NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Recommendation for Guidance Executive

Clinical guideline

CG30: Long-acting reversible contraception - the effective and appropriate use of long-acting reversible contraception

Publication date

October 2005

8-year surveillance report for GE (post consultation)

April 2014

Please note that the 8-year surveillance review did not include consideration of the section of the guideline on progestogen-only subdermal implant as this section of the guideline has already been scheduled for a rapid update via the Guideline Updates Standing Committee

Previous review dates

2-year review: 2007/2008 (no update)
5-year review: 2010/2011 (no update)

Key findings

			Potential impact on guidance	
			Yes	**No**
Evidence identified from literature search				✓
Feedback from Guideline Development Group				✓
Anti-discrimination and equalities considerations				✓
No update	Rapid update	Standard update	Transfer to static list	Change review cycle
✓				

Surveillance recommendation

GE is asked to consider the proposal to not update the Long-acting reversible contraception guideline at this time. The surveillance review proposal was consulted on for two weeks.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

8-year surveillance review of CG30: Long-acting reversible contraception - the effective and appropriate use of long-acting reversible contraception

Recommendation for Guidance Executive

Background information

Guideline issue date: October 2005
2-year review: 2007/2008 (no update)
5-year review: 2010/2011 (no update)
8-year review: 2013

NCC: Women's and Children's Health

Main conclusions of previous surveillance reviews

1. CG30 was previously reviewed for update in 2007 and 2010. At both review points, no new evidence was identified which would change the direction of guideline recommendations. The review recommendations at both review points were that the guideline should not be considered for an update.

2. However, subsequent to the 5-year review, it came to the attention of NICE that Implanon®, the progestogen-only subdermal implant recommended in the guideline, has been discontinued and replaced by Nexplanon®. Nexplanon® contains the same amount of the same drug as Implanon®, but the summaries of product characteristics for the two devices are not identical.

3. In the light of the change in the implant available, the section of the guideline that makes recommendations on progestogen-only subdermal implants was selected as one of the pilot topics for the rapid update programme and was signed-off by Guidance Executive as a rapid update topic in June 2013. As this section of the guideline has been scheduled to undergo a rapid update it was not considered during this 8-year surveillance review.

Eight-year surveillance review

4. A literature search for systematic reviews and randomised controlled trials was carried out for the period between October 2010 (the end of the search period for the last review) and August 2013 and relevant abstracts were assessed.

5. Clinical feedback on the guideline was obtained from members of the GDG through a questionnaire; three responses were received.

6. No new evidence was identified for any of the section of the guideline that may impact on current recommendations.

Summary of stakeholder feedback

7. Stakeholders were consulted about the following proposals over a two week consultation period:

- The guideline should not be updated at this time.
- The guideline should be read in conjunction with evidence summaries on two new formulations prepared by the Medicines and Prescribing Centre at NICE under their Evidence Summaries: New Medicines (ESNM) programme:
    - ESNM31 Long-acting reversible contraception: subcutaneous depot medroxyprogesterone acetate (DMPA-SC)
    - ESNMxx Long-acting reversible contraception: low-dose levonorgestrel intrauterine-releasing system (in development, expected publication date June 2014)

8. Five stakeholders commented on the surveillance review proposal during the two-week consultation period (see Appendix 2).

9. Two stakeholders agreed with the review proposal to not update the guideline at this time and three stakeholders did not agree.

10. Stakeholders that disagreed with the surveillance review proposal commented that there are new publications on:
    - bone fracture risk in women using depot medroxyprogesterone acetate (DMPA) although the finding of this study is in line with current recommendations and
    - the protective effect of DPMA against epitheliail ovarian cancer. However, this finding comes from a single case-control study and further evidence is needed to refute or confirm the findings of this case-control study before inclusion in the guideline.

11. Stakeholders that disagreed also commented that the guideline should be updated to include the combined vaginal ring (NuvaRing®) which was excluded from the guideline because it was not licensed in the UK when the guideline was published in 2005. However, the combined

vaginal ring (NuvaRing®), though now licenced in the UK, would not meet the definition of a long-acting reversible contraception (LARC) as used in the guideline, as as it would need to be administered at least once per cycle (21 days' ring use and 7-day break) as per its licenced indication. Long-acting reversible contraception (LARC) is defined in the guideline as methods that require administering less than once per cycle or month.

12. No comments were provided by any stakeholder on equality issues or areas excluded from the original scope.

Ongoing trials

13. None identified.

Anti-discrimination and equalities considerations

14. None identified.

Implications for other NICE programmes

15. A section of the guideline has already been scheduled to undergo a rapid update (progestogen-only subdermal implants) and is scheduled to be presented to the Rapid Updates Committee in April 2014.

16. A Quality Standard for contraceptive services (including emergency contraception) has been referred and been tentatively scheduled into the 2015/16 workplan with a provisional start date still to be agreed.

17. The guideline will remain on the active surveillance list.

Conclusion

18. Through the 8-year surveillance review of CG 30 no new evidence was identified that may impact guideline recommendations.

19. However, two new formulations of existing drugs have been identified and are the subject of evidence summaries prepared by the Medicines and Prescribing Centre at NICE under their Evidence Summaries: New Medicines (ESNM) programme:
    - ESNM31 Long-acting reversible contraception: subcutaneous depot medroxyprogesterone acetate (DMPA-SC)
    - ESNMxx Long-acting reversible contraception: low-dose levonorgestrel intrauterine-releasing system (in development, expected to be published in June 2014)

In light of the publication of these summaries it is felt that the guidance should not be updated at this time but evidence on the above will be considered further at the next review point in October 2015.

Surveillance recommendation

20. GE is asked to consider the proposal to not update the Long-acting reversible contraception guideline at this time. However, the guideline should be read in conjunction with evidence summaries on the two new formulations.

Mark Baker – Centre Director
Sarah Willett – Associate Director
Khalid Ashfaq – Technical Analyst

Centre for Clinical Practice
April 2014

Appendix 1 - Decision matrix

Surveillance and identification of triggers for updating CG30. The table below provides summaries of the evidence/intelligence that were identified.

Conclusions from previous reviews	Is there any new evidence/intelligence identified during this 8-year surveillance review (2013) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2013)
Contraceptive use and principles of care			
2-year review (2007/2008) Update not required after review of evidence 5-year review (2007/2008) Update not required after review of evidence	No. Fourteen studies were identified; findings of studies were consistent with guideline recommendations	No clinical feedback was provided for this section of the guideline	New evidence is consistent with guideline recommendations
Copper intrauterine devices (IUDs)			
2-year review (2007/2008) Update not required after review of evidence 5-year review (2007/2008) Update not required after review of evidence	No. Forty four studies were identified; findings of studies were consistent with guideline recommendations	No clinical feedback was provided for this section of the guideline	New evidence is consistent with guideline recommendations
Intrauterine system (IUS)			
2-year review (2007/2008) Update not required after review of evidence	No. Fourteen studies were identified consistent with guideline recommendations.	No clinical feedback was provided for this section of the guideline	New evidence is consistent with guideline recommendations. However, the guideline should be read in conjunction with the soon to

Conclusions from previous reviews	Is there any new evidence/intelligence identified during this 8-year surveillance review (2013) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2013)
5-year review (2007/2008) Update not required after review of evidence	Two of these studies relate to a new low-dose levonorgestrel intrauterine system that is due to launch in the UK and to be marketed as Jaydess® (Bayer). The Medicines and Prescribing Centre (MPC) at NICE is due to produce a report on this new low-dose levonorgestrel intrauterine system through the Evidence Summaries: New Medicines (ESNM) programme (expected publication date July 2014).		be published MPC report on this new low-dose levonorgestrel intrauterine system.
Progestogen-only injectable contraceptives (POICs)			
2-year review (2007/2008) Update not required after review of evidence 5-year review (2007/2008) Update not required after review of evidence.	No. Sixteen studies were identified that would not change the direction of current guideline recommendations. However, a report has been produced by the Evidence Summaries: New Medicines (ESNM) programme of the Medicines and Prescribing Centre (MPC) at NICE on a newly licenced subcutaneous formulation of medroxyprogesterone, called Sayana Press®.	Feedback from the GDG related to the need for guidance on Sayana Press® the new subcutaneous formulation of depot medroxyprogesterone acetate that was launched in the UK in 2013.	New evidence is consistent with guideline recommendations. However, the guideline should be read in conjunction with ESNM31 Long-acting reversible contraception: subcutaneous depot medroxyprogesterone acetate (DMPA-SC), the MPC report on Sayana Press®.
Progestogen-only subdermal implants			
2-year review (2007/2008) Update not required after review of	Section not reviewed as it has been scheduled to undergo a rapid update	Section not reviewed as it has been scheduled to undergo a	As this section of the guideline has been scheduled to undergo a rapid update it was not considered during

Conclusions from previous reviews	Is there any new evidence/intelligence identified during this 8-year surveillance review (2013) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 8-year surveillance review (2013)
evidence <u>5-year review (2007/2008)</u> Update not required after review of evidence Subsequently, it came to the attention of NICE that Implanon®, the progestogen-only subdermal implant recommended in the guideline, has been discontinued and replaced by Nexplanon®. Nexplanon® contains the same amount of the same drug as Implanon®, but the summaries of product characteristics for the two devices are not identical. In the light of the change in the implant available, the section of the guideline that makes recommendations on progestogen-only subdermal implants was considered as one of the pilots for the rapid update programme and was signed-off by Guidance Executive as a rapid update topic in June 2013.		rapid update	this 8-year surveillance review.

Appendix 2 - Consultation comments and response

Stakeholder	Do you agree that the guidance should not be updated?	Comments If you disagree please explain why	Response
British Association for Sexual Health and HIV (BASHH)	Disagree	Comments on proposal not to update the guidance 1. The combined vaginal ring (NuvaRing) was not included in the last guidance as it was not licensed in the UK. It is now licensed and should, by definition, be considered to be a LARC since it is administered once per cycle (and less than once per cycle if a woman chooses to omit the ring-free interval). 2. Re DMPA (depo provera), there is conflicting data about a potential increased risk of HIV acquisition (and transmission) with DMPA. WHOMEC and the USMEC state: ".....because of the inconclusive nature of the body of evidence on possible increased risk of HIV acquisition, women using progestogen-only injectable contraception should be strongly advised to also always use condoms, male or female, and other HIV preventive measures". I think that it might be wise for the NICE guidelines to add something similar to their current guidance. i.e. "DMPA is a safe and effective method of contraception for women with STIs, including HIV/AIDS. Because of the inconclusive nature of the body of evidence on possible increased risk of HIV acquisition, women using progestogen-only injectable contraception should be strongly advised to also always use condoms, male or female, and other HIV preventive measures" 3. There are references to information that was due to be published after the 2005 guidance was published e.g. "A UK version of the WHO-MEC document is currently under development by the FFPRHC and will be published by the end of 2005" which should now be updated. FFPRHC is now FSRH and DFFP is now DFSRH	Thank you for your comments. 1. Long-acting reversible contraception (LARC) is defined in this guideline asmethods that require administering less than once per cycle or month. The combined vaginal ring (NuvaRing®), though now licenced in the UK, would not meet this definition as it would need to be administered at least once per cycle (21 days' ring use and 7-day break) as per its licenced indication. The continuous use of NuvaRing® is outside the terms of the product licence. http://www.fsrh.org/pdfs/NuvaringProductReview240309.pdf http://www.medicinescomplete.com/mc/bnf/current/PHP4942-nuvaring.htm#PHP4942-nuvaring 2. The fact that there is inconsistent evidence regarding the increased risk of HIV acquisition among users of progestogen-only contraceptives compared with non-users is not new – it was acknowledged in the guideline (see p.30 and p.93 of the full guideline) and

Stakeholder	Do you agree that the guidance should not be updated?	Comments If you disagree please explain why	Response
			there is a recommendation to that effect: "Healthcare professionals should be aware that DMPA is a safe and effective method of contraception for women with STIs, including HIV/AIDS (safer sex using condoms should be encouraged in this group)" 3. We appreciate that ideally these should be updated. However, the purpose of this surveillance review is to identify new evidence that is likely to impact on current guideline recommendations; the current review process does not involve editorial amendments.
Merck Sharp & Dohme Ltd (MSD)	Agree - we support the proposal not to update the guideline at this time. This does not affect the rapid review of CG30 which is currently underway.		Thank you for your comment.
Pfizer Ltd	Disagree	<u>Comments on proposal not to update the guidance</u> Pfizer welcomes this review of the existing evidence to determine the suitability of an update to CG30 (2005).This remains an important area and while much has	Thank you for your comments. 1. NICE is aware that the progestogen-only subdermal implant, Implanon,

Stakeholder	Do you agree that the guidance should not be updated?	Comments If you disagree please explain why	Response
		been done in recent times, the rate of unwanted pregnancies remains high at >20% of conceptions {Conceptions in England and Wales, 2012. Office of National Statistics} with the associated annual medical cost of unintended pregnancy at around £662 million in 2011 {Unprotected Nation, 2013. Development Economics}. The implementation and development of this guideline should be addressed so that clinicians can be equipped with the most up to date information. Pfizer would like to recommend that the guideline be updated as there have been a number of important changes to the LARC field. The following new publications and treatments support our position: 1. Availability of new treatments in this area e.g. Sayana Press, Nuvaring and Nexplanon. These are innovative new products that are not evaluated in the current guideline and it should therefore be updated to reflect this. 2. A study on the UKGPRD database that analyses 312,395 women in the UK has found that bone fracture risk in women is not increased by using depot medroxyprogesterone acetate (DMPA) 3. Results from a multicentre, case-control study (Wilailak et al 2011) in twelve hospitals across Thailand (n=330 cases; 982 controls) suggest that the use of DMPA may be associated with a reduced risk of epithelial ovarian cancer.	recommended in the guideline has been discontinued and replaced by Nexplanon, and in the light of the change in the implant available, the section of the guideline that makes recommendations on progestogen-only subdermal implants is scheduled to undergo an update. This was pointed out in the 8-year surveillance review consultation document which also stated that a report has been produced by the Evidence Summaries: New Medicines (ESNM) programme of the Medicines and Prescribing Centre (MPC) at NICE on Sayana Press® and that the guideline should be read in conjunction with this MPC report on the drug. The combined vaginal ring (NuvaRing®), though now licenced in the UK, would not meet the definition of long-acting reversible contraception (LARC) in the guideline as as it would need to be administered at least once per cycle (21 days' ring use and 7-day break) as per its licenced indication. http://www.fsrh.org/pdfs/NuvaringProductReview240309.pdf http://www.medicinescomplete.com/mc/bnf/current/PHP4942-

Stakeholder	Do you agree that the guidance should not be updated?	Comments If you disagree please explain why	Response
			nuvaring.htm#PHP4942-nuvaring Long-acting reversible contraception (LARC) is defined in this guideline as methods that require administering less than once per cycle or month. 2. Thank you for bringing the UKGPRD database study (Lanza et al. 2013) to our attention. As you have stated, the study found that bone fracture risk in women is not increased by using depot medroxyprogesterone acetate (DMPA). This finding is in line with the guideline recommendation that "there is no evidence that DMPA use increases the risk of fracture" (p.13, full guideline) 3. Thank you for bringing the Wilailak et al. study to our attention. However, further evidence is needed to refute or confirm the findings of this case-control study before inclusion in the guideline.
Bayer plc (formally Schering Healthcare Ltd)	Agree that this guideline should not be updated	Comments on proposal not to update the guidance We note that *"a literature search for randomised controlled trials and systematic reviews was carried out for articles published between October 2010 (the end of the search period for 5-year review in 2010) and August 2013"* in order to inform this update proposal. Guidance from the EMEA committee for medicinal products for human use (CHMP) on clinical investigation of steroid contraceptives in women states that	Thank you for your comment and for providing references that may be relevant for consideration for the update of the sub-dermal implants section.These references will be passed on to the team responsible for the update. In terms of our process, it is not our aim to conduct a full systematic review of the

Stakeholder	Do you agree that the guidance should not be updated?	Comments If you disagree please explain why	Response
		"studies including an active comparator are not generally requested for efficacy purposes".[1] Furthermore, it has been suggested in an FDA briefing document that *"the clinical trial environment, where subjects may have frequent contact with investigators, may be paid to attend clinic visits, and may even keep daily diaries of their use of the product, is unlikely to generalize fully to the actual conditions under which women use contraceptive products."*[2] Given the above we suggest that restricting the search for new evidence to randomised controlled trials or systematic reviews may not be appropriate in the case of this guideline. 1. European Medicines Agency. Committee for Medicinal Products for Human use (CHMP). Guideline on Clinical Investigation of Steroid Contraceptives in Women. Doc. Ref. EMEA/CPMP/EWP/519/98 Rev 1. London, 27 July 2005. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003349.pdf (last accessed 11/03/2014) 2. FDA Briefing Document. Prepared by the Division of Reproductive and Urologic Products, Office of Drug Evaluation III, December 21, 2006. Advisory Committee for Reproductive Health Drugs. General Meeting. January 23 and 24, 2007. Available at: http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4274b1-01-fda.pdf (last accessed 11/03/2014) Please find below a list of citations to publications that are relevant to the guideline but that were published after the date of the search undertaken for the surveillance review. These publications may be relevant for consideration for the rapid update concerning sub-dermal implants. • O'neil-Callahan M, Peipert JF, Zhao Q, Madden T, Secura G. Twenty-four-month continuation of reversible contraception. Obstet Gynecol. 2013 Nov;122(5):1083-91. doi: 10.1097/AOG.0b013e3182a91f45.	whole guideline. We use intelligence from the GDG questionnaire, initial intelligence gathering and a high-level RCT and systematic review search to determine clinical areas within the guideline where new evidence exists that may have an impact on current guideline recommendations in addition to taking consideration of any safety aspects and drug licensing. All this information is used to form the basis of more focused searches for evidence on key topic areas if required. All of which informs the review proposal.

Stakeholder	Do you agree that the guidance should not be updated?	Comments If you disagree please explain why	Response
		• Short M, Dallay D, Omokanye S, Stauch K, Inki P. Acceptability of long-acting, progestin-only contraception in Europe: A two-year prospective, non-interventional study. Eur J Contracept Reprod Health Care. 2014 Feb;19(1):29-38. doi: 10.3109/13625187.2013.862230. Epub 2013 Nov 29. • Weisberg E, Bateson D, McGeechan K, Mohapatra L. A three-year comparative study of continuation rates, bleeding patterns and satisfaction in Australian women using a subdermal contraceptive implant or progestogen releasing-intrauterine system. Eur J Contracept Reprod Health Care. 2014 Feb;19(1):5-14. doi: 10.3109/13625187.2013.853034. Epub 2013 Nov 14.	
Faculty of Sexual and Reproductive Healthcare (FSRH)	Disagree	<u>Comments on proposal not to update the guidance</u> We feel that it may be appropriate to consider a full review at this stage. There are a number of new products which could be incorporated into the document. While, we acknowledge that professionals will be able to read the new product reviews that NICE will produce alongside the existing document, it would be usful to have all the information in the one resource as we feel this would increase access and useability of the document – especially by front line staff. This would also allow for the newly indentified evidence to be added as well as other newer studies such as: Lanza LLS, McQuay LJM, Rothman KJD, Bone HGM, Kaunitz AMM, Harel ZM, et al. Use of Depot Medroxyprogesterone Acetate Contraception and Incidence of Bone Fracture. [Article]. Obstetrics & Gynecology 2013;121(3):593-600. Continuation data from CHOICE project. Key areas include BMD and DMPA, Weight and DMPA, ectopic pregnancy data and perforation data in relation to intrauterine contraceptives (influence of	Thank you for your comment. We are glad that you acknowledge that “the findings of much of the research will not change the overall recommendations”. In addition, it is felt that the guidance should not be updated at this time in light of the publication of summaries by NICE on the new contraceptive products and evidence will be considered further at the next review point in 2015. In terms of our process, it is not our aim to conduct a full systematic review of the whole guideline. We use intelligence from the GDG questionnaire, initial intelligence gathering and a high-level RCT and systematic review search to determine clinical areas within the guideline where new evidence exists that may have an

Stakeholder	Do you agree that the guidance should not be updated?	Comments If you disagree please explain why	Response
		breastfeeding and experience of professional/number of insertions) We acknowledge that the findings of much of the research will not change the overall recommendations, but it would be a more up to date and comprehensive document. In additon, the vaginal ring was excluded from the original document because it was not available in the UK. This has not been the case now for several years. It would be classified as a LARC according to the definition of administration less than once a month. Some clarification is required as to whether it is a LARC or not. While evidence is limited on its superior efficacy over shorter acting methods, it would be useful to highlight it as an option, given its preferable bleeding patterns and other non-contraceptive benefits.	impact on current guideline recommendations in addition to taking consideration of any safety aspects and drug licensing. All this information is used to form the basis of more focused searches for evidence on key topic areas if required. All of which informs the review proposal. The combined vaginal ring (NuvaRing®), though now licenced in the UK, would not meet the definition of a long-acting reversible contraception (LARC) in the guideline as as it would need to be administered at least once per cycle (21 days' ring use and 7-day break) as per its licenced indication. http://www.fsrh.org/pdfs/NuvaringProductReview240309.pdf http://www.medicinescomplete.com/mc/bnf/current/PHP4942-nuvaring.htm#PHP4942-nuvaring Long-acting reversible contraception (LARC) is defined in this guideline as methods that require administering less than once per cycle or month.