Clinical Panel meeting date: 17 May 23

Paper Title: URN 1927 Literature Surveillance Report

Request

Clinical Panel is requested to consider the literature surveillance report findings and advise whether an updated evidence review should be commissioned from NICE.

Literature surveillance report

NICE prepared an evidence review “Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria" on behalf of NHS England Specialised Commissioning in 2020. Literature surveillance was requested to identify relevant studies published subsequently.

The bibliographic search strategies for this evidence review were performed in July 2020. These were re-run to capture literature published after this time to April 2023. In total, 358 references were identified across all databases. (Appendix A)

Following de-duplication, 256 unique references remained which were screened against the details in the PICO table (Appendix B) using their titles and abstracts. There were 54 references requested in full text for assessment against the details in the PICO table. (Appendix C)

Of the 54 full texts assessed:

- 45 studies are not relevant: (Appendix D)
    - 3 studies are unobtainable in full text.
    - 5 studies were already identified in the NICE evidence review.
    - 37 studies are not relevant according to the PICO details.

- 9 are relevant according to the PICO details: (Appendix E)
    - Table 4 provides details of 7 studies meeting the PICO details but that are unlikely to materially affect the conclusions of the NICE evidence review.
    - Table 5 provides details of 2 studies that meet the PICO details and may materially affect the conclusions of the NICE evidence review.

The terminology used in Appendix E to describe studies is that used by study authors.

Appendix A Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched in April 2023, where possible limiting the search to papers published in English language, to publication from 2020 onwards and to excluding conference abstracts and letters.

Database: MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily

Platform: Ovid
Version: Ovid MEDLINE(R) < 1946 to April 18, 2023 >
Search date: 18/4/2023
Number of results retrieved: 111
Search strategy:

1 Gender Dysphoria/
2 Gender Identity/
3 "Sexual and Gender Disorders"/
4 Transsexualism/
5 Transgender Persons/
6 Health Services for Transgender Persons/
7 exp Sex Reassignment Procedures/
8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw.
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw.
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw.
12 (male-to-female or m2f or female-to-male or f2m).tw.
13 or/1-12
14 exp Infant/ or Infant Health/ or Infant Welfare/
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn.
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/
17 Minors/
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn.
19 exp pediatrics/ (
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn.
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/
22 Puberty/
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
24 Schools/
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn.
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab.

28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab.
29 or/14-28
30 13 and 29
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
32 30 or 31
33 Gonadotropin-Releasing Hormone/
34 (pubert* adj3 block*).ti,ab.
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab.
36 (GnRH adj2 analog*).ti,ab.
37 GnRH*.ti,ab.
38 "GnRH agonist*".ti,ab.
39 Triptorelin Pamoate/
40 triptorelin.ti,ab.
41 arvekap.ti,ab.
42 ("AY 25650" or AY25650).ti,ab.
43 ("BIM 21003" or BIM21003).ti,ab.
44 ("BN 52014" or BN52014).ti,ab.
45 ("CL 118532" or CL118532).ti,ab.
46 Debio.ti,ab.
47 diphereline.ti,ab.
48 moapar.ti,ab.
49 pamorelin.ti,ab.
50 trelstar.ti,ab.
51 triptodur.ti,ab.
52 ("WY 42422" or WY42422).ti,ab.
53 ("WY 42462" or WY42462).ti,ab.
54 gonapeptyl.ti,ab.
55 decapeptyl.ti,ab.
56 salvacyl.ti,ab.
57 Buserelin/
58 buserelin.ti,ab.
59 bigonist.ti,ab.
60 ("hoe 766" or hoe-766 or hoe766).ti,ab.
61 profact.ti,ab.
62 receptal.ti,ab.
63 suprecur.ti,ab.
64 suprefact.ti,ab.
65 tiloryth.ti,ab.
66 histrelin.ti,ab.
67 "LHRH-hydrogel implant".ti,ab.
68 ("RL 0903" or RL0903).ti,ab.
69 ("SPD 424" or SPD424).ti,ab.
70 goserelin.ti,ab.
71 Goserelin/
72 ("ici 118630" or ici118630).ti,ab.
73 ("ZD-9393" or ZD9393).ti,ab.
74 zoladex.ti,ab.

75 leuprorelin.ti,ab.
76 carcinil.ti,ab.
77 enanton*.ti,ab.
78 ginecrin.ti,ab.
79 leuplin.ti,ab.
80 Leuprolide/
81 leuprolide.ti,ab.
82 lucrin.ti,ab.
83 lupron.ti,ab.
84 provren.ti,ab.
85 procrin.ti,ab.
86 ("tap 144" or tap144).ti,ab.
87 (a-43818 or a43818).ti,ab.
88 Trenantone.ti,ab.
89 staladex.ti,ab.
90 prostap.ti,ab.
91 Nafarelin/
92 nafarelin.ti,ab.
93 ("76932-56-4" or "76932564").ti,ab.
94 ("76932-60-0" or "76932600").ti,ab.
95 ("86220-42-0" or "86220420").ti,ab.
96 ("rs 94991 298" or rs94991298).ti,ab.
97 synarel.ti,ab.
98 deslorelin.ti,ab.
99 gonadorelin.ti,ab.
100 ("33515-09-2" or "33515092").ti,ab.
101 ("51952-41-1" or "51952411").ti,ab.
102 ("52699-48-6" or "52699486").ti,ab.
103 cetrorelix.ti,ab.
104 cetrotide.ti,ab.
105 ("NS 75A" or NS75A).ti,ab.
106 ("NS 75B" or NS75B).ti,ab.
107 ("SB 075" or SB075).ti,ab.
108 ("SB 75" or SB75).ti,ab.
109 gonadoliberin.ti,ab.
110 kryptocur.ti,ab.
111 cetrorelix.ti,ab.
112 cetrotide.ti,ab.
113 antagon.ti,ab.
114 ganirelix.ti,ab.
115 ("ORG 37462" or ORG37462).ti,ab.
116 orgalutran.ti,ab.
117 ("RS 26306" or RS26306).ti,ab.
118 ("AY 24031" or AY24031).ti,ab.
119 factrel.ti,ab.
120 fertagyl.ti,ab.
121 lutrelef.ti,ab.
122 lutrepulse.ti,ab.

123 relefact.ti,ab.
124 fertiral.ti,ab.
125 (hoe471 or "hoe 471").ti,ab.
126 relisorm.ti,ab.
127 cystorelin.ti,ab.
128 dirigestran.ti,ab.
129 or/33-128
130 32 and 129
131 limit 130 to english language
132 limit 131 to (letter or historical article or comment or editorial or news or case reports)
133 131 not 132
134 animals/ not humans/
135 133 not 134
136 limit 135 to yr="2020 -Current"

Database: Embase

Platform: Ovid
Version: Embase < 1974 to 2023 April 18>
Search date: 18/4/2023
Number of results retrieved: 195
Search strategy:

1 exp Gender Dysphoria/
2 Gender Identity/
3 "Sexual and Gender Disorders"/
4 Transsexualism/
5 exp Transgender/
6 Health Services for Transgender Persons/
7 exp Sex Reassignment Procedures/ or sex transformation/
8 (gender* adj3 (dysphori* or affirm* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw.
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw.
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw.
12 (male-to-female or m2f or female-to-male or f2m).tw.
13 or/1-12
14 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn.
16 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn.
17 exp pediatrics/
18 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn.
19 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/
20 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.

21 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn.
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab.
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab.
25 or/14-24
26 13 and 25
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
28 26 or 27
29 gonadorelin/
30 (pubert* adj3 block*).ti,ab.
31 ((gonadotrophin or gonadotropin) and releasing).ti,ab.
32 (GnRH adj2 analog*).ti,ab.
33 GnRH*.ti,ab.
34 "GnRH agonist*".ti,ab.
35 exp gonadorelin agonist/ or gonadorelin derivative/ or gonadorelin acetate/
36 Triptorelin/
37 triptorelin.ti,ab.
38 arvekap.ti,ab.
39 ("AY 25650" or AY25650).ti,ab.
40 ("BIM 21003" or BIM21003).ti,ab.
41 ("BN 52014" or BN52014).ti,ab.
42 ("CL 118532" or CL118532).ti,ab.
43 Debio.ti,ab.
44 diphereline.ti,ab.
45 moapar.ti,ab.
46 pamorelin.ti,ab.
47 trelstar.ti,ab.
48 triptodur.ti,ab.
49 ("WY 42422" or WY42422).ti,ab.
50 ("WY 42462" or WY42462).ti,ab.
51 gonapeptyl.ti,ab.
52 decapeptyl.ti,ab.
53 salvacyl.ti,ab.
54 buserelin acetate/ or buserelin/
55 buserelin.ti,ab.
56 bigonist.ti,ab.
57 ("hoe 766" or hoe-766 or hoe766).ti,ab.
58 profact.ti,ab.
59 receptal.ti,ab.
60 suprecur.ti,ab.
61 suprefact.ti,ab.
62 tiloryth.ti,ab.
63 histrelin/

64 histrelin.ti,ab.
65 "LHRH-hydrogel implant".ti,ab.
66 ("RL 0903" or RL0903).ti,ab.
67 ("SPD 424" or SPD424).ti,ab.
68 goserelin.ti,ab.
69 Goserelin/
70 ("ici 118630" or ici118630).ti,ab.
71 ("ZD-9393" or ZD9393).ti,ab.
72 zoladex.ti,ab.
73 leuprorelin/
74 leuprorelin.ti,ab.
75 carcinil.ti,ab.
76 enanton*.ti,ab.
77 ginecrin.ti,ab.
78 leuplin.ti,ab.
79 leuprolide.ti,ab.
80 lucrin.ti,ab.
81 lupron.ti,ab.
82 provren.ti,ab.
83 procrin.ti,ab.
84 ("tap 144" or tap144).ti,ab.
85 (a-43818 or a43818).ti,ab.
86 Trenantone.ti,ab.
87 staladex.ti,ab.
88 prostap.ti,ab.
89 nafarelin acetate/ or nafarelin/
90 nafarelin.ti,ab.
91 ("76932-56-4" or "76932564").ti,ab.
92 ("76932-60-0" or "76932600").ti,ab.
93 ("86220-42-0" or "86220420").ti,ab.
94 ("rs 94991 298" or rs94991298).ti,ab.
95 synarel.ti,ab.
96 deslorelin/
97 deslorelin.ti,ab.
98 gonadorelin.ti,ab.
99 ("33515-09-2" or "33515092").ti,ab.
100 ("51952-41-1" or "51952411").ti,ab.
101 ("52699-48-6" or "52699486").ti,ab.
102 cetrorelix/
103 cetrorelix.ti,ab.
104 cetrotide.ti,ab.
105 ("NS 75A" or NS75A).ti,ab.
106 ("NS 75B" or NS75B).ti,ab.
107 ("SB 075" or SB075).ti,ab.
108 ("SB 75" or SB75).ti,ab.
109 gonadoliberin.ti,ab.
110 kryptocur.ti,ab.
111 cetrorelix.ti,ab.

112 cetrotide.ti,ab.
113 antagon.ti,ab.
114 ganirelix/
115 ganirelix.ti,ab.
116 ("ORG 37462" or ORG37462).ti,ab.
117 orgalutran/
118 orgalutran.ti,ab.
119 ("RS 26306" or RS26306).ti,ab.
120 ("AY 24031" or AY24031).ti,ab.
121 factrel.ti,ab.
122 fertagyl.ti,ab.
123 lutrelef.ti,ab.
124 lutrepulse.ti,ab.
125 relefact.ti,ab.
126 fertiral.ti,ab.
127 (hoe471 or "hoe 471").ti,ab.
128 relisorm.ti,ab.
129 cystorelin.ti,ab.
130 dirigestran.ti,ab.
131 or/29-130
132 28 and 131
133 limit 132 to english language
134 133 not (letter or editorial).pt.
135 134 not (conference abstract or conference paper or conference proceeding or "conference review").pt.
136 nonhuman/ not (human/ and nonhuman/)
137 135 not 136
138 limit 137 to yr="2020 -Current"
139 elsevier.cr.
140 138 and 139
141 remove duplicates from 140

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR – Issue 4 of 12, April 2023
CENTRAL – Issue 4 of 12, April 2023
Search date: 21/4/2023
Number of results retrieved: CDSR – 1; CENTRAL - 5.

#1 [mh ^"Gender Dysphoria"]
#2 [mh ^"gender identity"]
#3 [mh ^"sexual and gender disorders"]
#4 [mh ^transsexualism]
#5 [mh ^"transgender persons"]
#6 [mh ^"health services for transgender persons"]
#7 [mh "sex reassignment procedures"]

#8 (gender* NEAR/3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)):ti,ab
#9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*):ti,ab
#10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*):ti,ab
#11 ((sex or gender*) NEAR/3 (reassign* or chang* or transform* or transition*)):ti,ab
#12 (male-to-female or m2f or female-to-male or f2m):ti,ab
#13 {or #1-#12}
#14 [mh infant] or [mh ^"infant health"] or [mh ^"infant welfare"]
#15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*):ti,ab
#16 [mh child] or [mh "child behavior"] or [mh ^"child health"] or [mh ^"child welfare"]
#17 [mh ^minors]
#18 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab
#19 [mh pediatrics]
#20 (pediatric* or paediatric* or peadiatric*):ti,ab
#21 [mh ^adolescent] or [mh ^"adolescent behavior"] or [mh ^"adolescent health"]
#22 [mh ^puberty]
#23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab
#24 [mh ^schools]
#25 [mh ^"Child Day Care Centers"] or [mh nurseries] or [mh ^"schools, nursery"]
#26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab
#27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") NEAR/2 (year or years or age or ages or aged)):ti,ab
#28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") NEAR/2 (year or years or age or ages or aged)):ti,ab
#29 {or #14-#28}
#30 #13 and #29
#31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab
#32 #30 or #31
#33 [mh ^"Gonadotropin-Releasing Hormone"]
#34 (pubert* NEAR/3 block*):ti,ab
#35 ((gonadotrophin or gonadotropin) and releasing):ti,ab
#36 (GnRH NEAR/2 analog*):ti,ab
#37 GnRH*:ti,ab
#38 "GnRH agonist*":ti,ab
#39 [mh ^"Triptorelin Pamoate"]
#40 triptorelin:ti,ab
#41 arvekap:ti,ab
#42 ("AY 25650" or AY25650):ti,ab
#43 ("BIM 21003" or BIM21003):ti,ab
#44 ("BN 52014" or BN52014):ti,ab
#45 ("CL 118532" or CL118532):ti,ab
#46 Debio:ti,ab

#47 diphereline:ti,ab
#48 moapar:ti,ab
#49 pamorelin:ti,ab
#50 trelstar:ti,ab
#51 triptodur:ti,ab
#52 ("WY 42422" or WY42422):ti,ab
#53 ("WY 42462" or WY42462):ti,ab
#54 gonapeptyl:ti,ab
#55 decapeptyl:ti,ab
#56 salvacyl:ti,ab
#57 [mh ^Buserelin]
#58 Buserelin:ti,ab
#59 bigonist:ti,ab
#60 ("hoe 766" or hoe-766 or hoe766):ti,ab
#61 profact:ti,ab
#62 receptal:ti,ab
#63 suprecur:ti,ab
#64 suprefact:ti,ab
#65 tiloryth:ti,ab
#66 histrelin:ti,ab
#67 "LHRH-hydrogel implant":ti,ab
#68 ("RL 0903" or RL0903):ti,ab
#69 ("SPD 424" or SPD424):ti,ab
#70 goserelin:ti,ab
#71 [mh ^goserelin]
#72 ("ici 118630" or ici118630):ti,ab
#73 ("ZD-9393" or ZD9393):ti,ab
#74 zoladex:ti,ab
#75 leuprorelin:ti,ab
#76 carcinil:ti,ab
#77 enanton*:ti,ab
#78 ginecrin:ti,ab
#79 leuplin:ti,ab
#80 [mh ^Leuprolide]
#81 leuprolide:ti,ab
#82 lucrin:ti,ab
#83 lupron:ti,ab
#84 provren:ti,ab
#85 procrin:ti,ab
#86 ("tap 144" or tap144):ti,ab
#87 (a-43818 or a43818):ti,ab
#88 Trenantone:ti,ab
#89 staladex:ti,ab
#90 prostap:ti,ab
#91 [mh ^Nafarelin]
#92 nafarelin:ti,ab
#93 ("76932-56-4" or "76932564"):ti,ab
#94 ("76932-60-0" or "76932600"):ti,ab

#95 ("86220-42-0" or "86220420"):ti,ab
#96 ("rs 94991 298" or rs94991298):ti,ab
#97 synarel:ti,ab
#98 deslorelin:ti,ab
#99 gonadorelin:ti,ab
#100 ("33515-09-2" or "33515092"):ti,ab
#101 ("51952-41-1" or "51952411"):ti,ab
#102 ("52699-48-6" or "52699486"):ti,ab
#103 cetrorelix:ti,ab
#104 cetrotide:ti,ab
#105 ("NS 75A" or NS75A):ti,ab
#106 ("NS 75B" or NS75B):ti,ab
#107 ("SB 075" or SB075):ti,ab
#108 ("SB 75" or SB75):ti,ab
#109 gonadoliberin:ti,ab
#110 kryptocur:ti,ab
#111 cetrorelix:ti,ab
#112 cetrotide:ti,ab
#113 antagon:ti,ab
#114 ganirelix:ti,ab
#115 ("ORG 37462" or ORG37462):ti,ab
#116 orgalutran:ti,ab
#117 ("RS 26306" or RS26306):ti,ab
#118 ("AY 24031" or AY24031):ti,ab
#119 factrel:ti,ab
#120 fertagyl:ti,ab
#121 lutrelef:ti,ab
#122 lutrepulse:ti,ab
#123 relefact:ti,ab
#124 fertiral:ti,ab
#125 (hoe471 or "hoe 471"):ti,ab
#126 relisorm:ti,ab
#127 cystorelin:ti,ab
#128 dirigestran:ti,ab
#129 {or #33-#128}
#130 #32 and #129
#131 #130 with Cochrane Library publication date Between Jan 2020 and Apr 2023 in Cochrane Reviews
#132 #130
#133 "conference":pt or (clinicaltrials or trialsearch):so
#134 #132 not #133
#135 #134 with Publication Year from 2020 to 2023, in Trials

Database: HTA
Platform: CRD
Version: HTA
Search date: 21/4/2023
Number of results retrieved: 0

Search strategy:

1 MeSH DESCRIPTOR Gender Dysphoria EXPLODE ALL TREES
2 MeSH DESCRIPTOR Gender Identity EXPLODE ALL TREES
3 MeSH DESCRIPTOR Sexual and Gender Disorders EXPLODE ALL TREES
4 MeSH DESCRIPTOR Transsexualism EXPLODE ALL TREES
5 MeSH DESCRIPTOR Transgender Persons EXPLODE ALL TREES
6 MeSH DESCRIPTOR Health Services for Transgender Persons EXPLODE ALL TREES
7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES
8 ((gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)))
9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*))
10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*))
11 (((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)))
12 (male-to-female or m2f or female-to-male or f2m)
13 ((transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*))
14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) IN HTA

Database: APA PsycInfo

Search date: 25/4/2023
Number of results retrieved: 46
Search Strategy:
---
1 Gender Dysphoria/
2 Gender Identity/ (
3 Transsexualism/
4 Transgender/
5 exp Gender Reassignment/
6 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (
7 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw.
8 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
9 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw.
10 (male-to-female or m2f or female-to-male or f2m).tw.
11 or/1-10
12 exp Infant Development/
13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn.
14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child Welfare/ or Child Psychiatry/
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn.
16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn.

17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/
18 Puberty/
19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn.
20 Schools/ or exp elementary school students/ or high school students/ or junior high school students/ or middle school students/
21 Child Day Care/ or Nursery Schools/
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn.
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab.
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab.
25 or/12-24
26 11 and 25
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
28 26 or 27
29 exp Gonadotropic Hormones/
30 (pubert* adj3 block*).ti,ab.
31 ((gonadotrophin or gonadotropin) and releasing).ti,ab.
32 (GnRH adj2 analog*).ti,ab.
33 GnRH*.ti,ab.
34 "GnRH agonist*".ti,ab.
35 triptorelin.ti,ab.
36 arvekap.ti,ab.
37 ("AY 25650" or AY25650).ti,ab.
38 ("BIM 21003" or BIM21003).ti,ab.
39 ("BN 52014" or BN52014).ti,ab.
40 ("CL 118532" or CL118532).ti,ab.
41 Debio.ti,ab.
42 diphereline.ti,ab.
43 moapar.ti,ab.
44 pamorelin.ti,ab.
45 trelstar.ti,ab.
46 triptodur.ti,ab.
47 ("WY 42422" or WY42422).ti,ab.
48 ("WY 42462" or WY42462).ti,ab.
49 gonapeptyl.ti,ab.
50 decapeptyl.ti,ab.
51 salvacyl.ti,ab.
52 buserelin.ti,ab.
53 bigonist.ti,ab.
54 ("hoe 766" or hoe-766 or hoe766).ti,ab.
55 profact.ti,ab.
56 receptal.ti,ab.
57 suprecur.ti,ab.

58 suprefact.ti,ab.
59 tiloryth.ti,ab.
60 histrelin.ti,ab.
61 "LHRH-hydrogel implant".ti,ab.
62 ("RL 0903" or RL0903).ti,ab.
63 ("SPD 424" or SPD424).ti,ab.
64 goserelin.ti,ab. (30)
65 ("ici 118630" or ici118630).ti,ab.
66 ("ZD-9393" or ZD9393).ti,ab.
67 zoladex.ti,ab.
68 leuprorelin.ti,ab.
69 carcinil.ti,ab.
70 enanton*.ti,ab.
71 ginecrin.ti,ab.
72 leuplin.ti,ab.
73 leuprolide.ti,ab.
74 lucrin.ti,ab.
75 lupron.ti,ab.
76 provren.ti,ab.
77 procrin.ti,ab.
78 ("tap 144" or tap144).ti,ab.
79 (a-43818 or a43818).ti,ab.
80 Trenantone.ti,ab.
81 staladex.ti,ab.
82 prostap.ti,ab.
83 nafarelin.ti,ab.
84 ("76932-56-4" or "76932564").ti,ab.
85 ("76932-60-0" or "76932600").ti,ab.
86 ("86220-42-0" or "86220420").ti,ab.
87 ("rs 94991 298" or rs94991298).ti,ab.
88 synarel.ti,ab.
89 deslorelin.ti,ab.
90 gonadorelin.ti,ab.
91 ("33515-09-2" or "33515092").ti,ab.
92 ("51952-41-1" or "51952411").ti,ab.
93 ("52699-48-6" or "52699486").ti,ab.
94 cetrorelix.ti,ab.
95 cetrotide.ti,ab.
96 ("NS 75A" or NS75A).ti,ab.
97 ("NS 75B" or NS75B).ti,ab.
98 ("SB 075" or SB075).ti,ab.
99 ("SB 75" or SB75).ti,ab.
100 gonadoliberin.ti,ab.
101 kryptocur.ti,ab.
102 cetrorelix.ti,ab.
103 cetrotide.ti,ab.
104 antagon.ti,ab.
105 ganirelix.ti,ab.

106 ("ORG 37462" or ORG37462).ti,ab.
107 orgalutran.ti,ab.
108 ("RS 26306" or RS26306).ti,ab.
109 ("AY 24031" or AY24031).ti,ab.
110 factrel.ti,ab.
111 fertagyl.ti,ab.
112 lutrelef.ti,ab.
113 lutrepulse.ti,ab.
114 relefact.ti,ab.
115 fertiral.ti,ab.
116 (hoe471 or "hoe 471").ti,ab.
117 relisorm.ti,ab.
118 cystorelin.ti,ab.
119 dirigestran.ti,ab.
120 or/29-119
121 28 and 120
122 limit 121 to english language
123 limit 122 to yr="2020 -Current"

Appendix B PICO Document from NICE evidence review

The review questions for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   b) what were the ages at which participants commenced treatment with GnRH analogues?
   c) what was the duration of treatment with GnRH analogues?

PICO Table

P – Population and Indication	Children and adolescents aged 18 years or less who have gender dysphoria, gender identity disorder or gender incongruence of childhood as defined by study: The following subgroups of children and adolescents with gender dysphoria, gender identity disorder or gender incongruence of childhood need to be considered: • Sex assigned at birth males. • Sex assigned at birth females. • The duration of gender dysphoria: less than 6 months, 6-24 months, and more than 24 months. • The age of onset of gender dysphoria. • The age at which treatment was initiated. • The age of onset of puberty. • Tanner stage at which treatment was initiated. • Children and adolescents with gender dysphoria who have a pre-existing diagnosis of autistic spectrum disorder. • Children and adolescents with gender dysphoria who had a significant mental health symptom load at diagnosis including anxiety, depression (with or without a history of self-harm and suicidality), suicide attempts, psychosis, personality disorder, Attention Deficit Hyperactivity Disorder and eating disorders. •
I – Intervention	Any GnRH analogue including: triptorelin*; buserelin; histrelin; goserelin (Zoladex); leuprorelin/leuprolide (Prostap); nafarelin.

	* Triptorelin (brand names Gonapeptyl and Decapeptyl) are used in Leeds Hospital, England. The search should include brand names as well as generic names.
C – Comparator(s)	One or a combination of: • Psychological support. • Social transitioning to the gender with which the individual identifies. • No intervention.
O – Outcomes	There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected. **All outcomes should be stratified by:** • The age at which treatment with GnRH analogues was initiated. • The length of treatment with GnRH analogues where possible. **<u>A: Clinical Effectiveness</u>** *Critical to decision making* • **Impact on gender dysphoria** This outcome is critical because gender dysphoria in adolescents and children is associated with significant distress and problems functioning. Impact on gender dysphoria may be measured by the Utrecht Gender Dysphoria Scale. Other measures as reported in studies may be used as an alternative to the stated measure. • **Impact on mental health** Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, eating disorders, depression/low mood and anxiety. These outcomes are critical because self-harm and thoughts of suicide have the potential to result in significant physical harm and for completed suicides the death of the young person. Disordered eating habits may cause significant morbidity in young people. Depression and anxiety are also critical outcomes because they may impact on social, occupational, or other areas of functioning of children and adolescents. The Child and Adolescent Psychiatric Assessment (CAPA) may be used to measure depression and anxiety. The impact on self-harm and suicidality (ideation and behaviour) may be measured using the Suicide Ideation Questionnaire Junior. Other measures may be used as an alternative to the stated measures. • **Impact on quality of life** This outcome is critical because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Quality of Life may be measured by the KINDL questionnaire, Kidscreen 52. Other measures as reported in studies may be used as an alternative to the stated measure. *Important to decision making* • **Impact on body image** This outcome is important because some transgender young people may desire to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. The Body Image Scale could be used as a measure. Other measures

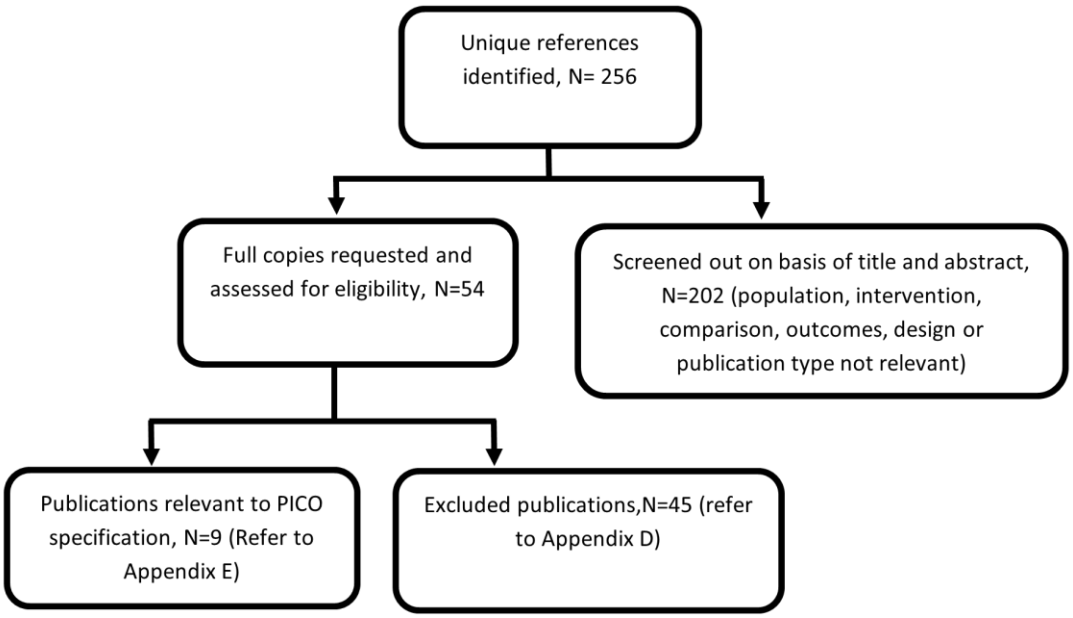
	as reported in studies may also be used as an alternative to the stated measure. • **Psychosocial impact** Examples of psychosocial impact are: coping mechanisms which may impact on substance misuse; family relationships; peer relationships. This outcome is important because gender dysphoria in adolescents and children is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning. The child behavioural check list (CBCL) may be used to measure the impact on psychosocial functioning. Other measures as reported in studies may be used as an alternative to the stated measure. • **Engagement with health care services** This outcome is important because patient engagement with healthcare services will impact on their clinical outcomes. Engagement with health care services may be measured using the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) questionnaire. Loss to follow up should also be ascertained as part of this outcome. Alternative measures to the YHC-SUN questionnaire may be used as reported in studies. • **Transitioning surgery – Impact on extent of and satisfaction with surgery** This outcome is important because some children and adolescents with gender dysphoria may proceed to transitioning surgery. Stated measures of the extent of transitioning surgery and satisfaction with surgery in studies may be reported. • **Stopping treatment** The proportion of patients who stop treatment with GnRH analogues and the reasons why. This outcome is important to patients because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents being treated for gender dysphoria. **B: Safety** • Short and long-term safety and adverse effects of taking GnRH analogues are important because GnRH analogues are not licensed for the treatment of adolescents and children with gender dysphoria. Aspects to be reported on should include: o Impact of the drug use such as its impact on bone density, arterial hypertension, cognitive development/functioning o Impact of withdrawing the drug such as, slipped upper femoral epiphysis, reversibility on the reproductive system, and any others as reported. **C: Cost effectiveness** Cost effectiveness studies should be reported.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.

Language	English only
Patients	Human studies only
Age	18 years or less
Date limits	2000-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints
Study design	Case reports, resource utilisation studies

Appendix C Evidence selection

The literature searches identified 257 unique references. These were screened using their titles and abstracts and 54 references were obtained and assessed for relevance. Of these, 9 references meet the PICO details and are listed in Appendix E. The remaining 45 references were excluded and are listed in Appendix D.

Figure 1 – Study selection flow diagram



Appendix D Excluded studies

Table 1 Unobtainable references

Study reference	Reason
Grimstad, F.W., Knoll, M.M. and Jacobson, J.D. (2021) "Oxandrolone use in trans-masculine youth appears to increase adult height: Preliminary evidence," *LGBT Health*, 8(4), pp. 300–306. Available at: https://doi.org/10.1089/lgbt.2020.0355.	Unavailable from British Library because of copyright restrictions
Waldner, R.C. *et al.* (2023) "Leuprolide acetate and QTC interval in gender-diverse youth," *Transgender Health*, 8(1), pp. 84–88. Available at: https://doi.org/10.1089/trgh.2021.0102.	Unavailable from British Library because of copyright restrictions
Lavender R, Shaw S, Maninger JK, Butler G, Carruthers P, Carmichael P, Masic U. Impact of Hormone Treatment on Psychosocial Functioning in Gender-Diverse Young People. LGBT Health. 2023 Mar 28. doi: 10.1089/lgbt.2022.0201. Epub ahead of print. PMID: 36989498.	Requested but not received from British Library at 11 May 23

Table 2 Studies already identified in NICE evidence review

Study reference	Included or excluded from evidence review
Achille, C. *et al.* (2020) "Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results," *International Journal of Pediatric Endocrinology*, 2020(1). Available at: https://doi.org/10.1186/s13633-020-00078-2.	Excluded study
Brik, T. *et al.* (2020) "Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria," *Archives of Sexual Behavior*, 49(7), pp. 2611–2618. Available at: https://doi.org/10.1007/s10508-020-01660-8.	Included study
Ghelani, R. *et al.* (2019) "Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria," *Journal of Pediatric Endocrinology and Metabolism*, 33(1), pp. 107–112. Available at: https://doi.org/10.1515/jpem-2019-0045.	Excluded study
Klaver, M. *et al.* (2020) "Hormonal treatment and cardiovascular risk profile in transgender adolescents," *Pediatrics*, 145(3). Available at: https://doi.org/10.1542/peds.2019-0741. https://doi.org/10.1542/peds.2021-049940.	Excluded study
Turban, J.L. *et al.* (2020) "Pubertal suppression for transgender youth and risk of suicidal ideation," *Pediatrics*, 145(2). Available at: https://doi.org/10.1542/peds.2019-1725.	Excluded study

Table 3 Studies that do not meet the PICO details

Study reference	Reason for exclusion
Alaniz, V.I. *et al.* (2023) "Menstrual suppression in adolescent and young adult transgender males," *Journal of Pediatric and Adolescent Gynecology*, 36(2), pp. 116–121. Available at: https://doi.org/10.1016/j.jpag.2022.10.007. .	Outcome (menses cessation) is not relevant
Bachrach, L.K. and Gordon, C.M. (2021) "Bone Health among transgender youth: What is a clinician to do?," *Pediatrics*, 148(4). Available at: https://doi.org/10.1542/peds.2021-051137.	Publication type - commentary
Baker, K.E. *et al.* (2021) "Hormone therapy, mental health, and quality of life among transgender people: A systematic review," *Journal of the Endocrine Society*, 5(4). Available at: https://doi.org/10.1210/jendso/bvab011.	Individual studies contributing to this systematic review were checked for relevance. Four of 20 included studies were relevant to the PICO. Three were identified in the 2020 evidence review – one was included and two were excluded. The fourth paper was published in Spanish and would be excluded (*Lopez de Lara* et al 2020).
Borrás, A. *et al.* (2021) "Endocrinological and ovarian histological investigations in assigned female at birth transgender people undergoing testosterone therapy," *Reproductive BioMedicine Online*, 43(2), pp. 289–297. Available at: https://doi.org/10.1016/j.rbmo.2021.05.010.	Population (adults), intervention (testosterone and surgery) and outcomes (gonadotrophin and sex hormone levels), ovarian histological analysis, gynaecological ultrasound scan) are not relevant
Butler, G. *et al.* (2022) "Discharge outcome analysis of 1089 transgender young people referred to paediatric endocrine clinics in England 2008–2021," *Archives of Disease in Childhood*, 107(11), pp. 1018–1022. Available at: https://doi.org/10.1136/archdischild-2022-324302.	Not all participants received GnRHa and outcome reported for those receiving GnRHa without GAH treatment is not relevant "Stopped identifying as gender variant after staring GnRHa"
Butler, G. (2020) "Gender incongruence," *Paediatrics and Child Health*, 30(12), pp. 407–410. Available at: https://doi.org/10.1016/j.paed.2020.09.001.	Publication type – narrative review
Canalichio, K.L. *et al.* (2020) "A non-surgical approach to 46,XY differences in sex development through hormonal suppression at puberty: A single-center case series study," *Endocrine*, 70(1), pp. 170–177. Available at: https://doi.org/10.1007/s12020-020-02409-y.	Population (46,XY differences in sex development) is not relevant
Ciancia, S., Dubois, V. and Cools, M. (2022) "Impact of gender-affirming treatment on bone health in transgender and gender diverse youth," *Endocrine Connections*, 11(11). Available at: https://doi.org/10.1530/ec-22-0280.	Publication type – narrative review
Chen, D. *et al.* (2021) "Psychosocial characteristics of transgender youth seeking gender-affirming medical treatment: Baseline findings from the Trans Youth Care Study," *Journal of Adolescent Health*, 68(6), pp. 1104–1111. Available at: https://doi.org/10.1016/j.jadohealth.2020.07.033.	Describes baseline characteristics of participants of the Trans Youth Care Study rather than treatment effects

Study reference	Reason for exclusion
de Nie, I. *et al.* (2021) "Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in transgender women," *Human Reproduction*, 37(2), pp. 297–308. Available at: https://doi.org/10.1093/humrep/deab240.	Outcome assessment (orchiectomy specimen histology) was performed after participants had received both GnRHas and oestrogen supplementation
Eitel, K.B. *et al.* (2023) "Leuprolide acetate for puberty suppression in transgender and gender diverse youth: A comparison of subcutaneous Eligard versus intramuscular lupron," *Journal of Adolescent Health*, 72(2), pp. 307–311. Available at: https://doi.org/10.1016/j.jadohealth.2022.09.017.	Outcomes (biochemical puberty suppression 1hr post GnRHa treatment and patient reported clinical puberty suppression) are not reported separately for participants receiving GnRHa only and those receiving GnRHA and GAH treatments
Fusco, F. *et al.* (2021) "Suppression of spermatogenesis by exogenous testosterone," *Current Pharmaceutical Design*, 27(24), pp. 2750–2753. Available at: https://doi.org/10.2174/1381612826666201207104340.	Publication type – narrative review
Grimstad, F. *et al.* (2021) "Breakthrough bleeding in transgender and gender diverse adolescents and young adults on long-term testosterone," *Journal of Pediatric and Adolescent Gynecology*, 34(5), pp. 706–716. Available at: https://doi.org/10.1016/j.jpag.2021.04.004.	Intervention (testosterone gender affirming therapy) is not relevant
Hastings, J. *et al.* (2021) "Medical care for nonbinary youth: Individualized gender care beyond a binary framework," *Pediatric Annals*, 50(9). Available at: https://doi.org/10.3928/19382359-20210818-03.	Publication type – narrative review
Kerman, H.M. *et al.* (2021) "Gender diverse youth on fertility and future family: A qualitative analysis," *Journal of Adolescent Health*, 68(6), pp. 1112–1120. Available at: https://doi.org/10.1016/j.jadohealth.2021.01.002	Study design – qualitative study
Kremen, J. *et al.* (2021) "Addressing legislation that restricts access to care for transgender youth," *Pediatrics*, 147(5). Available at: https://doi.org/10.1542/peds.2021-049940.	Publication type - commentary
Lee, J.Y. *et al.* (2022) "Interpretation of bone mineral density z-scores by dual-energy X-ray absorptiometry in transgender and gender diverse youth prior to gender-affirming medical therapy," *Journal of Clinical Densitometry*, 25(4), pp. 559–568. Available at: https://doi.org/10.1016/j.jocd.2022.07.002.	Describes baseline bone mineral density scores of participants rather than treatment effects
Lee, J.Y. *et al.* (2020) "Low bone mineral density in early pubertal transgender/gender diverse youth: Findings from the Trans Youth Care Study," *Journal of the Endocrine Society*, 4(9). Available at: https://doi.org/10.1210/jendso/bvaa065.	Describes baseline bone mineral density scores of participants rather than treatment effects

Study reference	Reason for exclusion
Loos, M.A.T.C. *et al.* (2021) "Development of hip bone geometry during gender-affirming hormone therapy in transgender adolescents resembles that of the experienced gender when pubertal suspension is started in early puberty," *Journal of Bone and Mineral Research*, 36(5), pp. 931–941. Available at: https://doi.org/10.1002/jbmr.4262.	Comparison is not relevant to PICO as outcomes were assessed at the start of GnRHa treatment and compared to assessment at the start and ≥ 2 years after GAH treatment, rather than being assessed prior and post GnRHa treatment
Martin, S., Sandberg, E.S. and Shumer, D.E. (2021) "Criminalization of gender-affirming care — interfering with essential treatment for transgender children and adolescents," *New England Journal of Medicine*, 385(7), pp. 579–581. Available at: https://doi.org/10.1056/nejmp2106314.	Publication type - commentary
Mejia-Otero, J.D., White, P. and Lopez, X. (2021) "Effectiveness of puberty suppression with gonadotropin-releasing hormone agonists in transgender youth," *Transgender Health*, 6(1), pp. 31–35. Available at: https://doi.org/10.1089/trgh.2020.0007.	Comparison (children with central precocious puberty) and outcomes (gonadotrophin and sex hormone levels) are not relevant
Millington, K. *et al.* (2020) "Physiological and metabolic characteristics of a cohort of transgender and gender-diverse youth in the United States," *Journal of Adolescent Health*, 67(3), pp. 376–383. Available at: https://doi.org/10.1016/j.jadohealth.2020.03.028.	Describes baseline physical and laboratory characteristics of participants of the Trans Youth Care Study rather than treatment effects
Nasomyont, N. *et al.* (2022) "Changes in bone marrow adipose tissue in transgender and gender non-conforming youth undergoing pubertal suppression: A pilot study," *Journal of Clinical Densitometry*, 25(4), pp. 485–489. Available at: https://doi.org/10.1016/j.jocd.2022.06.006.	Comparison (cisgender control group) is not relevant
Nokoff, N.J. *et al.* (2021) "Body composition and markers of Cardiometabolic Health in transgender youth on gonadotropin-releasing hormone agonists," *Transgender Health*, 6(2), pp. 111–119. Available at: https://doi.org/10.1089/trgh.2020.0029.	Comparison (cisgender control group) is not relevant
Nos, A.L. *et al.* (2022) "Association of gonadotropin-releasing hormone analogue use with subsequent use of gender-affirming hormones among transgender adolescents," *JAMA Network Open*, 5(11). Available at: https://doi.org/10.1001/jamanetworkopen.2022.39758.	Outcome (subsequent use of gender affirming hormones) is not relevant
Olsavsky, A.L. *et al.* (2023) "Associations among gender-affirming hormonal interventions, social support, and Transgender Adolescents' Mental Health," *Journal of Adolescent Health* [Preprint]. Available at: https://doi.org/10.1016/j.jadohealth.2023.01.031.	Minority of participants (12%) received puberty suppression treatment and outcomes are not reported separately for this group
Olson-Kennedy, J. *et al.* (2021) "Histrelin implants for suppression of puberty in youth with gender dysphoria: A comparison of 50 MCG/day (vantas) and 65 MCG/day (SUPPRELINLA)," *Transgender Health*, 6(1), pp. 36–42. Available at: https://doi.org/10.1089/trgh.2020.0055.	Outcomes (gonadotrophin and sex hormone levels) are not relevant
Ramos, G.G. *et al.* (2020) "Systematic review: Puberty suppression with gnrh analogues in adolescents with gender incongruity," *Journal of Endocrinological Investigation*, 44(6), pp. 1151–1158. Available at: https://doi.org/10.1007/s40618-020-01449-5.	Individual studies contributing to this systematic review were checked for relevance. Of the 11 included studies, ten were identified in the 2020 evidence review – six were included and four were excluded. The final study (*Klink et al, 2013*) was published within the original search dates, may

Study reference	Reason for exclusion
	have been an abstract published in a supplement and sifted out in preference for the included study *Klink et al, 2015*
Rew, L. *et al.* (2020) "Review: Puberty blockers for transgender and gender diverse youth—a critical review of the literature," *Child and Adolescent Mental Health*, 26(1), pp. 3–14. Available at: https://doi.org/10.1111/camh.12437.	Individual studies contributing to this critical review were checked for relevance. Of the nine included studies, six were identified in the 2020 evidence review - four were included and two were excluded. The remaining three studies were likely sifted out - two were case reports and one was an analysis where the minority of participants received GnRHAs.
Russell, I., Pearson, B. and Masic, U. (2020) "A longitudinal study of features associated with autism spectrum in clinic referred, gender diverse adolescents accessing puberty suppression treatment," *Journal of Autism and Developmental Disorders*, 51(6), pp. 2068–2076. Available at: https://doi.org/10.1007/s10803-020-04698-8.	Outcomes (from Social Responsiveness Scale 2 (SRS-2) School Age Form) are not relevant
Schulmeister, C. *et al.* (2022) "Growth in transgender/gender-diverse youth in the first year of treatment with gonadotropin-releasing hormone agonists," *Journal of Adolescent Health*, 70(1), pp. 108–113. Available at: https://doi.org/10.1016/j.jadohealth.2021.06.022.	Outcome (height velocity) is not relevant
Segev-Becker, A. *et al.* (2020) "Children and adolescents with gender dysphoria in Israel: Increasing referral and fertility preservation rates," *Endocrine Practice*, 26(4), pp. 423–428. Available at: https://doi.org/10.4158/ep-2019-0418.	Outcomes (fertility preservation, psychiatric morbidity and behavioural characteristics) are not reported separately for participants receiving GnRHa only and those receiving GnRHa and GAH treatments
Sermondade, N. *et al.* (2021) "Reproductive functions and fertility preservation in transgender women: A French case series," *Reproductive BioMedicine Online*, 43(2), pp. 339–345. Available at: https://doi.org/10.1016/j.rbmo.2021.04.016.	Population is not relevant as no confirmation of any participants receiving GnRHa treatment
Spurny-Dworak, B. *et al.* (2022) "Effects of sex hormones on brain GABA and glutamate levels in a cis- and transgender cohort," *Psychoneuroendocrinology*, 138, p. 105683. Available at: https://doi.org/10.1016/j.psyneuen.2022.105683.	Population (adults receiving GAH), comparison (cisgender adults) and outcomes (neurotransmitter functioning) are not relevant
Tordoff, D.M. *et al.* (2022) "Mental health outcomes in transgender and nonbinary youths receiving gender-affirming care," *JAMA Network Open*, 5(2). Available at: https://doi.org/10.1001/jamanetworkopen.2022.0978.	Population is not relevant as a minority of participants received puberty suppression treatments only at baseline and throughout the study period
van der Loos, M.A. *et al.* (2022) "Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: A cohort study in the Netherlands," *The Lancet Child &*	Outcomes (ongoing use of GAH and GAH use into adulthood) were not relevant

Study reference	Reason for exclusion
Adolescent Health, 6(12), pp. 869–875. Available at: https://doi.org/10.1016/s2352-4642(22)00254-1.	
Yasmin, E. (2021) “Fertility Care for persons considering gender transition,” *Obstetrics, Gynaecology & Reproductive Medicine*, 31(3), pp. 91–92. Available at: https://doi.org/10.1016/j.ogrm.2021.01.006.	Publication type - commentary

Appendix E Includable studies

Table 4 Studies that meet the PICO details but are unlikely to materially affect the conclusions of the NICE evidence review

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
Boogers et al, 2022 **Study design** Retrospective cohort study **Country** Netherlands	**Study setting** This was a retrospective cohort study of patients seen at the Center of Expertise on Gender Dysphoria in Amsterdam (a specialized tertiary gender clinic) **Sample size, age** The study identified 161 transgender girls seen at the clinic from 1972 until December 2018. **Inclusion criteria** Patients were included if they had a diagnosis of gender dysphoria and were treated with GnRHa and estradiol. Individuals with genetic disorders known to affect growth or who had discontinued treatment before adult	**Intervention** GnRHa followed by estradiol at a regular dose (2 mg) or high growth-reductive doses of estradiol (6 mg) or ethinyl estradiol (EE, 100-200 µg). The mean duration of puberty suppression with GnRHa was 2.4 ± 0.8 years. **Comparison** Non-comparative.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** ***Body image (growth velocity [height])*** Growth velocity slowed with GnRHa treatment for each subsequent year of puberty suppression. (no statistical significance reported) **Safety:** ***Bone age*** At baseline, bone age was within the physiological range. During puberty suppression bone maturation decreased, resulting in a bone age delayed by 1.6 ± 0.8 years at the start of GAH.	Although growth velocity was not previously reported, the results by *Boogers et al* are likely to be clinically negligible and therefore unlikely to affect conclusions. Bone age results broadly reflect those already identified in the 2020 evidence review.

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
	height was reached were excluded.			
Carmichael et al. 2021 **Study design** Prospective observational study **Country** UK	**Study setting** The study was conducted at the Gender Identity Development Service (GIDS) at the Tavistock and Portman NHS Foundation Trust, London, UK and involved adolescents with gender dysphoria. **Sample size, age** The sample size was 44 adolescents (median age at consent was 13.6 years, range 12.0-15.3). This cohort were recruited between April 2011 and April 2014 and commenced GnRHa treatment between June 2011 and April 2015. They were all recruited from patients referred to the GIDS. **Inclusion criteria** Participants were included in the study if they were	**Intervention** 44 participants received puberty suppressors using the GnRHa triptorelin from study entry until the end of the monotherapy pathway at 16 years or older. Participants were given triptorelin 3.75mg by intramuscular injection every 28 days during the treatment period. Treatment duration was from 1 to 4 or 5 years depending on time of initiation. **Comparison** Non-comparative.	**Critical outcomes** ***Impact on gender dysphoria*** • There was no change over 12 or 24 months in the Utrecht gender dysphoria scale (mean 4.8[4.6-5.0], 4.7[4.6-5.0] and 4.7[4.3-5.0] respectively since baseline). ***Impact on mental health*** • There was no change from baseline to 12 or 24 months in the youth self report (YSR) total t-score (mean 57.9[55-60.8], 57.6[54.5-60.6] and 58.4[54.6-62.2] respectively), nor reported YSR self-harm index scores (0[0,1], 0[0,1], 0[0,2]). **Important outcomes** ***Impact on body image*** • There was no change in body image scale (BIS) scores identified at 12, 24 or 36 months (mean 3.1[2.8-3.3], 3.2[3.0-3.4], 3[2.7-3.2] and 3.1[2.4-3.7] respectively). ***Psychosocial impact***	The outcomes demonstrate that despite mostly positive experiences of the participants, there was no change in outcomes concerning impact on gender dysphoria, mental health, body image, or psychosocial impact. These results broadly reflect those already identified in the 2020 evidence review. Adverse events were reported as mild and reflect those already identified in the 2020 evidence review.

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
	diagnosed with gender dysphoria according to the DSM-5 criteria, registered at the clinic, were in established puberty and had normal endocrine function and karyotype consistent with birth registered sex.		• There was no change from baseline to 12 or 24 months for the Child Behaviour Checklist (CBCL) total t-scores at 12, 24 and 36 months. There was no significant changes in parent reported CBCL self-harm index scores from baseline to 12, 24 or 26 months. • At 6-15 months of treatment 46% reported only positive changes, including feeling happier, relieved, less facial hair or stopping menses.37% reported both positive and negative changes such as feeling happier but also experiencing hot flushes and headaches. A further 12% reported overall negative changes, namely hot flushes, tiredness. 5% reported no change. At 15-24 months 55% reported solely positive changes and 17% both positive and negative. ***Stopping treatment*** • At the end of the GnRHa pathway 98% (43) patients elected to commence cross-sex	

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
			hormones. One patient decided to stop GnRHa due to continued uncertainty regarding side-effects of cross-sex hormones. **Safety** ***Cognitive development/functioning*** • Childrens Global Assessment Scare (CGAS) scores demonstrated a minimal increase in score from baseline at 12,24 and 36 months (mean 62.0[59.6-66.2], 64.1[59.9-68.3], 65.7[59.6-71.8],66[58.1-73.9] respectively. ***Change in bone density*** • There was no change from baseline in spine Bone mineral density (BMD) at 12 months nor in hip BMD at 24 and 36 months, but at 24 months lumbar spine Bone Mineral Content (BMC) and BMD were higher than at baseline (BMC +6.0 (95% CI: 4.0, 7.9); BMD +0.05 (0.03, 0.07)). ***Adverse effects***	

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
			• All participants achieved adequate suppression of gonadotropins and sex hormones by 6 months (mean LH 0.5IU/L; mean FSH 1.4IU/L) and maintained this throughout the study. • All adverse events were minor. Mild headaches or hot flushes were reported in 25% at 0-6months, 23% at 7-12 month and 22% at 13-24months.	
Navabi et al. 2021 **Study design** Retrospective cohort study **Country** Canada	**Study setting** The study was conducted at the endocrine diversity clinic of the Children's Hospital of Eastern Ontario (CHEO), Canada and involved children and adolescents with gender dysphoria. **Sample size, age** Medical records of 198 <18-year-olds were reviewed who were seen at the endocrine diversity clinic at CHEO from January 2006 to April 2017. 172 participants	**Intervention** GnRHa formulation of leuprolide acetate. Dosing schedule commences with 3 doses of 7.5mg intramuscularly every 4 weeks, followed by 11.25mg intramuscularly every 12 weeks after confirmation of puberty suppression. **Comparison** Non-comparative.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • No important outcomes reported **Safety** ***Change in bone density*** • Bone mineral density profiles were measured pre- and post-initiation on GnRHa treatment with leuprolide acetate. At baseline, transgender females had lower lumbar spine (LS), and left total hip (LTH) areal bone mineral density (aBMD) and LS bone mineral apparent density (BMAD) z scores.	Bone density results broadly reflect those identified in the 2020 evidence review.

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
	were included. 119 self-identified as transgender males (age 15.2+/-1.8 [SD] years; 90% Tanner 4-5), 51 as transgender females (age 15.4+/-2.0 years; 80.3% Tanner 4-5) and 2 as nonbinary. **Inclusion criteria** Participants were included in the study if they were diagnosed with gender dysphoria according to the DSM-5 criteria and had at least 1 dual-energy radiograph absorptiometry (DXA) measurement.		• There was a significant reduction in LS, LTH and TBLH aBMD z scores in transgender males (change post- pre mean of -0.74[-0.85 to -0.63, p<0.001], -0.33[-0.4 to -0.26, p<0.001] and -0.34[-0.43 to -0.25, p<0.001] respectively). • There was also a significant reduction in LS, LTH and TBLH aBMD z scores in transgender females (change post-pre mean of -0.33 [-0.46 to -0.19, p<0.001)], -0.46 [-0.6 to -0.31, p<0.001] and -0.34[-0.48 to -0.21, p<0.001] respectively). • Nil fractures were identified.	
Perl et al, 2020 **Study design** Retrospective, single-centre observational study. **Country** Israel	**Study setting** Retrospective, single-centre observational study. Medical files of 48 patients at the Israeli Paediatric Gender Dysphoria Clinic, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center who sought medical attention for gender dysphoria (GD)	**Intervention** Pubertal suppression therapy consisted of a depot preparation of the GnRHa D-Trp-6-LHRH (Decapeptyl; Ferring Pharmaceuticals Ltd., Malmo¨, Sweden) at a dose of 3.75 mg administered by intramuscular injection every 4 weeks.	Data extraction included vital signs, anthropometric measurements and hormone levels. BP was measured during a clinic visit within 1-4 weeks of GnRHa using a Welch Allyn Vital Signs Monitor VSM 300 (Welch Allyn, Inc., Beaverton, OR), and converted to BP percentiles. • Normal BP = BP values were <90th percentile	The results show that patients starting GnRHa had a significant increase in diastolic blood pressure after a mean average of 3 months of treatment. The results are non-comparative, so it is not possible to determine if GnRHa is responsible for the

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
	between 2013 and 2018 were reviewed. **Sample size, age**, 15 transgender male adolescents who had sought medical attention due to gender dysphoria. Mean age at initiation of pubertal suppression was 14.4 – 1.0 years. **Inclusion criteria** • Treated solely with GnRHa for ≥2 months • BP had to be recorded at the following timepoints: before pubertal suppression and after pubertal suppression • Tanner stage 2 or higher of breast development	Given for a mean period of 3 ± 1 months. **Comparison** Non-comparative. BP results stratified by BP percentiles for assigned sex at birth (female) using reference ranges in the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.	• Prehypertension = either SBP and/or DBP levels ‡90th percentile to <95th percentile • Hypertension = either SBP and/or diastolic BP levels ‡95th percentile. Changes in body weight status by BMI standard deviation score. **Critical Outcomes** • No critical outcomes reported **Important outcomes** • No important outcomes reported **Safety** ***Blood pressure*** • BP levels and percentiles (mean SBP 115 – 7 mmHg [71 – 19 percentiles] and mean DBP: 64 – 10 mmHg [56 – 26 percentiles]) were normal at initiation of GnRHa. • DBP percentiles increased significantly after GnRHa treatment (from the 56.0 - 26.0 percentile to 74.0 - 9.0 percentile, p = 0.019), and that increase remained significant	increase in BP. Additionally, a follow-up period of 3 months is too short to evaluate long-term effects of GnRHas on BP. Therefore, no conclusions can be drawn. Although blood pressure was not previously reported, the results by *Perl et al* are likely to be clinically negligible and therefore unlikely to affect conclusions.

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
			after adjusting for the change in BMI SDS (p = 0.047). • SBP percentiles did not change significantly, and the BP levels were within the normal range and did not meet the criteria for paediatric hypertension. ***Changes in body weight status*** • Weight status at initiation of GnRHa was normal (mean BMI-SDS 0.2 – 0.9). • BMI standard deviation did not increase significantly during GnRHa therapy (p=0.198).	
Perl et al, 2020 **Study design** Retrospective, single-centre observational study. **Country** Israel	**Study setting** Retrospective, single-centre observational study. Medical files of 86 patients at the Israeli Paediatric Gender Dysphoria Clinic, Dana-Dwek Children's Hospital, Tel Aviv Sourasky Medical Center who sought medical attention for gender dysphoria (GD) between February 2013 and December 2020 were reviewed.	**Intervention** For pubertal suppression, an intramuscular injection of depot preparation GnRHa D-Trp-6-LHRH (Decapeptyl, Ferring Pharmaceuticals Ltd., Malmo, Sweden) at a dose of 3.75 mg was administered every 4 weeks. GnRHa administered for a mean period of 9 ± 6 months.	Data extraction included vital signs, anthropometric measurements and hormone levels. BP was measured during a clinic visit within 1-4 weeks of GnRHa using a Welch Allyn Vital Signs Monitor VSM 300 (Welch Allyn, Inc., Beaverton, OR), and converted to BP percentiles. • Normal BP = BP values were <90th percentile • Prehypertension = either SBP and/or DBP levels between 90-95th percentile	The results show that no significant changes in SBP or DSP or BMI SDS were detected in transgender females taking GnRHa for 9 months. The results are non-comparative so no conclusions can be drawn. Although blood pressure was not previously reported, the results by *Perl et*

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
	Sample size, age 19 transgender female adolescents who had sought medical attention due to gender dysphoria. Mean age at initiation of pubertal suppression was 15.7 ± 1.6 years. **Inclusion criteria** • Treated solely with GnRHa for ≥2 months • BP had to be recorded at the following timepoints: before pubertal suppression and after pubertal suppression **Exclusion criteria** • Diagnosis of type I diabetes mellitus	**Comparison** Non-comparative. Measurements were converted to BP percentiles for the assigned sex at birth (male) published by the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. A p value of ≤0.05 was considered significant.	• Hypertension = either SBP and/or diastolic BP levels ≥95th percentile. Changes in body weight status by BMI standard deviation score. **Critical Outcomes** • No critical outcomes reported **Important outcomes** • No important outcomes reported **Safety** ***Blood pressure*** At initiation of GnRHa treatment: • Four (21%) adolescents reported smoking, with one having prehypertension, none reported alcohol consumption or drug abuse. Four (21%) reported a diagnosis of anxiety, all with normal BP. • Mean SBP was 116 ± 8 mmHg (55 ± 29 percentile) with three participants having systolic prehypertension. • Mean DBP was 70 ± 9 mmHg (64 ± 27 percentile), with three participants having diastolic prehypertension (one participant	*al* are likely to be clinically negligible and therefore unlikely to affect conclusions.

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
			had both systolic and diastolic prehypertension). During 9 ± 6 months GnRHa treatment: • The mean SBP and DBP percentiles also did not change significantly after GnRHa treatment (p=0.673 and p=0.6, respectively). • No systolic hypertension criteria were met, while diastolic pre-hypertension was detected in three participants who did not have evidence of it at baseline. One reported smoking and one reported anxiety diagnosis. • There was a significant negative correlation, at this time point, between testosterone levels and DBP percentiles (p=0.004, r=−0.656), but none were found between BP percentiles and estradiol, LH, or FSH levels. ***Changes in body weight status*** At initiation of GnRHa treatment: • Mean BMI-SDS −0.21 ± 1.42. Three participants were underweight with BMI-SDS <−2.	

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
			During 9 ± 6 months GnRHa treatment: • BMI-SDS did not change significantly (p=0.728).	
Schagen et al, 2020 **Study design** Observational prospective study **Country** Not stated.	**Study setting** Observational, prospective data from 1998 to 2009 collected. Not stated where data came from. **Sample size, age** 51 transgirls and 70 transboys receiving GnRHa and 36 transgirls and 42 transboys receiving GnRHa and gender-affirming hormones, subdivided into early- and late-pubertal groups. Tanner stage was used to define early- and late-pubertal groups, with the early-pubertal group defined as Tanner stage 2 or 3 at the start of GnRHa treatment, and the late-pubertal group as Tanner stage 4 or 5.	**Intervention** The first phase of treatment consisted of intramuscular injections of GnRHa 3.75 mg (Triptorelin-CR (Ferring Pharmaceuticals, Denmark). The first 2 injections were administered with a 2-week interval followed by injections every 4 weeks to suppress endogenous sex steroid production. **Comparison** Non-comparative. To calculate z-scores based on age and sex, the National Health and Nutrition Examination Surveys (NHANES) references values were used. Because changes in aBMD might partly be due	Bone densitometry was performed by DXA scan using Hologic QDR 4500 (Hololologic Inc., Waltham, MA, USA): 1. Before GnRHa administration 2. Every subsequent year after **Critical Outcomes** • No critical outcomes reported **Important outcomes** • No important outcomes reported **Safety** ***Bone mineral apparent density of lumbar spine*** • no change during 2 years of GnRHa treatment in transgirls or early pubertal transboys (p=0.84, p=0.09 and p=0.69). • In the late-pubertal transboys, a small but significant decrease in BMAD of the lumbar spine was found.	Bone density and serum bone marker results broadly reflect those identified in the 2020 evidence review.

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
	Inclusion criteria Adolescents fulfilling the following criteria: • Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for gender identity disorder (the term used at the time) • Tanner stage 2 or above.	to altered growth during treatment, we also studied BMAD (g/cm3) calculated as described by Ward et al (15). BMAD z-scores were calculated using LMS data from an English reference population (15). To calculate z-scores the reference population of the birthassigned sex was used. For adolescents older than 17 years no reference values of BMAD are available; therefore, reference values of 17-year-olds were used to calculate the z-score at older ages	***Bone mineral density of the femoral neck*** • significant decrease in late-pubertal transgirls and in both groups of transboys (p= 0.007, p = 0.015, and p < 0.001, respectively). ***Bone mineral apparent density z-scores*** • at baseline z-scores for lumbar and femoral higher in transboys than transgirls. • The BMAD z-score of the lumbar spine significantly decreased in all 4 groups ($p \leq$ 0.001) BMAD z-score of femoral neck significantly decreased in all groups (p = 0.006, p = 0.002, and p <0.001) except for the early-pubertal transgirls (p = 0.25). • The aBMD values of the lumbar spine and hip in 4 transboys and 11 transgirls remained stable during 3 years of GnRHa treatment. The z-scores on the other hand declined. ***Serum bone markers***	

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
			• At baseline no difference in serum levels between early and late pubertal groups in transgirls. • Bone levels significantly higher in early pubertal transboys compared to late pubertal. • After 2 years of GnRHa treatment serum levels of all 4 bone markers showed a significant decrease in both groups of transgirls and in early-pubertal transboys, which was most marked during the first year of treatment. • Serum levels of P3NP and 1CTP showed a smaller but significant decrease in late-pubertal transboys whereas serum levels of P1NP and osteocalcin did not change in this group.	
Willemsen et al. 2022 **Study design** Retrospective cohort study **Country** Netherlands	**Study setting** The study is part of the Amsterdam Cohort of Gender dysphoria (ACOG) study which includes the complete population of all ages seen at the gender identity clinic of the	**Intervention** The mean duration of puberty suppression was 3.1+/- 0.9 years. Specific treatment or dosing was not reported. **Comparison** Non-comparative.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** ***Impact on body image*** • At baseline, mean height was 158.3 ± 8.5 cm (female height Standard Deviation Score (SDS)	The results demonstrate growth deceleration during puberty suppression. This may impact positively on body image. However, the results are non-comparative so no

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
	Amsterdam University Medical Center. **Sample size, age** The sample size was 146 transgender boys. They were divided into 2 subgroups based on growth potential. The pubertal group consisted of 61 transgender boys with a mean age of 12.7±1 years. The post pubertal group consisted of 85 individuals with a mean age of 15.1±9 years. The datasets were obtained from the ACOG dataset from 1972 until December 2018. **Inclusion criteria** Transgender boys (assigned female sex at birth) were included in the study if they were diagnosed with gender dysphoria according to the DSM-5 criteria, registered at the clinic, had started puberty suppression before age 16 years,		+0.1 ± 1.5, male height SDS −0.1 ± 1.5). • During the puberty suppressive phase, height increased by 8.6 cm (95% CI, 7.5-9.6) to 166.9 ± 7.0 cm at start of gender-affirming hormone treatment (GAHT). Female height SDS decreased to −0.2 ± 1.0 (decrease of −0.2; 95% CI, −0.5 to 0.1). • Transgender boys with bone age >12 years at the start of puberty suppression treatment declined more in height SDS during PS compared with transgender boys with BA ≤12 years (difference between groups −0.6; 95% CI, −0.7 to −0.4) (Fig. 1), but height SDS at start of GAHT did not differ between the groups (difference 0.3; 95% CI, −0.3 to 0.9). **Safety** ***Change in bone density*** • Puberty suppression resulted in a deceleration of bone maturation. At the beginning of puberty suppression, bone age (BA) was comparable to	conclusions can be drawn. Bone maturation results broadly reflect those identified in the 2020 evidence review.

Study	Population	Intervention and comparison	Outcomes reported	Reason why unlikely to affect conclusions
	received testosterone treatment for a minimum of 6 months and if they had reached the age of 18 years at the time of data collection		Chronological Age (CA) with a BA – CA of −0.3 ± 0.9 years. This difference was greater among those with BA ≤12 at the start of puberty suppression treatment compared with those with BA >12 years (difference, 0.7 years; 95% CI, 0.2-1.2).	

Table 5 Studies that meet the PICO details and may materially affect the conclusions of the existing evidence review

Study details	Population	Interventions	Study outcomes	Reason why may affect conclusions
Becker-Hebly et al, 2020 **Study design** Cohort study **Study setting**	**Sample size, age** The sample size was 75 adolescents and young adults (n=64 birth-assigned female/trans-male and n = 11 trans-female/birth-assigned male adolescents) who had received some form of (psychosocial or	**Intervention** Four different intervention groups: 1. No medical intervention yet (psychosocial intervention only) (n=21)	Dimensions of psychosocial health were measured at initial uptake and on average two years later (M treatment duration=21.4 months). Behavioural and emotional problems were assessed via the German version of the 1991 Youth Self Report[1] (YSR) for those aged 11 to 18 and the adult version	Results are reported for the critical outcome of quality of life – no evidence was available in the 2020 evidence review. Results that may be clinically impactful are

[1] Self-report measure providing T-scores according to the T-distribution (norm range between 40 and 60). Presuming a T-distribution to be normal (M=50; SD=10), confidence intervals that are not within the normal range (and therefore do not include M=50) differ significantly from those of the German norm.

The study was conducted at the University Medical Centre Hamburg-Eppendorf, Germany and involved patients under routine care from the Gender Identity Service (GIS). **Country** Germany	medical) intervention at the Hamburg GIS since 2013. Adolescents were 15.6 years old at baseline on average (SD = 1.2) and 17.4 (SD = 1.7) at follow-up. **Inclusion criteria** Participants were included in the study if they met the following criteria: 1. maintenance of persistent gender dysphoria (GD) 2. increased distress due to incongruent body characteristics (usually after the first onset of pubertal changes) and a request for gender affirming (GA0 interventions 3. a psychiatric or psychological assessment revealing the absence of severe psychiatric problems that may interfere with the	2. Puberty suppression only, GnRHa (n=11) 3. GAH only (oestrogen/testosterone interventions) (n=32) (outside of scope of PICO) 4. GAH and GAS, mainly mastectomy (n=11) (outside of scope of PICO) **Comparison** Non-comparative. German norm population-based, age- and gender-specific T-scores for the YSR, ASR and total problem score. Raw scores for the Kidscreen-27 and the SF-8 were transformed into T-scores to allow comparison across the two different measures and with the age-equivalent norm.	(ASR) for those older than 18 years old. Global functioning was assessed using the Children's Global Assessment Scale (CGAS)[2] via clinician's reports. Health-related quality of life was assessed via the Kidscreen-27[3] in those 11-18 years and the SF-8 (a short form of the SF-36) for those over 18 years. **Critical Outcomes** ***Impact on mental health*** No medical intervention: • YSR Total problem T score at baseline 64.29 (SD = 9.33), 95% CI 60.04; 68.53. Follow-up 64.86 (SD = 9.68), 95% CI 60.45; 69.26. Overall score increased by 0.57. GnRHa only: • YSR Total problem T score at baseline 62.27 (SD = 8.96), 95% CI 56.26; 68.29. Follow-up 61.91 (SD = 10.55), 95% CI	reported for the safety outcome of Cognitive development/functioning

[2] CGAS outcomes are reported without reference to the norm. This clinician rated instrument is divided into 10-point intervals from 10 to 100, with higher scores (above 80) indicating good global functioning.

[3] Self-report measure providing T-scores according to the T-distribution (norm range between 40 and 60). Presuming a T-distribution to be normal (M=50; SD=10), confidence intervals that are not within the normal range (and therefore do not include M=50) differ significantly from those of the German norm.

	diagnostic procedures or treatment (such as acute suicidality or psychosis) 4. adequate psychological and social support during treatment 5. a demonstrated knowledge and understanding of both the physical and social consequences of gender affirmation The inclusion criteria for a repeated measurement approximately 2 years later were as follows: 1. complete questionnaire sets and informed consent at baseline 2. informed consent to participate in the follow-up study 3. min. 11 years of age at baseline 4. maintenance of persistent GD according to the diagnostic criteria (DSM-5) 5. a request for GA interventions in the absence of severe psychiatric problems (eligibility for medical interventions).	Differences between the intervention groups were assessed by a descriptive approach.	54.82; 69.00. Overall score decreased by 0.36. YSR/ASR total problem T scores at baseline and at follow-up are above the norm for both the no medical intervention group and the GnRHa only group. On a score out of 100, a change of less than 1 is not considered to be a clinically meaningful difference. The paper did not report any cross group comparison, therefore no comment can be made regarding comparison between the no medical intervention group and the GnRHa only group. ***Impact on Quality of Life*** No medical intervention: • T Mental dimension score at baseline 34.86 (SD = 6.27), 95% CI 32.00; 37.71. At follow-up 36.37 (SD = 7.71), 95% CI 32.85; 39.88. Score improved by 1.51 points. • T Physical dimension score at baseline 37.51 (SD = 8.27), 95% CI 33.74; 41.27. At follow-up 42.51 (SD = 10.40), 95% CI 37.78; 47.25. Score improved by 5 points. GnRHa only:	

	Exclusion criteria 1. Aged < 11years 2. Severe psychiatric problems (e.g. psychosis) 3. Prior medical treatment 4. Unfulfilled diagnostic criteria for GD 5. Diagnostic procedure still ongoing		• T Mental dimension score at baseline 39.04 (SD = 9.25), 95% CI 32.82; 45.25. At follow-up 43.17 (SD = 10.20), 95% CI 36.31; 50.01. Score improved by 4.13 points. • T Physical dimension score at baseline 43.43 (SD = 8.61), 95% CI 37.65; 49.22. At follow-up 49.57 (SD = 11.64), 95% CI 41.75; 57.39. Score improved by 6.14 points. Kidscreen-27/SF-8 scores below norm at baseline for both dimensions in the no medical intervention group and GnRHa only group. Scores remain below baseline for both dimensions in the no medical intervention group and the mental dimension in the GnRHa only group at two-year follow-up. The physical dimension score is just below norm (95% CI 41.75; 57.39) in the GnRHa group at two-year follow-up which is possibly a clinically meaningful improvement. The paper did not report any cross group comparison, therefore no comment can be made regarding comparison between the no medical intervention group and the GnRHa only group.	

			Important outcomes • No important outcomes reported **Safety** ***Cognitive development/functioning*** No medical intervention: • CGAS global functioning score baseline 68.10 (SD = 11.23), 95% CI 62.98; 73.21. Follow-up 70.00 (SD = 12.25), 95% CI 64.43; 75.57. Overall score improved by 1.9 points. GnRHa only: • CGAS global functioning score baseline 67.27 (SD = 11.91), 95% CI 59.27; 75.27. Follow-up 81.82 (SD = 7.51), 95% CI 76.77; 86.86. Overall score improved by 14.55 points. CGAS global functioning score remained below 80 at baseline and two-year follow-up for the no medical intervention group, with an increase in score of only 1.9 points. On a 100-point scale, this is not considered to be a clinically meaningful improvement. CGAS global functioning score was below 80 at baseline but improved to 81.82 (95% CI 76.77, 86.86) at	

			two-year follow-up. This was an improvement on 14.55 which might suggest clinically meaningful improvements. However, there were no population norm data to compare to. The paper did not report any cross group comparison, therefore no comment can be made regarding comparison between the no medical intervention group and the GnRHa only group.	

Study details	Population	Interventions	Study outcomes	Reason why may affect conclusions
van der Loos, M.A. *et al.* (2023) **Study design** Retrospective cohort study **Study setting** Center of Expertise on Gender Dysphoria of the Amsterdam UMC, location Vrije Universiteit Amsterdam (VUmc),	**Sample size, age** The cohort is comprised of the Amsterdam Cohort of Gender dysphoria (ACOG) who underwent diagnostic assessment and/or medical treatment for gender dysphoria between 1972 and December 31, 2018. N=1766 children and adolescents **Characteristics** AMAB 689 (39%) AFAB 1077 (61%)	**Intervention** Intramuscular or subcutaneous triptorelin (GnRHa), 3.75 mg every 4 weeks or 11.25 mg every 12 weeks, to suppress pubertal development when at least 12 years old. In addition, Tanner genital or breast stage of at least 2 was required for AMAB and AFAB to start GnRHa, respectively. If GD persisted, adolescents were	**Critical Outcomes** No critical outcomes reported **Important Outcomes** • **Transitioning surgery – Impact on extent of and satisfaction with surgery** *People undergoing gender-affirming surgery overall and stratified by puberty stage at start of GnRHa.* **AMAB** Total Sample N= 162 (puberty stage missing in 7 records) Early puberty = 35	Results are reported for the important outcome of transitioning surgery – no evidence was available in the 2020 evidence review

Study details	Population	Interventions	Study outcomes	Reason why may affect conclusions
between 1972 and December 31, 2018. **Country** Netherlands	*Age at first visit, y* AMAB 11.5 (8.0-15.2) AFAB 14.1 (10.5-16.0) *Started GnRHa* AMAB 266 (47%) AFAB 616 (73%) *Age at start of GnRHa, y* AMAB 14.0 (12.8-16.1) AFAB 15.5 (12.9-16.8) AFAB, assigned female at birth; AMAB, assigned male at birth; GAH, gender-affirming hormone; GnRHa, gonadotropin-releasing hormone agonist **Inclusion criteria** Pubertal adolescents who followed the Dutch Protocol, as used from 1997 onward, which could include GnRHa with or without subsequent GAH, as well as prepubertal children for whom a "watchful waiting" approach was adopted. People with all kinds of gender identity were included.	eligible for puberty induction with GAH from age ≥16 years The protocol was later adapted so that adolescents could start GnRHa before age 12 if puberty had started, and those who had already been treated with GnRHa for several years were eligible to start GAH from age 15 years. **Comparison** No comparison	Late puberty = 120 *Orchiectomy = 115 (71%)* Early puberty = 26 (74%) Late puberty = 82 (68%) *Vaginoplasty = 112 (69%)* Early puberty = 26 (74%) Late puberty = 79 (66%) *Breast augmentation = 21 (13%)* Early puberty = 4 (11%) Late puberty = 12 (10%) *Adam's apple reduction = 3 (1.9%)* Early puberty = 0 Late puberty = 3 (2.5%) *Voice feminization surgery = 3 (1.9%)* Early puberty = 0 Late puberty = 3 (2.5%) *Facial feminization surgery = 6 (3.7%)* Early puberty = 0 Late puberty = 6 (5.0%) **AFAB** Total sample = 353 (puberty stage missing in 8 records) Early puberty = 9 Late puberty = 336 *Mastectomy = 280 (79%)* Early puberty = 3 (33%)	

Study details	Population	Interventions	Study outcomes	Reason why may affect conclusions
			Late puberty = 265 (79%) *Hysterectomy = 193 (55%)* Early puberty = 9 (100%) Late puberty = 177 (53%) *Salpingo-oophorectomy = 190 (54%)* Early puberty = 9 (100%) Late puberty = 175 (52%) *Colpectomy = 58 (16%)* Early puberty = 3 (33%) Late puberty = 54 (16%) *Metoidioplasty/phalloplasty = 37 (10%)* Early puberty = 1 (11%) Late puberty = 35 (10%) • **Stopping treatment** *Discontinuation of GnRHa treatment* A temporal trend in people stopping GnRHa was not observed. Of all 266 AMAB who started GnRHa at our center, 9 (3.4%) discontinued treatment. ○ Six (2.3%) ceased treatment because of abating GD.	

Study details	Population	Interventions	Study outcomes	Reason why may affect conclusions
			○ In 2 AMAB (0.8%), GnRHa treatment ended due to psychological or social issues hindering transition. ○ In 1 individual (0.4%), GnRHa was discontinued due to compliance issues. Of all 616 AFAB, 5 (0.8%) broke off GnRHa. ○ In 3 (0.5%), remission of GD led to discontinuation. ○ In 2 (0.3%), GnRHa was suspended due to compliance issues. **Safety** No outcomes reported	

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