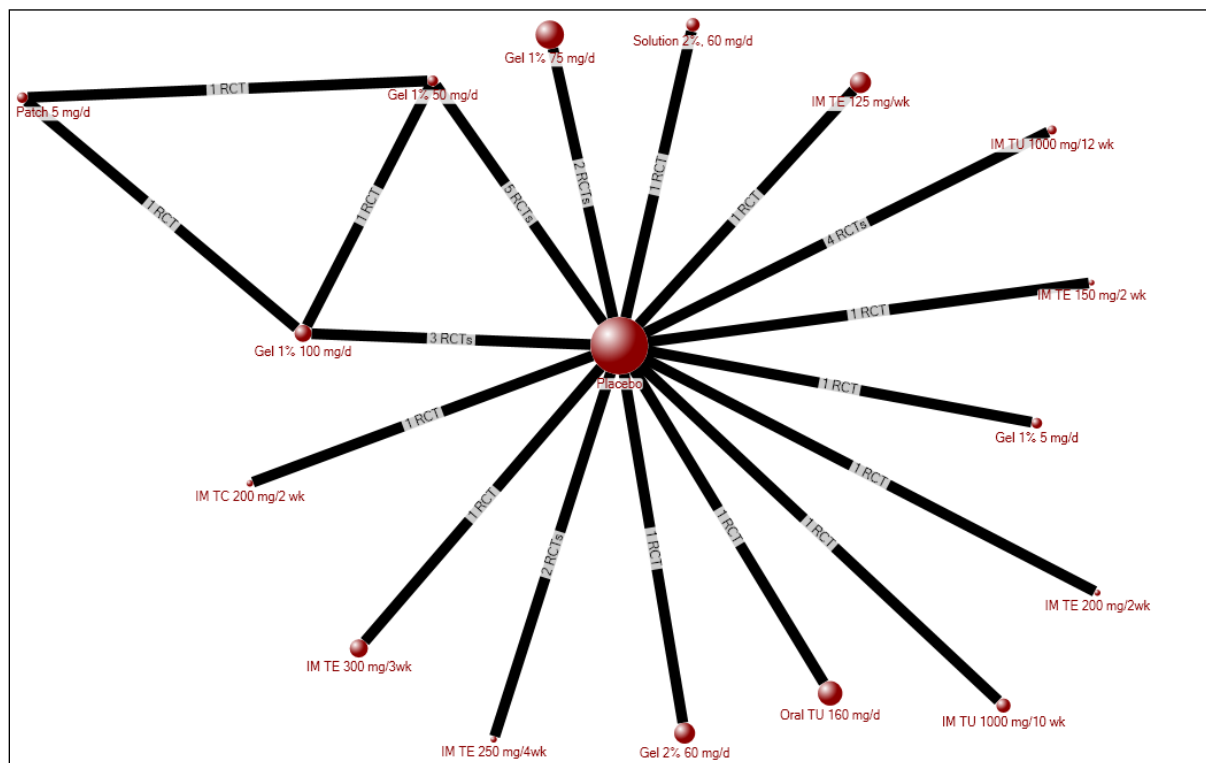
C) Erectile function



D) Serious adverse events

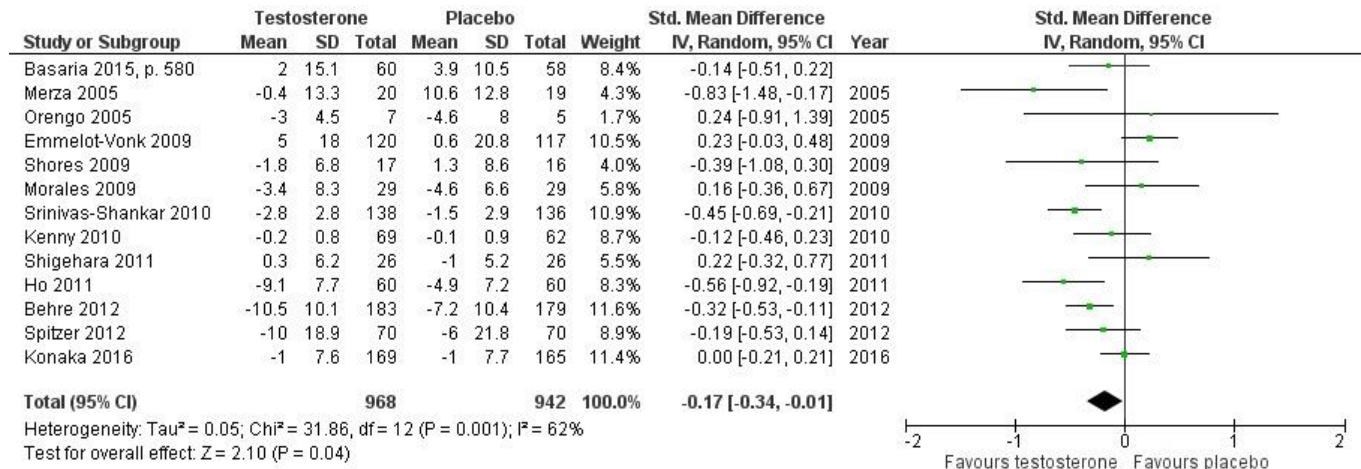


E) Withdrawals due to adverse events



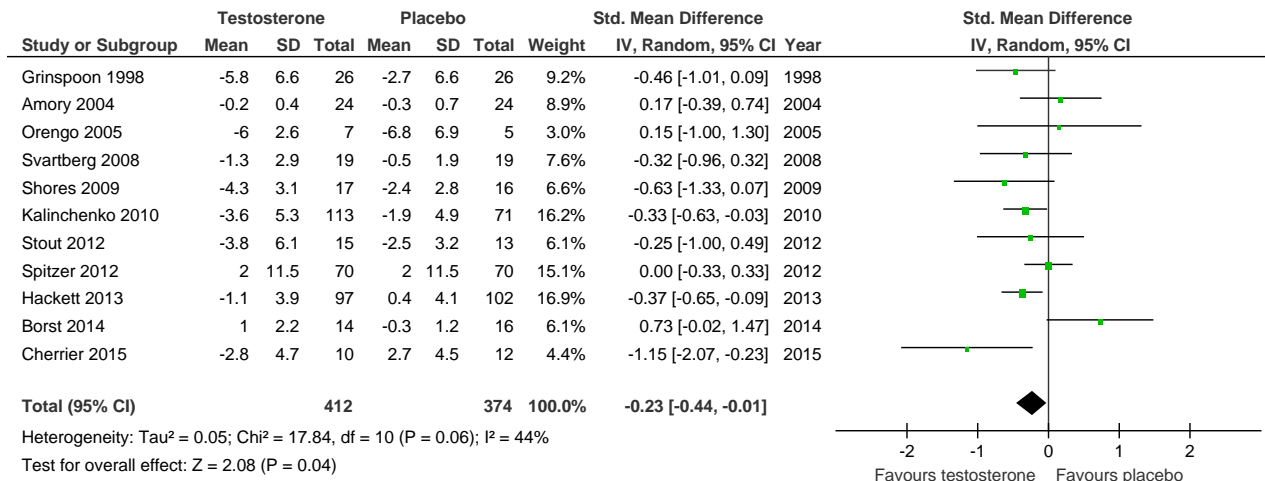
eAppendix 8: Pair-wise meta-analyses and network meta-analyses

eFigure 2: Individual trial results, quality of life, among men without major comorbidities

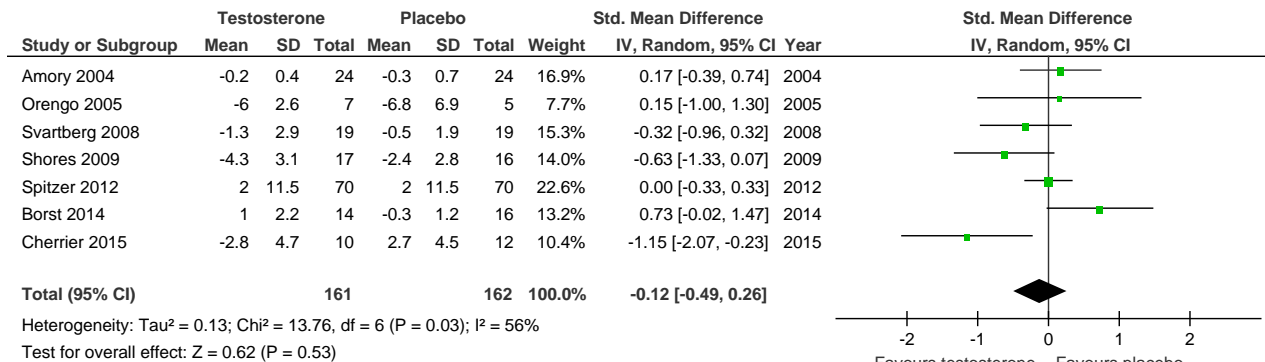


eFigure 3: Individual trial results, depression

A) All trials



B) Trials involving men without major comorbidities



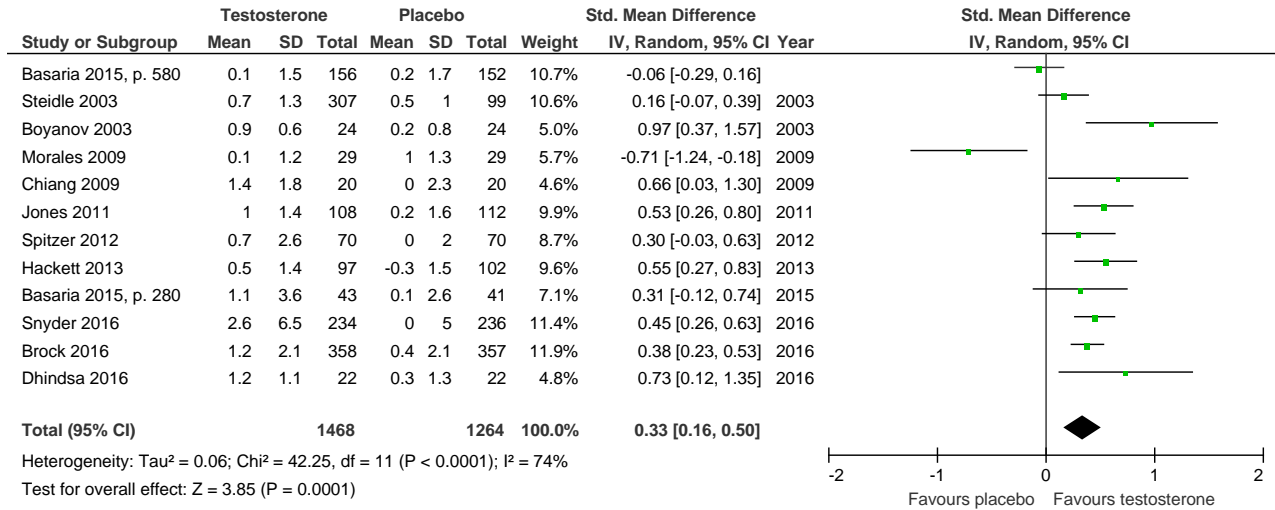
eTable 5: Depression – Bayesian network meta-analysis*

Treatment	Standardized mean difference (95% credible interval)									
	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	IM TU, 1000 mg/12 wk	IM TE, 125 mg/ wk	IM TE, 200 mg/ 3 wk	IM TE, 300 mg/ 3 wk	IM Sustanon, 100 mg/ 2 wk
Patch, 5 mg/d	-0.10 (-2.43,2.32)	—								
Gel 1%, 50 mg/d	0.17 (-1.72,2.00)	0.27 (-2.76,3.22)	—							
Gel 1%, 75 mg/d	-0.63 (-2.35,1.10)	-0.54 (-3.46,2.37)	-0.80 (-3.33,1.74)	—						
Gel 1%, 100 mg/d	-0.38 (-1.71,0.65)	-0.28 (-3.12,2.20)	-0.55 (-2.87,1.55)	0.25 (-2.00,2.18)	—					
IM TU, 1000 mg/12 wk	-0.34 (-1.29,0.61)	-0.24 (-2.82,2.31)	-0.51 (-2.55,1.59)	0.29 (-1.67,2.22)	0.04 (-1.32,1.72)	—				
IM TE 125 mg/wk	0.69 (-1.02,2.42)	0.79 (-2.12,3.67)	0.52 (-1.97,3.10)	1.32 (-1.12,3.76)	1.07 (-0.87,3.31)	1.03 (-0.94,3.00)	—			
IM TE, 200 mg/2 wk	0.18 (-1.47,1.91)	0.28 (-1.38,1.92)	0.01 (-2.42,2.56)	0.82 (-1.58,3.20)	0.56 (-1.32,2.81)	0.53 (-1.38,2.51)	-0.51 (-2.88,1.91)	—		
IM TE, 300 mg/3 wk	-0.46 (-2.13,1.22)	-0.36 (-3.26,2.50)	-0.63 (-3.10,1.89)	0.17 (-2.22,2.53)	-0.08 (-1.95,2.12)	-0.12 (-2.05,1.81)	-1.15 (-3.54,1.29)	-0.64 (-3.02,1.67)	—	
IM Sustanon, 100 mg/2 wk†	-0.25 (-1.98,1.43)	-0.15 (-3.09,2.72)	-0.42 (-2.93,2.11)	0.38 (-2.11,2.79)	0.13 (-1.84,2.33)	0.09 (-1.92,2.06)	-0.94 (-3.39,1.45)	-0.44 (-2.87,1.92)	0.21 (-2.23,2.58)	—

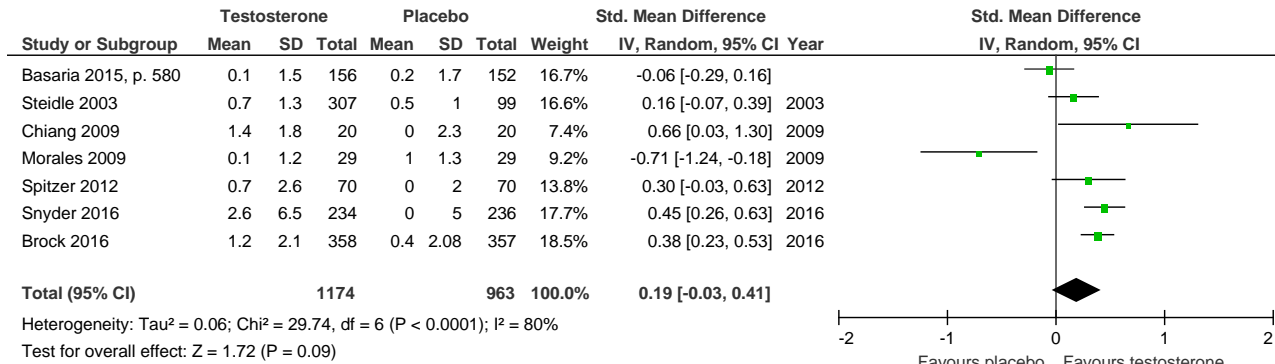
Note: IM = intramuscular, TE = testosterone enanthate, TU = testosterone undecanoate.
 *Random effects model. Analysis based on change from baseline. A negative SMD indicates improvement in depression. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.
 †Blend of testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, and testosterone decanoate.

eFigure 4: Individual trial results, libido

A) All trials



B) Trials involving men with no major comorbidities



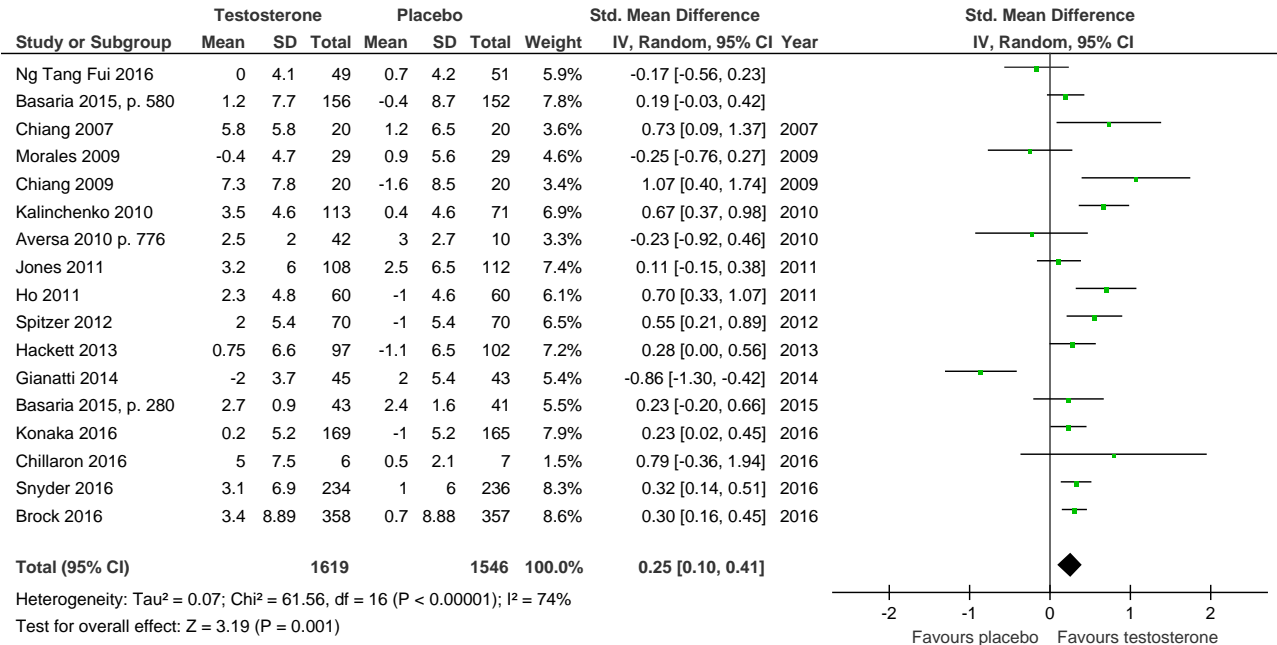
eTable6: Libido – Bayesian network meta-analysis*

	Standardized mean difference (95% credible interval)										
	Placebo	Patch, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Solution 2%, 60 mg/d	Oral TU, 120 mg/d	Oral, TU 160 mg/d	IM TU, 1000 mg/ 12 wk	IM TC, 250 mg/2wk
Patch, 5 mg/d	0.17 (-0.13,0.46)	—									
Gel 1%, 50 mg/d	0.32 (0.10,0.55)	0.15 (-0.10,0.42)	—								
Gel 1%, 75 mg/d	-0.06 (-0.49,0.36)	-0.23 (-0.75,0.29)	-0.38 (-0.87,0.10)	—							
Gel 1%, 100 mg/d	0.43 (0.16,0.69)	0.26 (0.00,0.52)	0.11 (-0.14,0.35)	0.49 (-0.01,0.99)	—						
Gel 2%, 60 mg/d	0.54 (0.09,0.99)	0.37 (-0.17,0.91)	0.21 (-0.29,0.72)	0.60 (-0.01,1.22)	0.11 (-0.41,0.63)	—					
Solution 2%, 60 mg/d	0.39 (-0.01,0.79)	0.22 (-0.28,0.72)	0.07 (-0.39,0.53)	0.45 (-0.12,1.04)	-0.04 (-0.52,0.44)	-0.15 (-0.75,0.46)	—				
Oral TU, 120 mg/d	1.00 (0.31,1.68)	0.83 (0.08,1.58)	0.68 (-0.05,1.39)	1.06 (0.25,1.87)	0.57 (-0.17,1.30)	0.46 (-0.36,1.28)	0.61 (-0.18,1.39)	—			
Oral TU, 160 mg/d	-0.72 (-1.35,-0.10)	-0.89 (-1.58,-0.19)	-1.04 (-1.70,-0.38)	-0.66 (-1.41,0.10)	-1.15 (-1.83,0.47)	-1.26 (-2.01,-0.49)	-1.11 (-1.84,-0.37)	-1.72 (-2.66,-0.78)	—		
IM TU, 1000 mg/12 wk	0.57 (0.11,1.03)	0.40 (-0.14,0.95)	0.25 (-0.26,0.76)	0.63 (0.00,1.26)	0.14 (-0.38,0.67)	0.03 (-0.61,0.68)	0.18 (-0.42,0.79)	-0.43 (-1.25,0.41)	1.29 (0.52,2.07)	—	
IM TC, 250 mg/2wk	0.71 (0.01,1.41)	0.55 (-0.21,1.30)	0.39 (-0.34,1.12)	0.78 (-0.05,1.59)	0.29 (-0.46,1.04)	0.18 (-0.65,0.99)	0.33 (-0.47,1.13)	-0.28 (-1.25,0.72)	1.44 (0.49,2.37)	0.14 (-0.70,0.97)	—

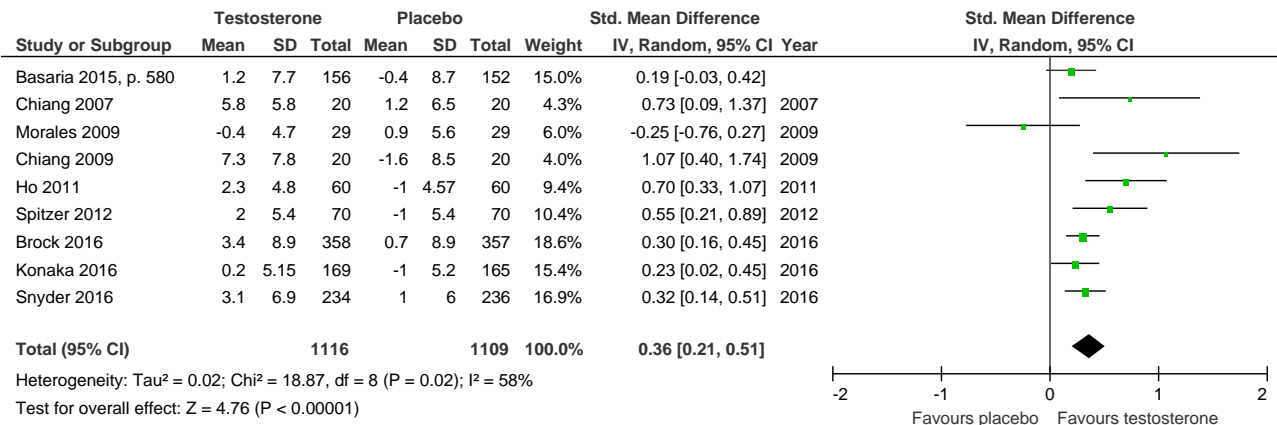
Note: IM = intramuscular injection, TC = testosterone cypionate, TU = testosterone undecanoate.
 *Random effects model. Analysis based on change from baseline. A positive SMD indicates improvement in libido. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

eFigure 5: Individual trial results, erectile function

A) All trials



B) Trials involving men without major comorbidities



eTable7: Erectile function at end of treatment – Bayesian network meta-analysis*

	Standardized mean difference (95% credible interval)									
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Solution 2%, 60 mg/d	Oral, TU 160 mg/d	IM TU, 1000 mg/10 wk	IM TU, 1000 mg/12 wk	IM TE 250 mg/4wk
Gel 1%, 50 mg/d	0.65 (-0.11,1.42)	—								
Gel 1%, 75 mg/d	0.26 (-0.60,1.11)	-0.39 (-1.55,0.76)	—							
Gel 1%, 100 mg/d	0.55 (-0.70,1.80)	-0.10 (-1.57,1.35)	0.29 (-1.23,1.82)	—						
Gel 2%, 60 mg/d	0.11 (-1.11,1.33)	-0.54 (-1.99,0.90)	-0.15 (-1.66,1.34)	-0.44 (-2.18,1.31)	—					
Solution 2%, 60 mg/d	0.30 (-0.90,1.51)	-0.35 (-1.79,1.07)	0.04 (-1.43,1.53)	-0.25 (-1.99,1.50)	0.19 (-1.54,1.92)	—				
Oral TU, 160 mg/d	-0.47 (-1.41,0.43)	-1.12 (-2.34,0.05)	-0.73 (-2.02,0.51)	-1.03 (-2.60,0.52)	-0.59 (-2.14,0.95)	-0.78 (-2.31,0.73)	—			
IM TU, 1000 mg/10 wk	0.17 (-0.77,1.19)	-0.48 (-1.69,0.78)	-0.09 (-1.35,1.24)	-0.38 (-1.92,1.25)	0.06 (-1.47,1.66)	-0.13 (-1.63,1.46)	0.65 (-0.65,2.04)	—		
IM TU, 1000 mg/ 12 wk	0.21 (-0.36,0.76)	-0.44 (-1.40,0.49)	-0.05 (-1.10,0.96)	-0.34 (-1.72,1.02)	0.10 (-1.24,1.44)	-0.09 (-1.44,1.23)	0.68 (-0.29,1.68)	0.03 (-1.13,1.12)	—	
IM TE 250 mg/4wk	0.22 (-1.00,1.45)	-0.43 (-1.88,1.01)	-0.04 (-1.54,1.46)	-0.33 (-2.08,1.41)	0.11 (-1.63,1.84)	-0.08 (-1.80,1.62)	0.69 (-0.83,2.22)	0.04 (-1.57,1.57)	0.01 (-1.33,1.36)	—

Note: IM = intramuscular injection, TE = testosterone enanthate, TU = testosterone undecanoate.
 *Random effects model. Analysis based on change from baseline. A positive SMD indicates improvement in erectile function. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

eTable 8: Total testosterone level after 3 months of treatment – Bayesian network meta-analysis*

*Random effects model. Analysis is based on mean total testosterone level after treatment. A positive mean difference indicates a statistically significant improvement in total testosterone level. Significant changes are indicated by use of bold and colour (green indicates that the treatment is significantly better than the reference, while red indicates that the treatment is significantly worse than the reference). White indicates no significant difference between treatment and reference.

Treatment	Reference	Mean difference (95% credible intervals)
Patch 4.8 mg/d	Placebo	12.46(-3.49,28.17)
Patch 5 mg/d		5.06(0.88,9.25)
Gel 1% 50 mg/d		6.54(3.51,9.65)
Gel 1% 75 mg/d		7.48(-2.02,17.01)
Gel 1% 100 mg/d		9.82(6.19,13.44)
Oral TU 120 mg/d		4.31(-4.08,12.69)
Oral TU 160 mg/d		3.64(-4.69,11.86)
Testosterone pellets 1200 mg		6.40(-5.08,17.89)
IM TU 1000 mg/12 wk		8.91(2.80,15.08)
IM TE 100 mg/wk		12.12(3.48,20.83)
IM TE 200 mg/2wk		6.26(-2.80,15.34)
IM TE 250 mg/3wk		12.78(1.28,24.21)
IM TC 200 mg/2 wk		3.25(-6.32,12.89)
IM TC 200 mg/4 wk		1.73(-8.61,12.15)
Durateston, IM, 250 mg/4wk		2.13(-8.21,12.60)
Patch 5 mg/d	Patch 4.8 mg/d	-7.40(-23.71,9.17)
Gel 1% 50 mg/d		-5.91(-21.92,10.35)
Gel 1% 75 mg/d		-4.98(-23.37,13.63)
Gel 1% 100 mg/d		-2.64(-18.80,13.74)
Oral TU 120 mg/d		-8.15(-26.04,9.82)
Oral TU 160 mg/d		-8.82(-22.30,4.67)
Testosterone pellets 1200 mg		-6.06(-18.69,6.69)
IM TU 1000 mg/12 wk		-3.55(-20.42,13.57)
IM TE 100 mg/wk		-0.34(-18.30,17.61)
IM TE 200 mg/2wk		-6.20(-24.42,12.21)
IM TE 250 mg/3wk		0.32(-10.51,11.25)
IM TC 200 mg/2 wk		-9.21(-27.76,9.46)
IM TC 200 mg/4 wk		-10.72(-29.59,8.36)
Durateston, IM, 250 mg/4wk		-10.33(-29.25,8.69)
Gel 1% 50 mg/d	Patch 5 mg/d	1.48(-2.69,5.71)
Gel 1% 75 mg/d		2.41(-7.90,12.76)
Gel 1% 100 mg/d		4.76(0.40,9.04)
Oral TU 120 mg/d		-0.75(-10.16,8.55)

Oral TU 160 mg/d		-1.43(-10.82,7.80)
Testosterone pellets 1200 mg		1.34(-10.92,13.53)
IM TU 1000 mg/12 wk		3.85(-3.58,11.27)
IM TE 100 mg/wk		7.06(-2.53,16.60)
IM TE 200 mg/2wk		1.19(-8.83,11.18)
IM TE 250 mg/3wk		7.72(-4.58,19.84)
IM TC 200 mg/2 wk		-1.81(-12.35,8.73)
IM TC 200 mg/4 wk		-3.33(-14.50,7.86)
Durateston, IM, 250 mg/4wk		-2.94(-14.12,8.32)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	0.93(-8.98,10.93)
Gel 1% 100 mg/d		3.27(-0.68,7.16)
Oral TU 120 mg/d		-2.23(-11.30,6.62)
Oral TU 160 mg/d		-2.91(-11.82,5.84)
Testosterone pellets 1200 mg		-0.14(-12.11,11.71)
IM TU 1000 mg/12 wk		2.37(-4.49,9.22)
IM TE 100 mg/wk		5.57(-3.60,14.72)
IM TE 200 mg/2wk		-0.29(-9.83,9.28)
IM TE 250 mg/3wk		6.24(-5.72,18.05)
IM TC 200 mg/2 wk		-3.30(-13.42,6.78)
IM TC 200 mg/4 wk		-4.81(-15.66,5.96)
Durateston, IM, 250 mg/4wk		-4.42(-15.28,6.46)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	2.34(-7.87,12.46)
Oral TU 120 mg/d		-3.17(-15.86,9.38)
Oral TU 160 mg/d		-3.84(-16.49,8.72)
Testosterone pellets 1200 mg		-1.07(-15.98,13.79)
IM TU 1000 mg/12 wk		1.44(-9.92,12.73)
IM TE 100 mg/wk		4.64(-8.23,17.49)
IM TE 200 mg/2wk		-1.22(-14.30,11.90)
IM TE 250 mg/3wk		5.31(-9.66,20.08)
IM TC 200 mg/2 wk		-4.23(-17.84,9.24)
IM TC 200 mg/4 wk		-5.74(-19.84,8.38)
Durateston, IM, 250 mg/4wk		-5.35(-19.41,8.93)
Oral TU 120 mg/d	Gel 1% 100 mg/d	-5.51(-14.69,3.57)
Oral TU 160 mg/d		-6.18(-15.23,2.79)
Testosterone pellets 1200 mg		-3.41(-15.41,8.57)
IM TU 1000 mg/12 wk		-0.91(-8.03,6.24)
IM TE 100 mg/wk		2.30(-7.08,11.64)
IM TE 200 mg/2wk		-3.56(-13.34,6.30)
IM TE 250 mg/3wk		2.96(-9.16,14.85)
IM TC 200 mg/2 wk		-6.57(-16.82,3.69)
IM TC 200 mg/4 wk		-8.08(-19.02,2.89)
Durateston, IM, 250 mg/4wk		-7.69(-18.61,3.38)

Oral TU 160 mg/d	Oral TU 120 mg/d	-0.67(-12.46,11.10)
Testosterone pellets 1200 mg		2.09(-12.01,16.29)
IM TU 1000 mg/12 wk		4.60(-5.79,14.94)
IM TE 100 mg/wk		7.81(-4.20,19.92)
IM TE 200 mg/2wk		1.95(-10.36,14.39)
IM TE 250 mg/3wk		8.47(-5.65,22.61)
IM TC 200 mg/2 wk		-1.06(-13.92,11.70)
IM TC 200 mg/4 wk		-2.58(-16.00,10.91)
Durateston, IM, 250 mg/4wk		-2.18(-15.61,11.22)
Testosterone pellets 1200 mg	Oral TU 160 mg/d	2.77(-5.26,10.82)
IM TU 1000 mg/12 wk		5.28(-5.00,15.64)
IM TE 100 mg/wk		8.48(-3.53,20.45)
IM TE 200 mg/2wk		2.62(-9.56,14.98)
IM TE 250 mg/3wk		9.15(1.17,17.13)
IM TC 200 mg/2 wk		-0.39(-13.19,12.34)
IM TC 200 mg/4 wk		-1.90(-15.18,11.34)
Durateston, IM, 250 mg/4wk		-1.51(-14.84,11.86)
IM TU 1000 mg/12 wk	Testosterone pellets 1200 mg	2.51(-10.54,15.55)
IM TE 100 mg/wk		5.71(-8.62,19.97)
IM TE 200 mg/2wk		-0.15(-14.76,14.51)
IM TE 250 mg/3wk		6.38(-0.25,13.01)
IM TC 200 mg/2 wk		-3.16(-18.21,11.86)
IM TC 200 mg/4 wk		-4.67(-20.16,10.75)
Durateston, IM, 250 mg/4wk		-4.28(-19.96,11.21)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	3.21(-7.33,13.81)
IM TE 200 mg/2wk		-2.66(-13.63,8.30)
IM TE 250 mg/3wk		3.87(-9.22,16.79)
IM TC 200 mg/2 wk		-5.66(-17.05,5.71)
IM TC 200 mg/4 wk		-7.18(-15.50,1.16)
Durateston, IM, 250 mg/4wk		-6.79(-15.25,1.65)
IM TE 200 mg/2wk	IM TE 100 mg/wk	-5.86(-18.36,6.71)
IM TE 250 mg/3wk		0.66(-13.63,15.00)
IM TC 200 mg/2 wk		-8.87(-21.88,4.14)
IM TC 200 mg/4 wk		-10.38(-23.84,3.13)
Durateston, IM, 250 mg/4wk		-9.99(-23.47,3.48)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	6.53(-8.23,21.04)
IM TC 200 mg/2 wk		-3.01(-16.17,10.25)
IM TC 200 mg/4 wk		-4.52(-18.16,9.20)
Durateston, IM, 250 mg/4wk		-4.13(-17.94,9.72)
IM TC 200 mg/2 wk	IM TE 250 mg/3wk	-9.53(-24.53,5.59)
IM TC 200 mg/4 wk		-11.05(-26.44,4.43)
Durateston, IM, 250 mg/4wk		-10.65(-26.22,4.95)

IM TC 200 mg/4 wk	IM TC 200 mg/2 wk	-1.51(-15.53,12.52)
Durateston, IM, 250 mg/4wk		-1.12(-15.17,13.08)
Durateston, IM, 250 mg/4wk	IM TC 200 mg/4 wk	0.39(-8.03,8.79)

eTable 9: Total testosterone level after 6 months of treatment – Bayesian network meta-analysis*

*Random effects model. Analysis based mean total testosterone level after treatment. A positive MD indicates a statistically significant improvement in total testosterone level. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments.

Treatment	Reference	Mean difference (95% credible interval)
Patch 4.8 mg/d	Placebo	10.69(-1.17,22.73)
Patch 5 mg/d		8.45(0.51,16.35)
Gel 1% 50 mg/d		7.94(4.36,11.49)
Gel 1% 75 mg/d		5.76(-0.75,12.29)
Gel 1% 100 mg/d		7.47(3.50,11.40)
Gel 2% 60 mg/d		19.80(13.59,26.00)
Gel 2.5%, 125 mg/d		12.13(2.00,22.09)
Gel (scrotal) 2.5%, 25 mg/d		7.89(-2.18,17.86)
Oral TU 120-160 mg/d		5.68(-0.52,11.88)
Oral TU 160 mg/d		1.84(-2.44,6.10)
Testosterone pellets 1200 mg		4.69(-2.86,12.17)
IM TU 1000 mg/12 wk		8.07(3.71,12.46)
IM TE 150 mg/2wk		12.72(5.10,20.29)
IM TE 200 mg/2wk		10.10(2.68,17.61)
IM TE 250 mg/3wk		11.02(3.59,18.55)
IM TE 300 mg/3wk		18.25(10.92,25.60)
IM TE 50-400 mg/1-2 wk		14.74(4.55,25.01)
IM TC 200 mg/2 wk		3.21(-4.73,11.12)
Patch 5 mg/d	Patch 4.8 mg/d	-2.24(-16.71,11.98)
Gel 1% 50 mg/d		-2.75(-15.42,9.56)
Gel 1% 75 mg/d		-4.94(-18.49,8.60)
Gel 1% 100 mg/d		-3.22(-15.94,9.31)
Gel 2% 60 mg/d		9.11(-4.41,22.45)
Gel 2.5%, 125 mg/d		1.44(-14.32,16.85)
Gel (scrotal) 2.5%, 25 mg/d		-2.80(-18.53,12.61)
Oral TU 120-160 mg/d		-5.01(-18.65,8.35)
Oral TU 160 mg/d		-8.85(-20.06,2.21)
Testosterone pellets 1200 mg		-6.01(-16.78,4.72)

IM TU 1000 mg/12 wk		-2.62(-14.99,9.53)
IM TE 150 mg/2wk		2.03(-12.24,16.16)
IM TE 200 mg/2wk		-0.59(-14.66,13.38)
IM TE 250 mg/3wk		0.33(-9.00,9.68)
IM TE 300 mg/3wk		7.56(-6.50,21.52)
IM TE 50-400 mg/1-2 wk		4.05(-11.55,19.64)
IM TC 200 mg/2 wk		-7.49(-21.86,6.80)
Gel 1% 50 mg/d	Patch 5 mg/d	-0.51(-9.17,8.26)
Gel 1% 75 mg/d		-2.70(-12.88,7.57)
Gel 1% 100 mg/d		-0.98(-9.71,7.83)
Gel 2% 60 mg/d		11.35(1.38,21.45)
Gel 2.5%, 125 mg/d		3.68(-2.57,9.89)
Gel (scrotal) 2.5%, 25 mg/d		-0.56(-6.82,5.64)
Oral TU 120-160 mg/d		-2.77(-12.83,7.29)
Oral TU 160 mg/d		-6.61(-15.60,2.37)
Testosterone pellets 1200 mg		-3.76(-14.64,7.17)
IM TU 1000 mg/12 wk		-0.38(-9.40,8.59)
IM TE 150 mg/2wk		4.27(-6.77,15.19)
IM TE 200 mg/2wk		1.65(-9.12,12.46)
IM TE 250 mg/3wk		2.57(-8.35,13.50)
IM TE 300 mg/3wk		9.80(-1.00,20.57)
IM TE 50-400 mg/1-2 wk		6.29(-6.46,19.33)
IM TC 200 mg/2 wk		-5.25(-16.35,5.95)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	-2.19(-9.54,5.26)
Gel 1% 100 mg/d		-0.47(-5.79,4.89)
Gel 2% 60 mg/d		11.86(4.68,19.05)
Gel 2.5%, 125 mg/d		4.19(-6.52,14.80)
Gel (scrotal) 2.5%, 25 mg/d		-0.05(-10.72,10.61)
Oral TU 120-160 mg/d		-2.26(-9.34,4.96)
Oral TU 160 mg/d		-6.10(-11.64,-0.46)
Testosterone pellets 1200 mg		-3.25(-11.55,5.08)
IM TU 1000 mg/12 wk		0.13(-5.49,5.79)
IM TE 150 mg/2wk		4.78(-3.58,13.19)
IM TE 200 mg/2wk		2.16(-5.97,10.48)
IM TE 250 mg/3wk		3.08(-5.14,11.45)
IM TE 300 mg/3wk		10.31(2.17,18.53)
IM TE 50-400 mg/1-2 wk		6.80(-4.00,17.62)
IM TC 200 mg/2 wk		-4.74(-13.42,3.94)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	1.71(-5.94,9.34)
Gel 2% 60 mg/d		14.04(5.05,22.97)
Gel 2.5%, 125 mg/d		6.37(-5.71,18.31)
Gel (scrotal) 2.5%, 25 mg/d		2.14(-9.89,14.03)

Oral TU 120-160 mg/d		-0.07(-9.16,8.90)
Oral TU 160 mg/d		-3.91(-11.78,3.88)
Testosterone pellets 1200 mg		-1.07(-10.98,8.82)
IM TU 1000 mg/12 wk		2.31(-5.63,10.19)
IM TE 150 mg/2wk		6.96(-3.13,17.01)
IM TE 200 mg/2wk		4.35(-5.60,14.23)
IM TE 250 mg/3wk		5.26(-4.59,15.19)
IM TE 300 mg/3wk		12.50(2.64,22.31)
IM TE 50-400 mg/1-2 wk		8.99(-3.00,21.03)
IM TC 200 mg/2 wk		-2.55(-12.74,7.68)
Gel 2% 60 mg/d	Gel 1% 100 mg/d	12.33(5.03,19.71)
Gel 2.5%, 125 mg/d		4.66(-6.17,15.34)
Gel (scrotal) 2.5%, 25 mg/d		0.42(-10.35,11.17)
Oral TU 120-160 mg/d		-1.79(-9.10,5.58)
Oral TU 160 mg/d		-5.63(-11.50,0.28)
Testosterone pellets 1200 mg		-2.78(-11.34,5.78)
IM TU 1000 mg/12 wk		0.60(-5.31,6.53)
IM TE 150 mg/2wk		5.25(-3.38,13.81)
IM TE 200 mg/2wk		2.63(-5.77,11.14)
IM TE 250 mg/3wk		3.55(-4.93,12.14)
IM TE 300 mg/3wk		10.78(2.42,19.14)
IM TE 50-400 mg/1-2 wk		7.28(-3.63,18.18)
IM TC 200 mg/2 wk		-4.27(-13.06,4.61)
Gel 2.5%, 125 mg/d	Gel 2% 60 mg/d	-7.67(-19.47,3.96)
Gel (scrotal) 2.5%, 25 mg/d		-11.91(-23.69,-0.16)
Oral TU 120-160 mg/d		-14.11(-22.91,-5.33)
Oral TU 160 mg/d		-17.96(-25.47,-10.36)
Testosterone pellets 1200 mg		-15.11(-24.85,-5.36)
IM TU 1000 mg/12 wk		-11.73(-19.31,-4.11)
IM TE 150 mg/2wk		-7.08(-16.88,2.74)
IM TE 200 mg/2wk		-9.70(-19.39,-0.03)
IM TE 250 mg/3wk		-8.78(-18.41,1.02)
IM TE 300 mg/3wk		-1.55(-11.11,8.12)
IM TE 50-400 mg/1-2 wk		-5.05(-16.93,6.87)
IM TC 200 mg/2 wk		-16.59(-26.63,-6.52)
Gel (scrotal) 2.5%, 25 mg/d	Gel 2.5%, 125 mg/d	-4.24(-10.53,1.98)
Oral TU 120-160 mg/d		-6.45(-18.26,5.33)
Oral TU 160 mg/d		-10.29(-21.22,0.66)
Testosterone pellets 1200 mg		-7.44(-19.87,5.14)
IM TU 1000 mg/12 wk		-4.06(-14.99,6.89)
IM TE 150 mg/2wk		0.59(-12.00,13.23)
IM TE 200 mg/2wk		-2.03(-14.56,10.54)

IM TE 250 mg/3wk		-1.11(-13.58,11.45)
IM TE 300 mg/3wk		6.12(-6.29,18.59)
IM TE 50-400 mg/1-2 wk		2.62(-11.57,17.04)
IM TC 200 mg/2 wk		-8.92(-21.55,3.89)
Oral TU 120-160 mg/d	Gel (scrotal) 2.5%, 25 mg/d	-2.21(-14.01,9.62)
Oral TU 160 mg/d		-6.05(-16.91,4.92)
Testosterone pellets 1200 mg		-3.21(-15.72,9.40)
IM TU 1000 mg/12 wk		0.18(-10.74,11.14)
IM TE 150 mg/2wk		4.82(-7.68,17.43)
IM TE 200 mg/2wk		2.21(-10.23,14.82)
IM TE 250 mg/3wk		3.13(-9.48,15.73)
IM TE 300 mg/3wk		10.36(-2.02,22.83)
IM TE 50-400 mg/1-2 wk		6.85(-7.36,21.24)
IM TC 200 mg/2 wk		-4.69(-17.36,8.11)
Oral TU 160 mg/d	Oral TU 120-160 mg/d	-3.84(-11.38,3.69)
Testosterone pellets 1200 mg		-1.00(-10.73,8.75)
IM TU 1000 mg/12 wk		2.39(-5.28,10.08)
IM TE 150 mg/2wk		7.03(-2.78,16.80)
IM TE 200 mg/2wk		4.42(-5.26,14.13)
IM TE 250 mg/3wk		5.33(-4.33,15.11)
IM TE 300 mg/3wk		12.57(2.91,22.18)
IM TE 50-400 mg/1-2 wk		9.06(-2.84,21.05)
IM TC 200 mg/2 wk		-2.48(-12.54,7.57)
Testosterone pellets 1200 mg	Oral TU 160 mg/d	2.84(-3.35,9.02)
IM TU 1000 mg/12 wk		6.23(1.04,11.41)
IM TE 150 mg/2wk		10.87(2.16,19.57)
IM TE 200 mg/2wk		8.26(-0.33,16.82)
IM TE 250 mg/3wk		9.18(3.03,15.42)
IM TE 300 mg/3wk		16.41(7.93,25.00)
IM TE 50-400 mg/1-2 wk		12.90(1.81,23.95)
IM TC 200 mg/2 wk		1.36(-7.75,10.40)
IM TU 1000 mg/12 wk	Testosterone pellets 1200 mg	3.38(-4.67,11.50)
IM TE 150 mg/2wk		8.03(-2.77,18.77)
IM TE 200 mg/2wk		5.42(-5.01,16.06)
IM TE 250 mg/3wk		6.33(0.97,11.73)
IM TE 300 mg/3wk		13.57(3.19,24.08)
IM TE 50-400 mg/1-2 wk		10.06(-2.53,22.73)
IM TC 200 mg/2 wk		-1.48(-12.38,9.46)
IM TE 150 mg/2wk	IM TU 1000 mg/12 wk	4.65(-4.13,13.37)
IM TE 200 mg/2wk		2.03(-6.70,10.69)
IM TE 250 mg/3wk		2.95(-5.08,11.11)
IM TE 300 mg/3wk		10.18(1.58,18.75)

IM TE 50-400 mg/1-2 wk		6.68(-4.45,17.75)
IM TC 200 mg/2 wk		-4.86(-13.89,4.19)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	-2.61(-13.28,8.17)
IM TE 250 mg/3wk		-1.70(-12.39,9.20)
IM TE 300 mg/3wk		5.54(-5.10,16.15)
IM TE 50-400 mg/1-2 wk		2.03(-10.78,14.82)
IM TC 200 mg/2 wk		-9.51(-20.53,1.51)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	0.92(-9.64,11.36)
IM TE 300 mg/3wk		8.15(-2.38,18.61)
IM TE 50-400 mg/1-2 wk		4.64(-7.93,17.27)
IM TC 200 mg/2 wk		-6.90(-17.80,4.00)
IM TE 300 mg/3wk	IM TE 250 mg/3wk	7.23(-3.23,17.75)
IM TE 50-400 mg/1-2 wk		3.73(-8.88,16.28)
IM TC 200 mg/2 wk	IM TE 300 mg/3wk	-7.81(-18.75,3.15)
IM TE 50-400 mg/1-2 wk		-3.51(-16.11,8.94)
IM TC 200 mg/2 wk		-15.05(-25.92,-4.21)
IM TC 200 mg/2 wk	IM TE 50-400 mg/1-2 wk	-11.54(-24.57,1.32)

eTable 10: Total testosterone levels at the end of treatment – Bayesian network meta-analysis*

*Random effects model. Analysis is based on mean total testosterone level after treatment. A positive mean difference indicates a statistically significant improvement in total testosterone level. Significant changes are indicated by use of bold and colour (green indicates that the treatment is significantly better than the reference, while red indicates that the treatment is significantly worse than the reference). White indicates no significant difference between treatment and reference.

Treatment	Reference	Mean difference (95% credible interval)
Patch 4.8 mg/d	Placebo	8.00(-3.40,19.24)
Patch 5 mg/d		4.74(1.65,7.84)
Gel 1% 5 mg/d		3.66(-4.21,11.57)
Gel 1% 50 mg/d		6.54(4.27,8.85)
Gel 1% 75 mg/d		6.49(0.92,12.04)
Gel 1% 100 mg/d		9.76(6.92,12.61)
Gel 2% 60 mg/d		19.76(12.66,26.85)
Gel 2.5%, 125 mg/d		8.44(0.75,16.16)
Gel (scrotal) 2.5%, 25 mg/d		4.19(-3.53,11.91)
Solution 2%, 60 mg/d		8.47(0.47,16.40)
Oral TU 120 mg/d		4.32(-2.98,11.63)
Oral TU 160 mg/d		1.40(-2.28,5.08)
Oral TU 120-160 mg/d		5.69(-1.33,12.73)
Testosterone pellets 1200 mg		2.77(-3.99,9.50)
IM TU 1000 mg/9 wk		16.32(6.99,25.58)
IM TU 1000 mg/10 wk		5.70(0.07,11.29)

IM TU 1000 mg/12 wk		8.45(5.99,10.90)
IM TE 100 mg/wk		9.52(4.08,14.91)
IM TE 125 mg/wk		6.76(-3.38,16.87)
IM TE 150 mg/2wk		12.71(4.36,21.09)
IM TE 200 mg/2wk		10.67(5.96,15.35)
IM TE 250 mg/3wk		8.33(2.98,13.71)
IM TE 300 mg/3wk		18.26(9.96,26.49)
IM TE 50-400 mg/1-2 wk		14.74(3.91,25.46)
IM TC 200 mg/2 wk		3.20(-5.49,11.85)
IM TC 200 mg/4 wk		1.30(-6.39,8.98)
IM TC 250 mg/2wk		9.73(1.91,17.51)
Durateston, IM, 250 mg/4wk		1.67(-6.17,9.42)
Patch 5 mg/d	Patch 4.8 mg/d	-3.26(-14.89,8.56)
Gel 1% 5 mg/d		-4.34(-18.04,9.54)
Gel 1% 50 mg/d		-1.46(-12.93,10.15)
Gel 1% 75 mg/d		-1.51(-14.10,11.24)
Gel 1% 100 mg/d		1.76(-9.83,13.46)
Gel 2% 60 mg/d		11.76(-1.57,25.26)
Gel 2.5%, 125 mg/d		0.44(-13.20,14.18)
Gel (scrotal) 2.5%, 25 mg/d		-3.81(-17.47,9.95)
Solution 2%, 60 mg/d		0.47(-13.38,14.35)
Oral TU 120 mg/d		-3.68(-17.02,9.84)
Oral TU 160 mg/d		-6.60(-17.82,4.81)
Oral TU 120-160 mg/d		-2.31(-15.69,11.06)
Testosterone pellets 1200 mg		-5.23(-16.69,6.32)
IM TU 1000 mg/9 wk		8.32(-4.22,20.91)
IM TU 1000 mg/10 wk		-2.30(-14.89,10.43)
IM TU 1000 mg/12 wk		0.45(-11.02,12.05)
IM TE 100 mg/wk		1.52(-10.96,14.13)
IM TE 125 mg/wk		-1.24(-16.45,13.89)
IM TE 150 mg/2wk		4.71(-9.35,18.84)
IM TE 200 mg/2wk		2.67(-9.60,14.94)
IM TE 250 mg/3wk		0.33(-9.63,10.45)
IM TE 300 mg/3wk		10.26(-3.79,24.37)
IM TE 50-400 mg/1-2 wk		6.75(-8.90,22.49)
IM TC 200 mg/2 wk		-4.80(-19.10,9.52)
IM TC 200 mg/4 wk		-6.70(-20.28,7.08)
IM TC 250 mg/2wk		1.73(-11.91,15.43)
Durateston, IM, 250 mg/4wk		-6.33(-20.01,7.57)
Gel 1% 5 mg/d	Patch 5 mg/d	-1.08(-9.49,7.42)
Gel 1% 50 mg/d		1.80(-1.49,5.16)
Gel 1% 75 mg/d		1.76(-4.64,8.14)

Gel 1% 100 mg/d		5.02(1.52,8.49)
Gel 2% 60 mg/d		15.02(7.19,22.80)
Gel 2.5%, 125 mg/d		3.70(-3.39,10.73)
Gel (scrotal) 2.5%, 25 mg/d		-0.55(-7.68,6.53)
Solution 2%, 60 mg/d		3.73(-4.85,12.32)
Oral TU 120 mg/d		-0.41(-8.32,7.44)
Oral TU 160 mg/d		-3.33(-8.17,1.43)
Oral TU 120-160 mg/d		0.95(-6.78,8.61)
Testosterone pellets 1200 mg		-1.97(-9.42,5.39)
IM TU 1000 mg/9 wk		11.58(1.73,21.42)
IM TU 1000 mg/10 wk		0.96(-5.42,7.38)
IM TU 1000 mg/12 wk		3.72(-0.31,7.66)
IM TE 100 mg/wk		4.78(-1.44,10.97)
IM TE 125 mg/wk		2.02(-8.51,12.56)
IM TE 150 mg/2wk		7.97(-0.95,16.86)
IM TE 200 mg/2wk		5.93(0.94,10.87)
IM TE 250 mg/3wk		3.59(-2.64,9.81)
IM TE 300 mg/3wk		13.52(4.66,22.31)
IM TE 50-400 mg/1-2 wk		10.01(-1.36,21.18)
IM TC 200 mg/2 wk		-1.54(-10.74,7.65)
IM TC 200 mg/4 wk		-3.44(-11.77,4.80)
IM TC 250 mg/2wk		4.99(-3.43,13.41)
Durateston, IM, 250 mg/4wk		-3.07(-11.56,5.28)
Gel 1% 50 mg/d	Gel 1% 5 mg/d	2.88(-5.34,11.08)
Gel 1% 75 mg/d		2.83(-6.84,12.54)
Gel 1% 100 mg/d		6.10(-2.30,14.48)
Gel 2% 60 mg/d		16.10(5.47,26.65)
Gel 2.5%, 125 mg/d		4.78(-6.22,15.83)
Gel (scrotal) 2.5%, 25 mg/d		0.53(-10.48,11.48)
Solution 2%, 60 mg/d		4.81(-6.33,15.99)
Oral TU 120 mg/d		0.66(-9.98,11.41)
Oral TU 160 mg/d		-2.26(-10.97,6.42)
Oral TU 120-160 mg/d		2.02(-8.54,12.63)
Testosterone pellets 1200 mg		-0.89(-11.28,9.45)
IM TU 1000 mg/9 wk		12.66(0.32,24.84)
IM TU 1000 mg/10 wk		2.04(-7.64,11.75)
IM TU 1000 mg/12 wk		4.79(-3.47,12.95)
IM TE 100 mg/wk		5.86(-3.72,15.40)
IM TE 125 mg/wk		3.10(-9.72,15.94)
IM TE 150 mg/2wk		9.05(-2.41,20.56)
IM TE 200 mg/2wk		7.01(-2.27,16.13)
IM TE 250 mg/3wk		4.67(-4.87,14.18)

IM TE 300 mg/3wk		14.60(3.17,26.00)
IM TE 50-400 mg/1-2 wk		11.08(-2.35,24.44)
IM TC 200 mg/2 wk		-0.46(-12.22,11.21)
IM TC 200 mg/4 wk		-2.37(-13.33,8.57)
IM TC 250 mg/2wk		6.07(-5.05,17.18)
Durateston, IM, 250 mg/4wk		-1.99(-13.08,9.06)
Gel 1% 75 mg/d	Gel 1% 50 mg/d	-0.05(-6.06,5.96)
Gel 1% 100 mg/d		3.22(0.05,6.36)
Gel 2% 60 mg/d		13.22(5.72,20.65)
Gel 2.5%, 125 mg/d		1.90(-5.89,9.68)
Gel (scrotal) 2.5%, 25 mg/d		-2.35(-10.23,5.47)
Solution 2%, 60 mg/d		1.93(-6.45,10.21)
Oral TU 120 mg/d		-2.22(-9.89,5.36)
Oral TU 160 mg/d		-5.14(-9.50,-0.83)
Oral TU 120-160 mg/d		-0.86(-8.26,6.53)
Testosterone pellets 1200 mg		-3.77(-10.93,3.32)
IM TU 1000 mg/9 wk		9.78(0.12,19.31)
IM TU 1000 mg/10 wk		-0.84(-6.93,5.22)
IM TU 1000 mg/12 wk		1.91(-1.49,5.22)
IM TE 100 mg/wk		2.98(-2.97,8.82)
IM TE 125 mg/wk		0.22(-10.17,10.56)
IM TE 150 mg/2wk		6.17(-2.50,14.84)
IM TE 200 mg/2wk		4.13(-0.98,9.17)
IM TE 250 mg/3wk		1.79(-4.11,7.62)
IM TE 300 mg/3wk		11.72(3.13,20.20)
IM TE 50-400 mg/1-2 wk		8.20(-2.93,19.12)
IM TC 200 mg/2 wk		-3.34(-12.34,5.62)
IM TC 200 mg/4 wk		-5.25(-13.24,2.71)
IM TC 250 mg/2wk		3.19(-4.96,11.30)
Durateston, IM, 250 mg/4wk		-4.87(-13.08,3.23)
Gel 1% 100 mg/d	Gel 1% 75 mg/d	3.26(-3.00,9.49)
Gel 2% 60 mg/d		13.27(4.21,22.29)
Gel 2.5%, 125 mg/d		1.95(-7.52,11.42)
Gel (scrotal) 2.5%, 25 mg/d		-2.30(-11.80,7.19)
Solution 2%, 60 mg/d		1.98(-7.79,11.68)
Oral TU 120 mg/d		-2.17(-11.46,7.10)
Oral TU 160 mg/d		-5.09(-11.81,1.62)
Oral TU 120-160 mg/d		-0.81(-9.76,8.21)
Testosterone pellets 1200 mg		-3.72(-12.49,5.06)
IM TU 1000 mg/9 wk		9.83(-1.12,20.61)
IM TU 1000 mg/10 wk		-0.79(-8.71,7.09)
IM TU 1000 mg/12 wk		1.96(-4.14,8.02)

IM TE 100 mg/wk		3.03(-4.78,10.84)
IM TE 125 mg/wk		0.27(-11.29,11.76)
IM TE 150 mg/2wk		6.21(-3.81,16.26)
IM TE 200 mg/2wk		4.18(-3.13,11.49)
IM TE 250 mg/3wk		1.84(-5.91,9.60)
IM TE 300 mg/3wk		11.76(1.77,21.71)
IM TE 50-400 mg/1-2 wk		8.25(-3.95,20.40)
IM TC 200 mg/2 wk		-3.30(-13.57,7.03)
IM TC 200 mg/4 wk		-5.20(-14.75,4.38)
IM TC 250 mg/2wk		3.24(-6.31,12.84)
Durateston, IM, 250 mg/4wk		-4.82(-14.54,4.73)
Gel 2% 60 mg/d	Gel 1% 100 mg/d	10.00(2.31,17.65)
Gel 2.5%, 125 mg/d		-1.32(-9.14,6.53)
Gel (scrotal) 2.5%, 25 mg/d		-5.57(-13.46,2.30)
Solution 2%, 60 mg/d		-1.29(-9.81,7.12)
Oral TU 120 mg/d		-5.43(-13.31,2.41)
Oral TU 160 mg/d		-8.35(-13.01,-3.72)
Oral TU 120-160 mg/d		-4.07(-11.66,3.46)
Testosterone pellets 1200 mg		-6.98(-14.31,0.32)
IM TU 1000 mg/9 wk		6.56(-3.21,16.30)
IM TU 1000 mg/10 wk		-4.05(-10.36,2.25)
IM TU 1000 mg/12 wk		-1.30(-5.08,2.39)
IM TE 100 mg/wk		-0.24(-6.33,5.86)
IM TE 125 mg/wk		-3.00(-13.56,7.45)
IM TE 150 mg/2wk		2.95(-5.87,11.76)
IM TE 200 mg/2wk		0.91(-4.37,6.24)
IM TE 250 mg/3wk		-1.43(-7.51,4.70)
IM TE 300 mg/3wk		8.50(-0.26,17.19)
IM TE 50-400 mg/1-2 wk		4.99(-6.29,16.05)
IM TC 200 mg/2 wk		-6.56(-15.67,2.62)
IM TC 200 mg/4 wk		-8.46(-16.58,-0.35)
IM TC 250 mg/2wk		-0.03(-8.32,8.21)
Durateston, IM, 250 mg/4wk		-8.09(-16.37,0.19)
Gel 2.5%, 125 mg/d	Gel 2% 60 mg/d	-11.32(-21.81,-0.76)
Gel (scrotal) 2.5%, 25 mg/d		-15.57(-26.01,-5.14)
Solution 2%, 60 mg/d		-11.29(-22.04,-0.61)
Oral TU 120 mg/d		-15.44(-25.55,-5.26)
Oral TU 160 mg/d		-18.36(-26.38,-10.40)
Oral TU 120-160 mg/d		-14.08(-24.01,-4.07)
Testosterone pellets 1200 mg		-16.99(-26.76,-7.21)
IM TU 1000 mg/9 wk		-3.44(-15.22,8.28)
IM TU 1000 mg/10 wk		-14.06(-23.21,-4.99)

IM TU 1000 mg/12 wk		-11.31(-18.81,-3.79)
IM TE 100 mg/wk		-10.24(-19.18,-1.26)
IM TE 125 mg/wk		-13.00(-25.43,-0.67)
IM TE 150 mg/2wk		-7.05(-18.02,3.89)
IM TE 200 mg/2wk		-9.09(-17.56,-0.59)
IM TE 250 mg/3wk		-11.43(-20.28,-2.55)
IM TE 300 mg/3wk		-1.50(-12.41,9.29)
IM TE 50-400 mg/1-2 wk		-5.02(-17.95,7.94)
IM TC 200 mg/2 wk		-16.56(-27.65,-5.38)
IM TC 200 mg/4 wk		-18.47(-28.79,-7.99)
IM TC 250 mg/2wk		-10.03(-20.60,0.55)
Durateston, IM, 250 mg/4wk		-18.09(-28.55,-7.51)
Gel (scrotal) 2.5%, 25 mg/d	Gel 2.5%, 125 mg/d	-4.25(-11.32,2.85)
Solution 2%, 60 mg/d		0.03(-11.01,11.05)
Oral TU 120 mg/d		-4.11(-14.77,6.43)
Oral TU 160 mg/d		-7.03(-15.56,1.49)
Oral TU 120-160 mg/d		-2.75(-13.20,7.62)
Testosterone pellets 1200 mg		-5.67(-15.93,4.50)
IM TU 1000 mg/9 wk		7.88(-4.23,19.98)
IM TU 1000 mg/10 wk		-2.74(-12.35,6.74)
IM TU 1000 mg/12 wk		0.02(-8.05,8.09)
IM TE 100 mg/wk		1.08(-8.38,10.49)
IM TE 125 mg/wk		-1.68(-14.40,11.04)
IM TE 150 mg/2wk		4.27(-7.05,15.61)
IM TE 200 mg/2wk		2.23(-6.41,10.86)
IM TE 250 mg/3wk		-0.11(-9.59,9.27)
IM TE 300 mg/3wk		9.82(-1.46,21.10)
IM TE 50-400 mg/1-2 wk		6.31(-7.08,19.61)
IM TC 200 mg/2 wk		-5.24(-16.86,6.39)
IM TC 200 mg/4 wk		-7.14(-18.05,3.70)
IM TC 250 mg/2wk		1.29(-9.68,12.14)
Durateston, IM, 250 mg/4wk		-6.77(-17.77,4.17)
Solution 2%, 60 mg/d	Gel (scrotal) 2.5%, 25 mg/d	4.28(-6.76,15.29)
Oral TU 120 mg/d		0.13(-10.41,10.69)
Oral TU 160 mg/d		-2.79(-11.32,5.78)
Oral TU 120-160 mg/d		1.49(-8.95,11.85)
Testosterone pellets 1200 mg		-1.42(-11.69,8.77)
IM TU 1000 mg/9 wk		12.13(-0.05,24.28)
IM TU 1000 mg/10 wk		1.51(-8.10,11.01)
IM TU 1000 mg/12 wk		4.26(-3.85,12.36)
IM TE 100 mg/wk		5.33(-4.13,14.73)
IM TE 125 mg/wk		2.57(-10.20,15.23)

IM TE 150 mg/2wk		8.52(-2.86,19.92)
IM TE 200 mg/2wk		6.48(-2.21,15.12)
IM TE 250 mg/3wk		4.14(-5.23,13.54)
IM TE 300 mg/3wk		14.07(2.81,25.31)
IM TE 50-400 mg/1-2 wk		10.55(-2.91,23.84)
IM TC 200 mg/2 wk		-0.99(-12.60,10.58)
IM TC 200 mg/4 wk		-2.90(-13.82,8.03)
IM TC 250 mg/2wk		5.54(-5.44,16.60)
Durateston, IM, 250 mg/4wk		-2.52(-13.52,8.43)
Oral TU 120 mg/d	Solution 2%, 60 mg/d	-4.15(-14.97,6.71)
Oral TU 160 mg/d		-7.07(-15.82,1.75)
Oral TU 120-160 mg/d		-2.79(-13.42,7.91)
Testosterone pellets 1200 mg		-5.70(-16.19,4.77)
IM TU 1000 mg/9 wk		7.85(-4.39,20.17)
IM TU 1000 mg/10 wk		-2.77(-12.56,7.00)
IM TU 1000 mg/12 wk		-0.02(-8.34,8.36)
IM TE 100 mg/wk		1.05(-8.64,10.74)
IM TE 125 mg/wk		-1.71(-14.70,11.26)
IM TE 150 mg/2wk		4.24(-7.33,15.76)
IM TE 200 mg/2wk		2.20(-6.98,11.47)
IM TE 250 mg/3wk		-0.14(-9.75,9.50)
IM TE 300 mg/3wk		9.79(-1.75,21.38)
IM TE 50-400 mg/1-2 wk		6.27(-7.18,19.70)
IM TC 200 mg/2 wk		-5.27(-17.13,6.58)
IM TC 200 mg/4 wk		-7.17(-18.19,4.01)
IM TC 250 mg/2wk		1.26(-9.92,12.47)
Durateston, IM, 250 mg/4wk		-6.80(-17.95,4.39)
Oral TU 160 mg/d	Oral TU 120 mg/d	-2.92(-11.18,5.30)
Oral TU 120-160 mg/d		1.36(-8.75,11.51)
Testosterone pellets 1200 mg		-1.55(-11.47,8.35)
IM TU 1000 mg/9 wk		11.99(0.22,23.80)
IM TU 1000 mg/10 wk		1.38(-7.80,10.65)
IM TU 1000 mg/12 wk		4.13(-3.60,11.79)
IM TE 100 mg/wk		5.20(-3.98,14.29)
IM TE 125 mg/wk		2.44(-10.06,15.00)
IM TE 150 mg/2wk		8.38(-2.65,19.47)
IM TE 200 mg/2wk		6.35(-2.24,15.06)
IM TE 250 mg/3wk		4.01(-5.04,13.13)
IM TE 300 mg/3wk		13.93(2.85,24.90)
IM TE 50-400 mg/1-2 wk		10.42(-2.47,23.36)
IM TC 200 mg/2 wk		-1.13(-12.50,10.16)
IM TC 200 mg/4 wk		-3.03(-13.54,7.52)

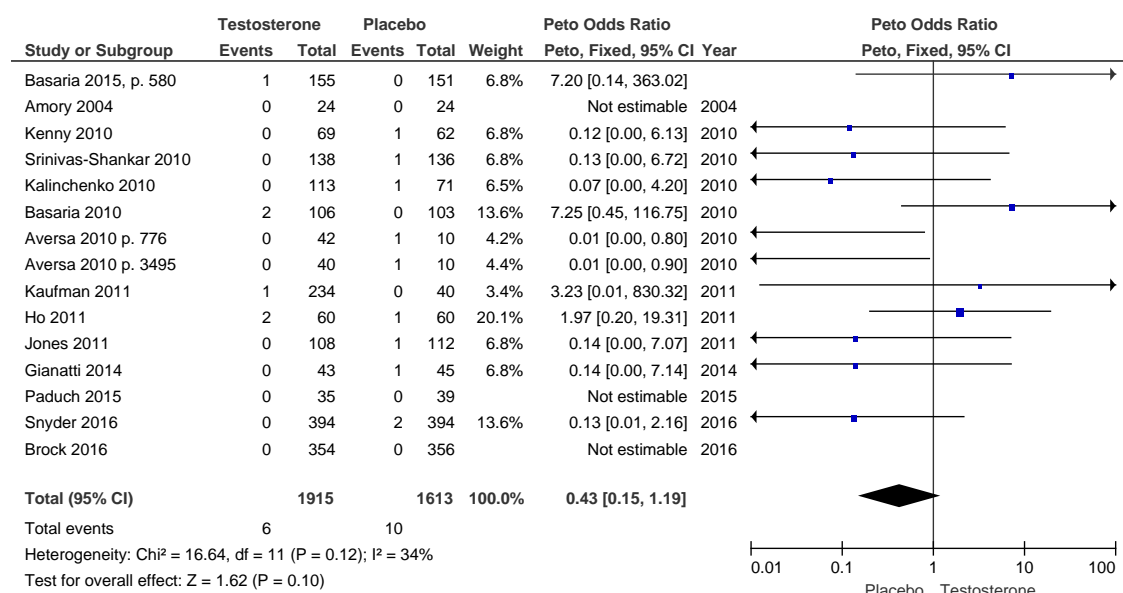
IM TC 250 mg/2wk		5.41(-5.24,16.03)
Durateston, IM, 250 mg/4wk		-2.65(-13.24,7.90)
Oral TU 120-160 mg/d	Oral TU 160 mg/d	4.28(-3.65,12.24)
Testosterone pellets 1200 mg		1.37(-5.02,7.65)
IM TU 1000 mg/9 wk		14.91(5.60,24.22)
IM TU 1000 mg/10 wk		4.30(-2.44,10.98)
IM TU 1000 mg/12 wk		7.05(2.88,11.22)
IM TE 100 mg/wk		8.12(1.58,14.65)
IM TE 125 mg/wk		5.36(-5.44,16.14)
IM TE 150 mg/2wk		11.30(2.17,20.50)
IM TE 200 mg/2wk		9.27(3.31,15.24)
IM TE 250 mg/3wk		6.93(1.62,12.24)
IM TE 300 mg/3wk		16.85(7.78,25.85)
IM TE 50-400 mg/1-2 wk		13.34(1.90,24.69)
IM TC 200 mg/2 wk		1.79(-7.65,11.19)
IM TC 200 mg/4 wk		-0.11(-8.45,8.32)
IM TC 250 mg/2wk		8.33(-0.32,16.90)
Durateston, IM, 250 mg/4wk		0.27(-8.25,8.73)
Testosterone pellets 1200 mg	Oral TU 120-160 mg/d	-2.91(-12.66,6.81)
IM TU 1000 mg/9 wk		10.63(-1.05,22.19)
IM TU 1000 mg/10 wk		0.02(-8.97,9.02)
IM TU 1000 mg/12 wk		2.77(-4.70,10.19)
IM TE 100 mg/wk		3.83(-5.07,12.72)
IM TE 125 mg/wk		1.08(-11.31,13.34)
IM TE 150 mg/2wk		7.02(-3.93,18.04)
IM TE 200 mg/2wk		4.99(-3.53,13.53)
IM TE 250 mg/3wk		2.65(-6.16,11.47)
IM TE 300 mg/3wk		12.57(1.68,23.38)
IM TE 50-400 mg/1-2 wk		9.06(-3.94,21.88)
IM TC 200 mg/2 wk		-2.49(-13.64,8.66)
IM TC 200 mg/4 wk		-4.39(-14.76,6.03)
IM TC 250 mg/2wk		4.05(-6.43,14.57)
Durateston, IM, 250 mg/4wk		-4.02(-14.52,6.43)
IM TU 1000 mg/9 wk	Testosterone pellets 1200 mg	13.55(3.98,23.17)
IM TU 1000 mg/10 wk		2.93(-5.76,11.79)
IM TU 1000 mg/12 wk		5.68(-1.39,12.77)
IM TE 100 mg/wk		6.75(-1.86,15.41)
IM TE 125 mg/wk		3.99(-8.13,16.03)
IM TE 150 mg/2wk		9.93(-0.73,20.72)
IM TE 200 mg/2wk		7.90(-0.28,16.12)
IM TE 250 mg/3wk		5.56(-0.16,11.31)
IM TE 300 mg/3wk		15.48(4.84,26.11)

IM TE 50-400 mg/1-2 wk		11.97(-0.87,24.56)
IM TC 200 mg/2 wk		0.43(-10.60,11.33)
IM TC 200 mg/4 wk		-1.48(-11.65,8.68)
IM TC 250 mg/2wk		6.96(-3.27,17.22)
Durateston, IM, 250 mg/4wk		-1.10(-11.31,9.12)
IM TU 1000 mg/10 wk	IM TU 1000 mg/9 wk	-10.62(-21.47,0.34)
IM TU 1000 mg/12 wk		-7.87(-17.42,1.71)
IM TE 100 mg/wk		-6.80(-17.58,3.97)
IM TE 125 mg/wk		-9.56(-23.43,4.23)
IM TE 150 mg/2wk		-3.61(-16.13,8.87)
IM TE 200 mg/2wk		-5.65(-16.09,4.77)
IM TE 250 mg/3wk		-7.99(-15.63,-0.43)
IM TE 300 mg/3wk		1.94(-10.58,14.38)
IM TE 50-400 mg/1-2 wk		-1.57(-15.93,12.57)
IM TC 200 mg/2 wk		-13.12(-25.76,-0.50)
IM TC 200 mg/4 wk		-15.02(-27.02,-2.97)
IM TC 250 mg/2wk		-6.59(-18.64,5.51)
Durateston, IM, 250 mg/4wk		-14.65(-26.65,-2.55)
IM TU 1000 mg/12 wk	IM TU 1000 mg/10 wk	2.75(-3.39,8.87)
IM TE 100 mg/wk		3.82(-4.02,11.63)
IM TE 125 mg/wk		1.06(-10.55,12.59)
IM TE 150 mg/2wk		7.00(-3.13,17.12)
IM TE 200 mg/2wk		4.97(-2.38,12.33)
IM TE 250 mg/3wk		2.63(-5.20,10.43)
IM TE 300 mg/3wk		12.55(2.61,22.50)
IM TE 50-400 mg/1-2 wk		9.04(-3.15,21.15)
IM TC 200 mg/2 wk		-2.51(-12.86,7.88)
IM TC 200 mg/4 wk		-4.41(-13.89,5.12)
IM TC 250 mg/2wk		4.03(-5.67,13.61)
Durateston, IM, 250 mg/4wk		-4.03(-13.63,5.52)
IM TE 100 mg/wk	IM TU 1000 mg/12 wk	1.07(-4.91,7.00)
IM TE 125 mg/wk		-1.69(-12.18,8.70)
IM TE 150 mg/2wk		4.25(-4.40,13.04)
IM TE 200 mg/2wk		2.22(-3.10,7.50)
IM TE 250 mg/3wk		-0.12(-5.92,5.72)
IM TE 300 mg/3wk		9.80(1.20,18.32)
IM TE 50-400 mg/1-2 wk		6.29(-4.89,17.26)
IM TC 200 mg/2 wk		-5.26(-14.26,3.76)
IM TC 200 mg/4 wk		-7.16(-14.34,0.12)
IM TC 250 mg/2wk		1.28(-6.89,9.44)
Durateston, IM, 250 mg/4wk		-6.78(-14.19,0.56)
IM TE 125 mg/wk	IM TE 100 mg/wk	-2.76(-14.21,8.71)

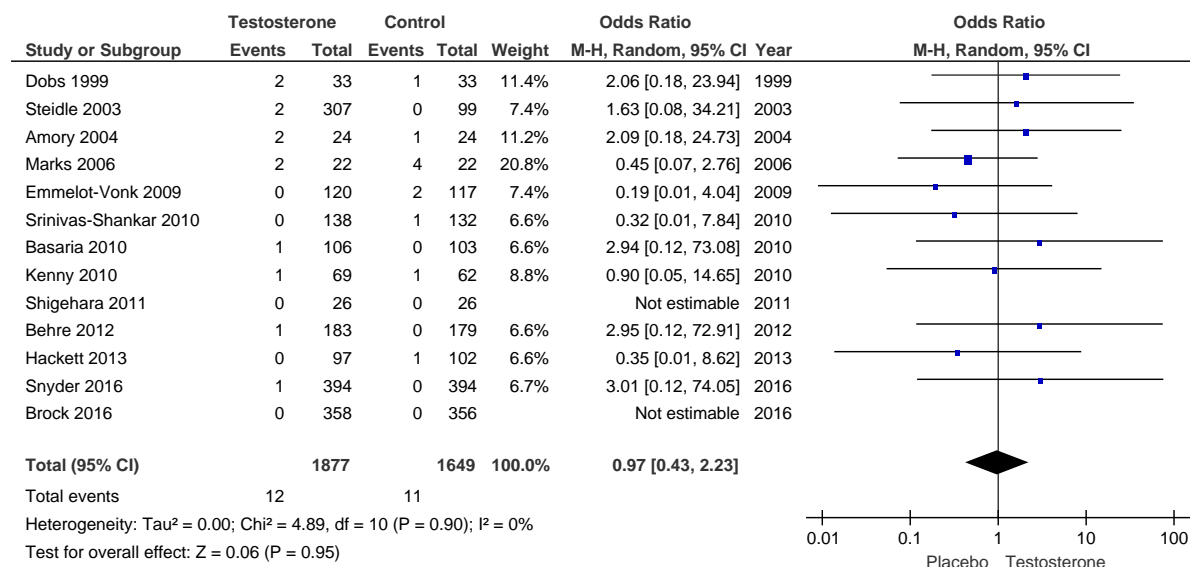
IM TE 150 mg/2wk		3.19(-6.80,13.17)
IM TE 200 mg/2wk		1.15(-6.03,8.28)
IM TE 250 mg/3wk		-1.19(-8.76,6.47)
IM TE 300 mg/3wk		8.74(-1.14,18.58)
IM TE 50-400 mg/1-2 wk		5.22(-6.94,17.26)
IM TC 200 mg/2 wk		-6.32(-16.59,3.99)
IM TC 200 mg/4 wk		-8.22(-17.53,1.14)
IM TC 250 mg/2wk		0.21(-9.33,9.74)
Durateston, IM, 250 mg/4wk		-7.85(-17.40,1.61)
IM TE 150 mg/2wk	IM TE 125 mg/wk	5.95(-7.16,19.13)
IM TE 200 mg/2wk		3.91(-7.29,15.04)
IM TE 250 mg/3wk		1.57(-9.82,13.12)
IM TE 300 mg/3wk		11.50(-1.54,24.55)
IM TE 50-400 mg/1-2 wk		7.98(-6.80,22.76)
IM TC 200 mg/2 wk		-3.56(-16.94,9.75)
IM TC 200 mg/4 wk		-5.47(-18.14,7.27)
IM TC 250 mg/2wk		2.97(-9.79,15.85)
Durateston, IM, 250 mg/4wk		-5.09(-17.80,7.77)
IM TE 200 mg/2wk	IM TE 150 mg/2wk	-2.04(-11.66,7.57)
IM TE 250 mg/3wk		-4.38(-14.31,5.56)
IM TE 300 mg/3wk		5.55(-6.15,17.34)
IM TE 50-400 mg/1-2 wk		2.04(-11.74,15.72)
IM TC 200 mg/2 wk		-9.51(-21.66,2.54)
IM TC 200 mg/4 wk		-11.41(-22.70,0.00)
IM TC 250 mg/2wk		-2.98(-14.42,8.45)
Durateston, IM, 250 mg/4wk		-11.04(-22.52,0.42)
IM TE 250 mg/3wk	IM TE 200 mg/2wk	-2.34(-9.48,4.87)
IM TE 300 mg/3wk		7.59(-1.89,17.04)
IM TE 50-400 mg/1-2 wk		4.07(-7.82,15.86)
IM TC 200 mg/2 wk		-7.47(-17.31,2.38)
IM TC 200 mg/4 wk		-9.37(-18.42,-0.35)
IM TC 250 mg/2wk		-0.94(-9.99,8.19)
Durateston, IM, 250 mg/4wk		-9.00(-18.14,0.03)
IM TE 300 mg/3wk	IM TE 250 mg/3wk	9.93(0.08,19.73)
IM TE 50-400 mg/1-2 wk		6.41(-5.72,18.40)
IM TC 200 mg/2 wk		-5.13(-15.34,5.05)
IM TC 200 mg/4 wk		-7.04(-16.28,2.31)
IM TC 250 mg/2wk		1.40(-8.03,10.77)
Durateston, IM, 250 mg/4wk		-6.66(-16.10,2.75)
IM TE 50-400 mg/1-2 wk	IM TE 300 mg/3wk	-3.51(-17.11,9.98)
IM TC 200 mg/2 wk		-15.06(-26.99,-3.12)
IM TC 200 mg/4 wk		-16.96(-28.18,-5.70)

IM TC 250 mg/2wk		-8.53(-19.81,2.78)
Durateston, IM, 250 mg/4wk		-16.59(-27.91,-5.27)
IM TC 200 mg/2 wk	IM TE 50-400 mg/1-2 wk	-11.55(-25.33,2.34)
IM TC 200 mg/4 wk		-13.45(-26.71,-0.08)
IM TC 250 mg/2wk		-5.01(-18.35,8.45)
Durateston, IM, 250 mg/4wk		-13.07(-26.35,0.29)
IM TC 200 mg/4 wk	IM TC 200 mg/2 wk	-1.90(-13.46,9.66)
IM TC 250 mg/2wk		6.53(-5.16,18.17)
Durateston, IM, 250 mg/4wk		-1.53(-13.18,10.07)
IM TC 250 mg/2wk	IM TC 200 mg/4 wk	8.44(-2.47,19.30)
Durateston, IM, 250 mg/4wk		0.37(-6.93,7.65)
Durateston, IM, 250 mg/4wk	IM TC 250 mg/2wk	-8.06(-19.21,2.97)

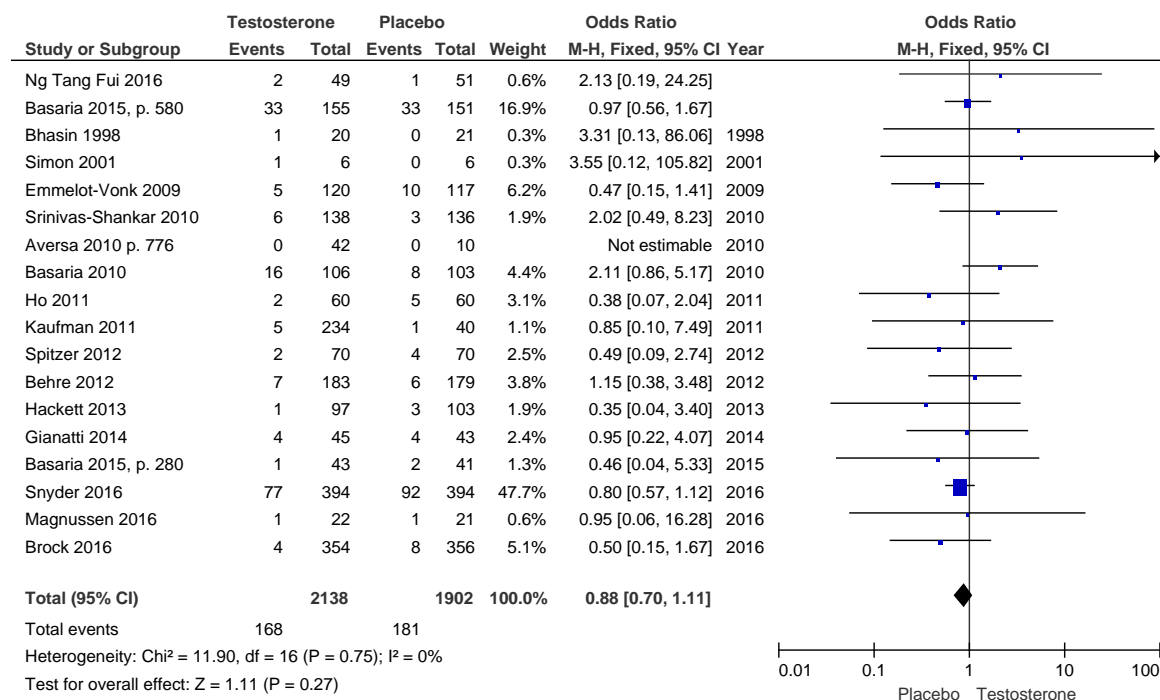
eFigure 6: Odds of myocardial infarction associated with the use of any testosterone v. placebo



eFigure 7: Odds of prostate cancer associated with the use of any testosterone v. placebo



eFigure 8: Odds of serious adverse events: any testosterone v. placebo

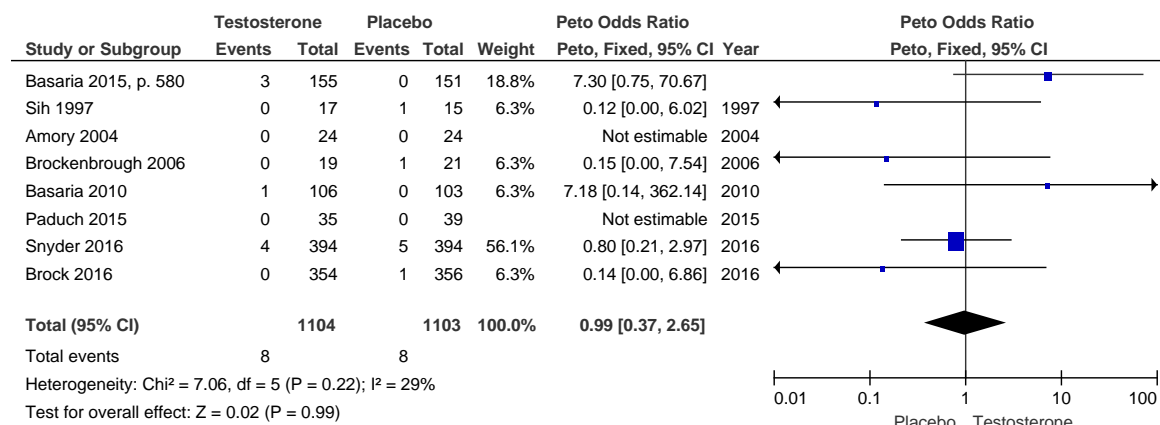
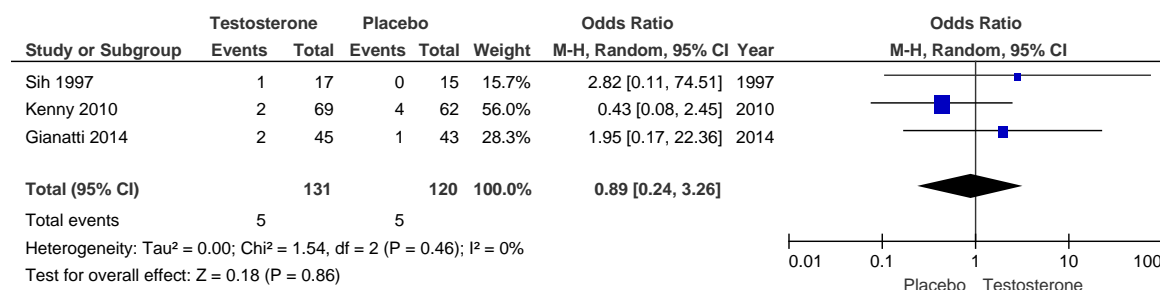
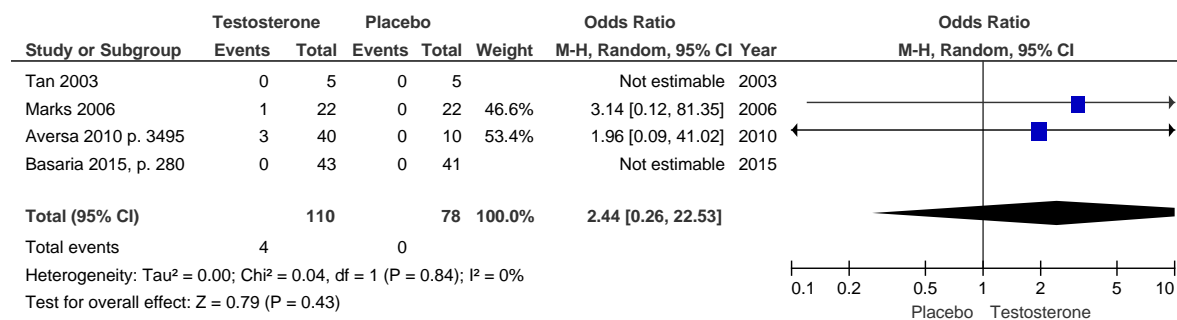


eTable 11: Odds of serious adverse events associated with individual testosterone products – Bayesian network meta-analysis

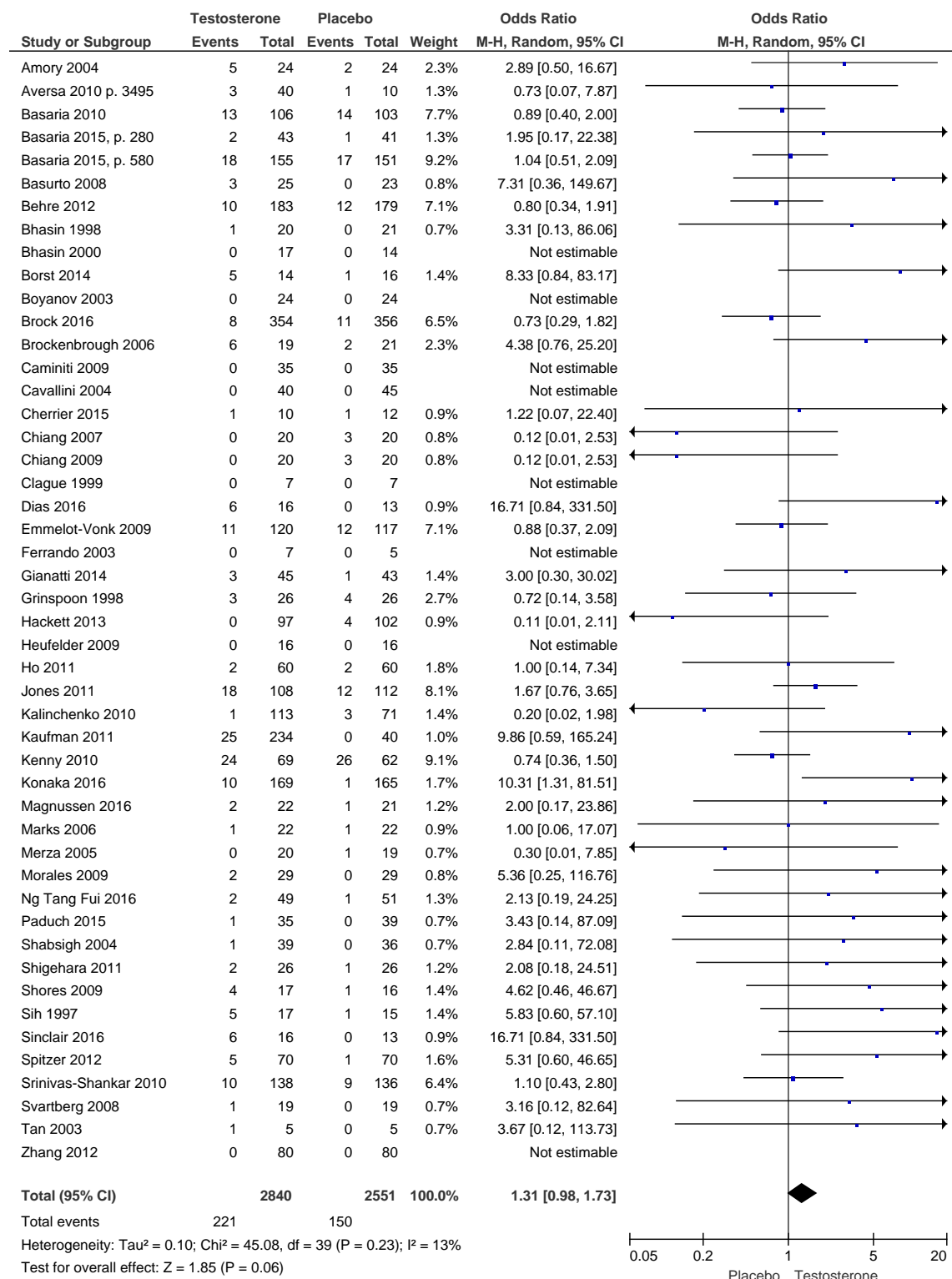
	Odds ratio (95% credible interval)*							
	Placebo	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 1.62%, 40.5 mg/d	Solution 2%, 60 mg/d	Oral TU, 160 mg/d	IM TU, 1000 mg/12 wk
Gel 1%, 50 mg/d	0.91 (0.46,2.10)	—						
Gel 1%, 75 mg/d	0.98 (0.25,3.55)	1.08 (0.21,4.42)	—					
Gel 1%, 100 mg/d	1.41 (0.39,4.06)	1.54 (0.31,5.25)	1.45 (0.23,7.53)	—				
Gel 1.62%, 40.5 mg/d	1.19 (0.11,40.82)	1.30 (0.10,48.76)	1.24 (0.09,51.17)	0.89 (0.07,35.34)	—			
Solution 2%, 60mg/d	0.47 (0.08,2.53)	0.51 (0.07,3.07)	0.48 (0.06,4.08)	0.34 (0.04,2.88)	0.38 (0.01,7.32)	—		
Oral TU 160 mg/d	0.45 (0.08,2.17)	0.49 (0.07,2.67)	0.46 (0.05,3.60)	0.32 (0.05,2.51)	0.36 (0.01,6.21)	0.94 (0.09,10.03)	—	
IM TU,1000 mg/12 wk	0.68 (0.23,1.94)	0.74 (0.18,2.56)	0.69 (0.13,3.70)	0.48 (0.11,2.55)	0.56 (0.01,7.68)	1.43 (0.20,11.31)	1.50 (0.23,10.76)	—

Note: IM = intramuscular injection, TU = testosterone undecanoate.

*Random effects model. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, while red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments. An additional 4 RCTs (Aversa 2010; Schubert 2004; Bhasin 1998; Simon 2001) could not be included in the network because they reported zero events in \geq treatment groups.

eFigure 9: Odds of stroke associated with the use of any testosterone v. placebo**eFigure 10: Odds of heart disease associated with the use of any testosterone v. placebo****eFigure 11: Odds of erythrocytosis associated with the use of any testosterone v. placebo**

eFigure 12: Odds of withdrawals due to adverse events associated with the use of any testosterone v. placebo



eTable 12: Odds of withdrawals due to adverse events associated with individual testosterone products – Bayesian network meta-analysis

	Odds ratio (95% credible interval)*																
	Placebo	Patch, 5 mg/d	Gel 1%, 5 mg/d	Gel 1%, 50 mg/d	Gel 1%, 75 mg/d	Gel 1%, 100 mg/d	Gel 2%, 60 mg/d	Solution 2%, 60 mg/d	Oral TU 160 mg/d	IM TU, 1000 mg/10 wk	IM TU, 1000 mg/12 wk	IM TE, 125 mg/ wk	IM TE, 150 mg/ 2 wk	IM TE, 200 mg/ 2 wk	IM TE, 250 mg/ 4 wk	IM TE, 300 mg/ 3 wk	IM TC, 200 mg/ 2 wk
Patch, 5 mg/d	6.82 (1.66, 32.14)	—															
Gel 1%, 5 mg/d	0.76 (0.27, 2.14)	0.11 (0.02, 0.63)	—														
Gel 1%, 50 mg/d	1.45 (0.77, 3.00)	0.21 (0.05, 0.86)	1.91 (0.59, 6.89)	—													
Gel 1%, 75 mg/d	1.30 (0.55, 3.57)	0.19 (0.03, 1.07)	1.71 (0.46, 7.48)	0.90 (0.29, 2.85)	—												
Gel 1%, 100 mg/d	1.03 (0.45, 2.40)	0.15 (0.03, 0.64)	1.36 (0.37, 5.19)	0.71 (0.25, 1.90)	0.79 (0.22, 2.61)	—											
Solution 2%, 60 mg/d	1.64 (0.57, 4.95)	0.24 (0.04, 1.42)	2.18 (0.50, 9.67)	1.14 (0.30, 3.98)	1.26 (0.28, 4.94)	1.60 (0.40, 6.12)	—										
Gel 2%, 60 mg/d	0.73 (0.21, 2.37)	0.11 (0.01, 0.67)	0.96 (0.19, 4.68)	0.50 (0.12, 1.88)	0.56 (0.11, 2.35)	0.70 (0.16, 2.93)	0.44 (0.08, 2.23)	—									
Oral TU 160 mg/d	0.87 (0.28, 2.77)	0.13 (0.02, 0.80)	1.15 (0.25, 5.43)	0.60 (0.15, 2.23)	0.67 (0.14, 2.77)	0.84 (0.20, 3.54)	0.53 (0.11, 2.61)	1.20 (0.23, 6.61)	—								
IM TU, 1000 mg/10 wk	2.14 (0.18, 33.83)	0.31 (0.02, 7.21)	2.85 (0.20, 53.28)	1.48 (0.11, 24.89)	1.64 (0.12, 28.93)	2.08 (0.16, 37.59)	1.29 (0.09, 25.16)	2.95 (0.20, 59.09)	2.47 (0.17, 49.97)	—							
IM TU, 1000 mg/12 wk	0.52 (0.21, 1.26)	0.08 (0.01, 0.40)	0.69 (0.17, 2.72)	0.36 (0.11, 1.05)	0.40 (0.10, 1.36)	0.50 (0.15, 1.68)	0.31 (0.08, 1.28)	0.72 (0.16, 3.21)	0.59 (0.14, 2.52)	0.24 (0.01, 3.42)	—						
IM TE, 125 mg/ wk	7.95 (0.97, 105.20)	1.20 (0.09, 22.88)	10.65 (1.03, 166.10)	5.47 (0.60, 77.02)	6.08 (0.60, 90.45)	7.72 (0.80, 115.20)	4.89 (0.44, 78.95)	11.35 (1.01, 179.70)	9.32 (0.83, 152.60)	3.88 (0.11, 140.30)	15.62 (1.59, 244.70)	—					

Supplemental Online Content: Elliott et al. Testosterone therapy in hypogonadal men: a systematic review and network meta-analysis.

IM TE, 150 mg/ 2 wk	1.01 (0.04, 22.84)	0.15 (0.00, 4.20)	1.34 (0.05, 34.59)	0.70 (0.03, 16.50)	0.77 (0.03, 18.63)	0.97 (0.04, 24.53)	0.62 (0.02, 17.03)	1.39 (0.05, 39.21)	1.16 (0.05, 33.97)	0.46 (0.01, 25.13)	1.95 (0.08, 49.97)	0.12 (0.00, 4.99)	—				
IM TE, 200 mg/ 2 wk	2.83 (0.49, 21.73)	0.42 (0.04, 4.94)	3.78 (0.49, 36.13)	1.96 (0.29, 16.21)	2.17 (0.28, 19.79)	2.73 (0.39, 24.40)	1.73 (0.22, 17.02)	3.93 (0.48, 41.61)	3.26 (0.40, 32.63)	1.38 (0.05, 28.67)	5.50 (0.74, 50.37)	0.35 (0.02, 6.55)	2.92 (0.08, 107.60)	—			
IM TE, 250 mg/ 4 wk	5.92 (1.43, 36.28)	0.89 (0.10, 8.37)	8.05 (1.33, 61.53)	4.12 (0.82, 27.64)	4.61 (0.77, 32.91)	5.81 (1.08, 41.07)	3.66 (0.59, 29.86)	8.31 (1.27, 72.32)	6.95 (1.08, 57.31)	2.88 (0.11, 57.41)	11.75 (2.13, 84.99)	0.75 (0.04, 11.64)	6.10 (0.20, 202.50)	2.15 (0.18, 25.19)	—		
IM TE, 300 mg/ 3 wk	0.72 (0.11, 4.20)	0.10 (0.01, 0.99)	0.93 (0.11, 7.44)	0.49 (0.06, 3.19)	0.54 (0.07, 3.89)	0.69 (0.09, 4.94)	0.43 (0.05, 3.45)	0.98 (0.10, 8.51)	0.82 (0.09, 7.04)	0.33 (0.01, 6.96)	1.38 (0.18, 10.17)	0.09 (0.00, 1.40)	0.71 (0.02, 23.91)	0.24 (0.02, 2.99)	0.12 (0.01, 1.18)	—	
IM TC, 200 mg/ 2 wk	5.77 (0.72, 76.47)	0.85 (0.06, 15.32)	7.73 (0.72, 116.20)	3.98 (0.43, 54.25)	4.37 (0.43, 64.41)	5.53 (0.60, 78.93)	3.52 (0.33, 54.96)	8.03 (0.71, 131.40)	6.60 (0.62, 104.30)	2.73 (0.09, 84.03)	11.06 (1.15, 170.30)	0.72 (0.03, 19.57)	5.92 (0.14, 282.40)	2.07 (0.10, 43.57)	0.95 (0.06, 17.27)	8.60 (0.51, 180.50)	—

Note: IM = intramuscular injection, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate.

*Random-effects model. Significant changes are indicated by use of bold and colour (green indicates that the row treatment is significantly better than the column treatment, which red indicates that the row treatment is significantly worse than the column treatment). White indicates no significant difference between treatments. An additional 23 studies (Basurto 2008, Bhasin 1998 (p. 140), Bhasin 1998 (p. 3155), Boyanov 2003, Caminiti 2009, Cavallini 2004, Chiang 2007, Chiang 2009, Clague 1999, Dobs 1999, Ferrando 2003, Hackett 2013, Heufelder 2009, Kaufman 2011, Merza 2005, Morales 2009, Schubert 2004, Shabsigh 2004, Svartberg 2008, Tan 2003, Zhang 2012, Dias 2016, Paduch 2015) were removed from the network meta-analysis because zero events were reported in one or both groups.

eTable 13: Summary of harms outcomes reported in non-randomized studies

Author, year	Population	Treatment (no. in group)	Outcome	Comments
Retrospective cohort				
Cheetham 2017	≥ 40 yr with documented androgen deficiency	<ul style="list-style-type: none"> • Ever TRT (8,808) • Never TRT (35,527) <p>Mean follow-up: 4.4 years (median 3.4 years, IQR, 1.7-6.5 years)</p>	<ul style="list-style-type: none"> • Stroke: AHR 0.64 (95% CI 0.52, 0.80) • Acute MI: AHR 0.74 (95% CI 0.63, 0.86) • CVD: AHR 0.76 (95% CI 0.61, 0.93) 	Entry into cohort was based on filling a prescription for TRT (patch 13.6%, gel 34.7%, injectable 51.6%).
Layton 2015	New users of TRT	<ul style="list-style-type: none"> • Gel (109,810) • Injection (103,555) • Patch (9,255) <p>Mean treatment duration between 96 days (patch) and 122 days (injection)</p>	<ul style="list-style-type: none"> • Injection v. gel • MI: AHR 1.64 (95% CI 0.57, 4.69) • Stroke: AHR 1.28 (0.27, 6.02) 	No significant difference in MI or stroke between injection and gel users. No data available for patch v. injection or gel users.
Pastuszak 2015	New TRT users or had been off TRT for ≥ 3 or mo	<ul style="list-style-type: none"> • Gel (1% 50–100mg/d or 1.62% 20.25–80.1 mg/d) (47) • IM TE or TC, 100–200mg/wk (57) • Pellets (75mg/3–6 mo) (74) <p>Duration: 36 mo</p>	<ul style="list-style-type: none"> • Erythrocytosis: Gel: 12.8% of patients Injection: T 66.7% Pellets: 35.1% • Prostate cancer: 1 case of prostate cancer diagnosed in pellet group. No new cases of prostate cancer among men with previous prostate cancer. 	Erythrocytosis defined as hematocrit ≥50%; Erythrocytosis occurred significantly earlier in the injection group (10.5±9.1 mo) compared with the gel (14.0±12.6 mo) or pellet (16.4 ±10.7mo) groups.
Ramasamy 2015	≥ 65 yr and ≥3 hypogonadal symptoms	<ul style="list-style-type: none"> • TRT, dose NR (153) • No TRT, dose NR (64) <p>Duration: Median follow-up 3.8 (TRT) v. 3.4 yr (TRT)</p>	<ul style="list-style-type: none"> • MI: 1 event in TRT group v. 0 in no TRT group • Stroke: 2 events in TRT v. 1 in no TRT group 	All events (except 1 death which took place after 6 months of follow-up) occurred after 2 or more years.
Vigen 2013	Men who underwent coronary angiography	<ul style="list-style-type: none"> • TRT, dose NR (1223) • No TRT (7486) <p>Mean follow-up: 840 d</p>	<ul style="list-style-type: none"> • Cardiovascular events†: AHR 1.29, 95% CI 1.04 to 1.58 	Entry into cohort was based on filling a prescription for TRT (patch, gel, or injectable). Data reported as TRT v. no TRT. Length of follow-up differed by group.
Shores 2012	> 40 yr treated at a VA medical center, inpatient or outpatient	<ul style="list-style-type: none"> • No TRT (633) • TRT (398) <p>Duration: 20.2 mo</p>	<ul style="list-style-type: none"> • Prostate cancer: No treatment: 13/633 men; TRT: 7/398 men 	Data reported as TRT v. no TRT. TRTs included injectable, patch, or gel.
Rhoden 2006	Negative prostate biopsy prior to starting TRT	<ul style="list-style-type: none"> • IM testosterone, dose and type NR (33) • Gel 1%, dose NR (25) <p>Duration: 12 mo</p>	<ul style="list-style-type: none"> • Prostate cancer: 1 case in the IM group 	
Guay 2000	Men with ED and primary or secondary hypogonadism	<ul style="list-style-type: none"> • IM TE, 200–300 mg/2–3 wk (25) • Patch, 5 mg/d (16) 	<ul style="list-style-type: none"> • Prostate cancer: 3 cases (NR to which treatment group the patients belonged) 	

Duration: 2–3 mo				
Prospective cohort				
Debruyne 2017	≥18 yr with a diagnosis of hypogonadism	<ul style="list-style-type: none"> • TRT, dose NR (750) • No TRT (249) Duration: 36 mo (23,900 person-mo)	<ul style="list-style-type: none"> • Prostate cancer: incidence rate ratio 0.52 (95% CI 0.22 to 1.26) 	68% of TRT users received topical gels, 31% injectables, and 2% oral products
Traish 2017	Symptoms of hypogonadism	<ul style="list-style-type: none"> • TU, 1000mg/12wk (360) • No TRT (296) Median follow-up: 7 yr	<ul style="list-style-type: none"> • CVD: 0 in TU group v. 19 in no TRT group • Nonfatal MI: 0 in TU group v. 26 in no TRT group • Nonfatal stroke: 0 in TU group v. 30 in no TRT group • Prostate cancer: 7 in TU group v. 12 in no TRT group 	CVD in no TRT group attributed to MI (5), stroke (4), heart failure (7), thromboembolism (2), lung embolism (1), and pneumonia and lung failure (1)
Yassin 2017	Treated or untreated hypogonadal men	<ul style="list-style-type: none"> • TRT, dose NR (42) • No treatment (162) Duration: 6 yr	<ul style="list-style-type: none"> • Prostate cancer: 7 (16.7%) in TRT group vs. 84 (51.9%) in untreated group 	Data reported as a positive biopsy for prostate cancer; lower severity of prostate cancer in terms of staging and grading in the TRT group than in the untreated group
Jung 2016	Symptoms of hypogonadism	<ul style="list-style-type: none"> • TU, 1000 mg/3 mo + lifestyle modification (54) • Lifestyle modification (52) Treatment duration: 8 mo	<ul style="list-style-type: none"> • Prostate cancer: 0 in both groups • MI: 0 in both groups • Stroke: 0 in both groups 	Prospective, controlled study
Francomano 2014	Severely obese men (mean BMI 42) with ≥ 2 symptoms of hypogonadism	<ul style="list-style-type: none"> • DPE (12) • DPE + IM TU, 1000 mg/12 wk (12) Duration: 54 wk + 24 wk observational period following withdrawal of treatment	<ul style="list-style-type: none"> • WAE: zero in both groups • SAE: zero in both groups 	
Aydogdu 2013	IHH	<ul style="list-style-type: none"> • Sustanon, 250 mg/3wk (28) • Gel 1%, 50 mg/d (24) Duration: 24 wk	<ul style="list-style-type: none"> • SAE: zero in all groups 	
Blick 2013	HIV/AIDS	<ul style="list-style-type: none"> • Androgel 1%, gel, 50 mg/d (92) • Testim 1%, gel, 50 mg/d (75) Duration: 12 mo	<ul style="list-style-type: none"> • Erythrocytosis: zero in both groups • Prostate cancer: zero in both groups • WAE: zero in both groups 	
Aversa 2012	Middle-aged men with LOH and MetS	<ul style="list-style-type: none"> • No treatment (20) • IM TU, 12 wk (40) Duration: 36 mo	<ul style="list-style-type: none"> • MI: 1 in control group • Erythrocytosis: 4 in TU group 	
Wang 2004	19–68 yr	<ul style="list-style-type: none"> • Gel 1%, 50 mg/d (NR) • Gel 1%, 75 mg/d (NR) • Gel 1%, 100 mg/d (NR) Total: 163 men Duration: 36 mo†	<ul style="list-style-type: none"> • Prostate cancer: 1 in 75 mg/d group, 2 in 100 mg/d group • Skin reactions: 12 men 	

Hajjar 1997	Elderly men	<ul style="list-style-type: none"> • No treatment (27) • IM TE or TC 200mg/2-3 wk (45) <p>Duration: at least 2 yr</p>	<ul style="list-style-type: none"> • Myocardial infarction: 1 in TRT group • Stroke: No treatment: 1/23; TRT: 1/26 • Diabetes: No treatment: 0/23; TRT: 1/26 • Erythrocytosis¶: No treatment: 0/27; TRT: 11/45 	Safety outcomes were reported based on a subset of people assigned to each group
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Note: AHR = adjusted hazard ratio, DPE = diet plus exercise, ED = erectile dysfunction, IHH = idiopathic hypogonadotropic hypogonadism, IM = intramuscular injection, LOH = late-onset hypogonadism, MetS = metabolic syndrome, MI = myocardial infarction, NR = not reported, SAE = serious adverse event, TC = testosterone cypionate, TE = testosterone enanthate, TU = testosterone undecanoate, TRT = testosterone replacement therapy, T = testosterone, VA = Veterans Affairs, WAE = withdrawal due to adverse events.

†Composite outcome of all-cause mortality, myocardial infarction, and ischemic stroke. MI, stroke and CV death were also reported separately; however the length of observation time differed between groups.

‡ This study was completed after an initial 6-month randomized study for an additional 36 months; participants had a total of 42 months of gel exposure.

¶ Reported as polycythemia for the treatment group. Zero count inferred for the control group.