NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

Review consultation document

Review of Clinical Guideline (CG30) - The effective and appropriate use of long-acting reversible contraception

1. Background information

Guideline issue date: 2005
2 year review: 2007
5 year review: 2011
National Collaborating Centre: Women's and Children's Health

2. Consideration of the evidence

Literature search

From initial intelligence gathering and a high-level randomised control trial (RCT) search clinical areas were identified to inform the development of clinical questions for focused searches. Through this stage of the process 47 studies were identified relevant to the guideline scope. The identified studies were related to the following clinical areas within the guideline:

- Effectiveness and acceptability of long-acting reversible contraception (LARC)
- Risks (risk of LARC use on bone mineral density)
- Drug interactions (anti-epileptic drugs, antibiotics and antiretrovirals)
- Management of adverse effects

Four clinical questions were developed based on the clinical areas above, qualitative feedback from other NICE departments and the views expressed by the Guideline Development Group, for more focused literature searches. The results of the focused searches are summarised in the table below. All references identified through the initial intelligence gathering, high-level RCT search and the focused searches can be viewed in Appendix 1.

Clinical area 1: Effectiveness and acceptability		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q1: What is the efficacy and acceptability of long-acting reversible contraception?	Forty seven studies were identified through the focused search relating to this clinical question. Studies focused on efficacy, safety (particularly in specific groups including women with HIV/AIDs and adolescents) and acceptability (relating to patient satisfaction, insertion, continuation rates, weight gain, amenorrhea, breast feeding, infection risk, cancer risk and cardiovascular risk). <u>Efficacy</u> Seventeen studies were identified which reported on the efficacy of LARC including intrauterine devices (IUDs), depot-medroxyprogesterone acetate (DMPA), norethisterone enantate (NET-EN), levonorgestrel-releasing intrauterine system (LNG-IUS), Norplant and Implanon. In addition, a systematic review was identified which reported a hierarchy of contraceptive effectiveness: female sterilisation, LNG-IUS and implants,	No new evidence was identified which would change the direction of current guideline recommendations.

	copper IUDs, hormonal contraceptives (including injections) and barrier methods. *Implanon (three studies)* • A prospective cohort study found that adolescents who used Implanon were less likely to become pregnant compared to those using DMPA or combined oral contraceptives (COCs). • A systematic review concluded that Norplant remained effective for up to seven years although effectiveness decreased among women weighing >70 kg. • A systematic review reported the efficacy of the Sino-implant (II). *IUDs (eight studies)* • An RCT assessed the clinical performance of the frameless copper IUD (GyneFix) versus conventional IUDs. The frameless IUD had more insertion failures, expulsions and pregnancies in the first year than the TCu380A, but fewer pregnancies from the second to eighth	

	year. In addition, a Cochrane systematic review evaluated frameless versus classical IUDs concluding that the frameless device performs similarly to TCu380A and appears to have a lower pregnancy rate in later years, although the absolute difference is small. • The cost-effectiveness of MLCU375, TCu380A and YuangongCu365 was evaluated in one study conducted in China. The YuangongCu365 was reported to be most effective although the TCu380A was more cost-effective. Further long-term study is required. • Two Cochrane systematic reviews were identified which focused on the efficacy of the copper IUD. One review concluded that the IUD was more effective than DMPA in the populations studied. The second review compared different types of copper IUDs to determine their efficacy. The TCu380A and the TCu380S were found to be more effective than other IUDs. A similar conclusion was reiterated in two additional systematic reviews. Furthermore, copper IUDs were found to be effective in a comparative study.	

	DMPA and NET-EN (five studies) • One study was identified which assessed the effectiveness of immediate administration of DMPA to immediate use of short-term hormonal methods (bridge method) until later DMPA initiation. Immediate DMPA use was associated with improved adherence to DMPA continuation and fewer pregnancies. • DMPA continuation rates at 12 months were found to be higher than Cyclofem in one study whilst DMPA was shown to be more effective than COCs or the patch in preventing repeat pregnancy in a study involving adolescents. • One systematic review was identified which reported little difference in effectiveness between DMPA and NET-EN. In addition, a systematic review evaluated the evidence relating to return to pregnancy after injection of DMPA or NET-EN. Extremely low pregnancy rates were found during the 2-week interval following the reinjection rate.	

	LNG-IUS (one study) • One study reported the effectiveness of the LNG-IUS. <u>Safety</u> *Adolescents (two studies)* • A systematic review was identified which assessed the literature relating to IUD use in adolescents. The available literature was limited however, compared with COCs, IUDs had similar or better continuation rates. Further study is required. • One study was identified comparing NET-EN with COCs among adolescents aged 14-19 years. The study concluded that NET-EN is a recommended contraception option for adolescents. *Women with HIV/AIDS (one study)* • A systematic review was identified which evaluated whether HIV-infected women who use hormonal or intrauterine contraception are at increased risk of HIV disease progression or other adverse health	

	outcomes. The review concluded that although the evidence relating to the safety of hormonal and intrauterine contraception in women with HIV is limited, it is generally reassuring regarding adverse health effects and disease progression. <u>Acceptability</u> *Patient satisfaction (six studies)* • One study compared patient satisfaction among IUD and Implanon users. IUD users reported a higher level of satisfaction than Implanon users at 6 months. • A retrospective chart review reported lower rates of complications and greater acceptability among IUS users compared with women using the IUD. A prospective study concluded that satisfaction and continuation rates were high among both IUS and IUD users and that insertion of these devices was well tolerated. • A study examining the views of women concerning LARC was identified whilst a retrospective study reported acceptability of DMPA as a form of contraception.	

	• A Cochrane systematic review was identified which determined the effectiveness of techniques to improve adherence to hormonal methods of contraception. The review concluded that few studies have shown real benefit of strategies to improve adherence and continuation. *Insertion (four studies)* • A systematic review assessed the literature relating to time of insertion of IUDs postpartum. Identified evidence was poor to fair quality, however some increase in expulsion rates occurred with immediate insertion compared with interval insertion. • A Cochrane systematic review concluded that immediate postpartum insertion of IUDs appeared safe and effective. Expulsion rates appeared to be higher than with interval insertion. • Two studies found that immediate insertion of either an LNG-IUS or an IUD following abortion was associated with high patient satisfaction.	

	Continuation rates (one study) • A small scale RCT was identified which included adolescents aged 14-18 years assigned to either IUD or LNG-IUS use. At six months follow-up continuation rates were higher for the LNG-IUS among this population, although this increase was not statistically significant. *Weight gain (two studies)* • Two studies demonstrated increased weight gain among adolescent users of DMPA or NET-EN compared with COC users, discontinuers and non-users of contraception. *Amenorrhea (one study)* • One retrospective study assessed complications associated with DMPA and NET-EN use. Secondary amenorrhea was the commonest side effect observed associated with use of DMPA and NET-EN.	

	Breast feeding (three studies) • One study compared the LNG-IUS with an IUD, a second study compared Implanon with an IUD and the third study evaluated the effect of an etonogestrel-releasing implant versus DMPA on breast-feeding performance, infant growth and infant development. No statistically significant differences were found between groups with regard to infant physical growth parameters and various infant development tests. *Infection risk (one study)* • One study was identified which evaluated the presence of abnormal vaginal flora in women using either a copper IUD or an IUS. More women with an IUD developed bacterial vaginosis compared with women with an IUS at 4-6 weeks and 6 months however, this was not statistically significant. *Cancer risk (two studies)* • A systematic review evaluated the risk of neoplasia associated with	

	IUD use. The review concluded that IUD use does not appear to increase the risk of neoplasia. • One study was identified which compared the incidence of pre-malignant and malignant cervical conditions during a period of 10 years use of inert and copper bearing IUDs. No association between IUD use and cancer risk was observed. *Cardiovascular risk (six studies)* • One study investigated the effect of DMPA (four groups with use for 1, 2, 3 or 4 years) versus a control group on low density and high density lipoproteins. The results of the study demonstrated a gradual non-significant increase of the low density/high density lipoprotein cholesterol ratio in DMPA users compared with the control group. • Three studies were identified which assessed the possible effects of the LNG-IUS on serum lipids. The studies concluded that the LNG-IUS had no adverse effect on lipid metabolism.	

	• A small scale study investigating the effect of Implanon on cardiovascular risk factors concluded that the implant did not exert a negative effect. • One study assessed the risk of venous thrombosis in women using DMPA, LNG-IUS or an implant. The risk of venous thrombosis was increased in the DMPA group whilst the use of LNG-IUS was not associated with an increased risk. The implant group was too small to draw meaningful conclusions from the data obtained.	
Clinical area 2: Risks (bone mineral density)		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q1: Are there risks associated with bone mineral density and the use of long-acting reversible contraception?	Through the focused search 31 studies relevant to the clinical question were identified. Studies focused on the LNG-IUS, DMPA, NET-EN, IUD, Implanon and Norplant. <u>Systematic reviews (four studies)</u> • A systematic review was identified which evaluated the association	No new evidence was identified which would invalidate current guideline recommendations.

	between progestogen-only contraceptive use and fracture risk or bone density. The review concluded that limited evidence suggests the use of progestogen-only contraceptives other than DMPA do not affect bone density. • One systematic review evaluated changes in bone density following discontinuation of DMPA. The review concluded that bone loss occurring with DMPA use is reversible however data on fracture risk in DMPA users were lacking. • A Cochrane systematic review evaluated the effects of hormonal contraceptives before menopause on the risk of fracture in women. The review concluded that there was not enough available evidence to determine whether steroidal contraceptives influence fracture risk. • The effect of hormonal contraceptives on adolescents' bone health was assessed in a systematic review. The review concluded that although data on skeletal health outcomes is sparse, recovery of bone density is likely.	

	<u>LNG-IUS versus IUD (two studies)</u> • Two studies assessed forearm bone density in women using the LNG-IUS versus women using the TCu380A intrauterine device (IUD). No significant difference in bone density was observed between the two groups in either study. <u>LNG-IUS versus etonorgestrel-releasing intrauterine system (two studies)</u> • One study compared forearm bone density before and 18 months after insertion in women using the etonorgestrel-releasing intrauterine system compared with women using the LNG-IUS. Lower bone density at the midshaft of the ulna was observed in both groups at 18 months post insertion compared with baseline however, no difference was observed at the distal radius. This study was continued to 36 months and reported bone density at this time point. Bone density was lower at 36 months in both groups compared to pre-insertion values.	

	<u>Implanon versus control (one study)</u> • A cross-sectional study compared bone density in women using Implanon for at least two years compared with a control group. The Implanon group had significantly lower bone density at the distal radius and ulna compared with the controls. <u>Norplant versus non-user controls (one study)</u> • The bone quality in Nigerian women aged 25-50 years using Norplant compared with non-user controls was evaluated in one study. The study concluded that the contraceptive decreased overall bone turnover but there was no deleterious effect on bone quality in women using Norplant for up to four years. <u>Subcutaneous DMPA versus intramuscular DMPA (one study)</u> • An RCT evaluated bone density changes after two years in women using subcutaneous DMPA versus women using intramuscular DMPA. The results of the study indicated that subcutaneous DMPA provided comparable efficacy and bone density safety to	

	intramuscular DMPA. <u>DMPA versus COCs, nonhormonal contraception or non-user controls (fourteen studies)</u> • One study was identified which compared changes in bone density during 48 months between first-time DMPA users and controls. Bone density declined in women using DMPA. Following discontinuation a prolonged recovery time was observed in those who had used DMPA for a longer period of time. Four additional studies presented results showing a decline in bone density in women using DMPA compared with controls. • The effect of DMPA versus COCs on bone density in a triethnic population was assessed in one study. Bone density was measured every six months for three years. Use of DMPA resulted in greater bone loss but was largely reversible in the spine. • A prospective cohort study evaluated the effect of DMPA and COCs versus an untreated control group on bone density in adolescents (ages 12-18 years). A significant loss in bone density was observed	

	in the DMPA group compared with the other groups however, the rate of change slowed in the DMPA group over the second 12 months of the study. A similar study carried out in adolescents aged 14-18 years compared DMPA versus non-users. DMPA was associated with a significant loss of bone density however gains in bone density were observed post-discontinuation of DMPA. A prospective cohort study conducted in adolescents aged 11-18 years compared the use of DMPA versus non-users on bone density. Baseline differences in cohort characteristics, however, precluded meaningful comparisons of bone density changes over time. • The effect of DMPA versus nonhormonal contraception on bone density in women aged 25-35 years was assessed in a prospective cohort study. A decline in bone density was observed in the DMPA group although this appeared to resolve following discontinuation. • A cross-sectional observational study evaluated the long-term effects of DMPA use on bone density compared with non-users. Bone density was significantly lower in the DMPA group. The same	

	result was reported in a similar study. • A cross-sectional study was identified which suggested that bone loss during DMPA use is reversible. • A case-control study was identified which evaluated whether the effect of DMPA on the skeleton is age specific. Two groups were included in the study (18-25 years and 35-45 years). The results of the study indicated that DMPA use is associated with a bone density deficit at the spine and hip when used before peak bone mass. A follow-up study investigated whether increased bone turnover in DMPA users after peak bone mass is associated with bone mineral loss. The study concluded that measurement of bone turnover does not predict bone loss in DMPA users. • A retrospective case-control analysis evaluated the relationship between DMPA use and fracture risk in females aged 20-44 years. The results of the study suggested that use of DMPA may be associated with a slightly increased risk of fractures.	

	DMPA versus IUD (one study) • One study compared the bone density of postmenopausal women who had used DMPA or an IUD until menopause. At one and 2-3 years following menopause, no significant differences were observed in bone density of postmenopausal women who had used these methods of contraception until menopause. DMPA versus NET-EN *Adolescents aged 15-19 years (two studies)* • Two studies compared the use of DMPA and NET-EN versus non-user controls on bone density in adolescents aged 15-19 years. The results of the studies indicated that users of NET-EN had a lower increase in bone density over time compared with the other user groups. One of the studies indicated, however, recovery of bone density in NET-EN users in a small sample of adolescents followed post-discontinuation.	

	Women aged 19-24 years (one study) • A cross-sectional study investigated bone density in young women with a history of mixed hormonal contraceptive use. Three groups were evaluated: injectable contraceptives (DMPA, NET-EN or both), mixed COCs and injectable users or non-user controls. The results suggested that bone density is lower in long-term users of injectable contraceptives but not when women have mixed injectable and COC use. *Women aged 40-49 years (one study)* • A study was identified which evaluated the use of DMPA and NET-EN versus non-user controls on bone density in women aged 40-49 years. The results of the study indicated that use of DMPA or NET-EN for at least 12 months affects bone density in this population.	

Clinical area 3: Drug interactions		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q1: Do anti-epileptic drugs, antibiotics and antiretrovirals interact with long-acting reversible contraception?	Through the focused search 4 studies relevant to the clinical question were identified. <u>Antiretrovirals (three studies)</u> Three studies were identified focusing on contraceptive efficacy of LARC in women taking antiretrovirals: • A systematic review concluded that DMPA may be safe to administer with certain antiretrovirals including efavirenz, nevirapine and nelfinavir. • Two comparative studies assessed the efficacy of DMPA in HIV-infected women on antiretroviral therapy (efavirenz, nevirapine and nelfinavir-containing regimens). Suppression in ovulation in HIV-infected women on antiretroviral therapy using DMPA was retained.	No new evidence was identified which would change the direction of current guideline recommendations.

	Anti-epileptic drugs (one study) One review article was identified which evaluated contraception in women taking anti-epileptic drugs. The article indicates that as IUDs do not rely on hormonal components for contraceptive efficacy, they are appropriate for use in women taking anti-epileptic drugs.	
Clinical area 4: Management of adverse effects		
Clinical question	Summary of evidence	Relevance to guideline recommendations
Q1: How can adverse effects associated with insertion of IUDs and IUS be managed?	Through the focused search 7 studies relevant to the clinical question were identified. Non-steroidal anti-inflammatory drugs (NSAIDs) (four studies) Four studies were identified which evaluated the use of NSAIDs on pain during insertion of intrauterine devices: • A Cochrane systematic review concluded that no interventions that have been properly evaluated reduce pain during or after IUD insertion. One poorly controlled trial was identified which suggested that topical lidocaine gel may reduce insertion-related pain although	No new evidence was identified which would change the direction of current guideline recommendations.

	further study is required. Another Cochrane systematic review evaluated the use of NSAIDs for pain associated with IUD use and at the time of insertion. NSAIDs were found to be effective in reducing menstrual blood loss and pain associated with IUD use. However, preventative treatment around the time of IUD insertion had mixed results. • Two RCT evaluated the effect of prophylactic ibuprofen versus placebo for insertion pain and IUD removal within 12 months of insertion. Prophylactic use of ibuprofen did not reduce insertion pain or removal rates. <u>Antibiotic prophylaxis (one study)</u> A Cochrane systematic review was identified which assessed the effectiveness of prophylactic antibiotics before IUD insertion in reducing IUD-related complications (including pelvic inflammatory disease and discontinuation within three months of insertion). The review concluded that use of oral doxyclycline 200 mg or azithromycin 500 mg before IUD insertion confers little benefit and had little effect on discontinuation within	

	three months of insertion. Mifepristone (one study) One study was identified related to the use of mifepristone on intermenstrual bleeding associated with use of LARC: • Comparative study comparing the effect of mifepristone versus no drug on intermenstrual bleeding in women with LNG-IUS. Mifepristone reduced the number of episodes of intermenstrual bleeding in LNG-IUS users. Misoprostol (one study) An RCT was identified which evaluated the safety and efficacy of misoprostol versus placebo in repeat IUS insertions. No significant difference in ease of insertion of IUS was observed between the two groups although adverse events related to the study drug were more common in the misoprostol group.	

Several ongoing clinical trials (publication dates unknown) were identified focusing on the acceptability of LARC and the use of topical lidocaine in reducing pain prior to insertion of intrauterine devices.

Guideline Development Group and National Collaborating Centre perspective

A questionnaire was distributed to GDG members and the National Collaborating Centre to consult them on the need for an update of the guideline. Five responses were received with respondents highlighting that since publication of the guideline the following literature has become available:

- A series of Faculty of Sexual and Reproductive Healthcare (FSRH) documents published through 2009-10 in particular: quick starting LARC (September 2010); contraception for women aged over 40 years (July 2010) and contraceptive choices for young people (March 2010).
- Update of UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) in November 2009.

Modifications to practice were highlighted by questionnaire respondents including:

- Implanon being replaced by Nexplanon (a type II variation of Implanon) and associated training implications (the FSRH Clinical Effectiveness Unit Statement, 2010).

Ongoing research relevant to the guideline was highlighted by GDG members including:

- Subcutaneous injectables (including subcutaneous DMPA which can be self-administered or administered by professional groups such as pharmacists).
- Use of contraception by women who are obese.

This feedback contributed towards the development of the clinical questions for the focused searches.

Implementation and post publication feedback

No new evidence relating to guideline recommendations was identified through post publication feedback. All enquiries were routine and did not reflect a need to update the guideline.

An analysis by the NICE implementation team indicated that this guideline has been useful in practice. In addition, the NICE Implementation Team reported on national trends and activity associated with recommendations in the guidance. Prescriptions for implants (Implanon) and IUS in primary care in England continued to increase following the introduction of this guidance. In contrast the numbers of prescriptions for injectable contraceptives (DMPA) appear to be decreasing slowly. Furthermore, the NHS Information Centre for Health and Social Care (2008) bulletin indicated that use of LARC continues to increase and now accounts for 23% of primary methods of contraception, compared to 18% in 2003-04.

No new evidence was identified through post publication enquiries or implementation feedback that would indicate a need to update the guideline.

Relationship to other NICE guidance

The following NICE guidance is related to CG30:

Related NICE guidance not included in CG30	
CG44: Heavy menstrual bleeding: investigation and treatment, 2007.	To be reviewed January 2013.
PH3: One to one	To be reviewed February 2010.

interventions to reduce the transmission of sexually transmitted infections (STIs) including HIV, and to reduce the rate of under 18 conceptions, especially among vulnerable and at risk groups, 2007.	
Related NICE guidance in progress	
Clinical guideline: Osteoporosis.	Currently in development. Publication date: TBC.
Public Health guidance: The provision of contraceptive services in appropriate settings for socially disadvantaged young people (up to the age of twenty five).	Currently in development. Publication date: TBC.

Anti-discrimination and equalities considerations

No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original guideline offers best practice advice for all women of reproductive age who may wish to regulate their fertility through the use of LARC methods and considers specific issues for the use of these methods in women during the menarche and before the menopause. The guideline also identifies specific issues that may be relevant to particular groups, including women with HIV, learning disabilities and physical disabilities, and under-16s.

Conclusion

Through the process no new evidence was identified which would invalidate or change the direction of current guideline recommendations. The LARC guideline (CG30) should not be updated at this time.

3. Review recommendation

The guideline should not be updated at this time.

The guideline will be reviewed again according to current processes.

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31.01.11

Appendix I

Aisien, A.O. & Enosolease, M.E. 2010. Safety, efficacy and acceptability of implanon a single rod implantable contraceptive (etonogestrel) in University of Benin Teaching Hospital. *Nigerian Journal of Clinical Practice*, 13, (3) 331-335.

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