DEPOT MEDROXYPROGESTERONE ACETATE VERSUS NORETHISTERONE OENANTHATE FOR LONG-ACTING PROGESTOGENIC CONTRACEPTION: A SYSTEMATIC REVIEW

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DECLARATION

I, Beverly Helen Draper, hereby declare that the work on this dissertation is based on my original research and has not, in whole or in part, been submitted towards another degree, at this university or elsewhere. The university is empowered to reproduce either the whole or any portion of the contents for the purposes of research.

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Signature

1/6/06

Date

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ABSTRACT

Background

Two injectable progestogen-only contraceptives (IPCs) depot medroxyprogesterone acetate (DMPA) and norethisterone oenanthate (NET-EN) continue to be extensively used in some countries, forming a large proportion of the health system's expenditure on contraception. Both these highly effective contraceptives receive wide acceptance amongst women in their fertile years. They differ in cost and frequency of administration. A systematic comparison was undertaken to investigate their rational use.

Objectives

To determine if there are differences between depot medroxyprogesterone acetate given at a dose of 150 mg IM every three months and norethisterone oenanthate given at a dose of 200mg IM every two months, in terms of contraceptive effectiveness, reversibility and discontinuation patterns, and adverse clinical effects.

Study design

A Cochrane systematic review was used to answer the question posed in the research objective. This included a systematic search for all available literature comparing DMPA and NET-EN, followed by appraisal of all studies for inclusion in the review. Meta-analysis was then applied to the included study.

Methodology

We searched the Cochrane Controlled Trials Register, MEDLINE using PubMed, EMBASE, POPLINE, Biblioline, LILACS, and PASCAL for randomised controlled trials of DMPA versus NET-EN for long-acting progestogenic contraception. Studies were included regardless of language, and databases were reviewed from 1963 when injectable progestogens were introduced. We also contacted manufacturers and researchers in the field.

All randomised controlled comparisons of DMPA given at a dose of 150 mg IM every three months versus NET-EN given at a dose of 200mg IM every two months, used for contraception, were included. Trials had to report on contraceptive efficacy and return to

fertility, discontinuation risks and reasons for discontinuation, and clinical effects, both menstrual and non-menstrual.
The primary reviewer and another reviewer independently assessed trial quality and extracted data obtained through applying the search strategy and the eligibility criteria. The primary reviewer attempted to contact authors where clarifications of the data were required, as well as all main manufacturers of the contraceptives.

Analysis
Data from the WHO trial were abstracted and analysed with the software package RevMan 4.2.

Results
Fifty six articles were accessed, of which four were trials that met the inclusion criteria. Three of these trials were later excluded, and one multi-centre trial by the World Health Organisation (WHO) with 13 individual trial centres involving 2376 women was included. There was no statistically significant difference between the two treatment groups for the frequency of discontinuation for either contraceptive after two years of use. The NET-EN group were 4% more likely to discontinue for personal reasons, and the DMPA group 5% more likely to discontinue for amenorrhoea. Accidental pregnancy did not differ between the groups over two years. Women on DMPA were 21% more likely to develop amenorrhoea. Mean changes in body weight and blood pressure did not differ between the study groups.

Conclusion
While the choice between DMPA and NET-EN as injectable progestogen-only contraceptives may vary between both health providers and patients, there is little difference between the effects of these methods, except that women on DMPA are more likely to develop amenorrhoea.

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ABBREVIATIONS

CI	Confidence interval
DMPA	Depot medroxyprogesterone acetate
DoH	Department of Health
IM	Intramuscular
IMS	Intercontinental Medical Statistics
IPC	Injectable progestogen-only contraceptives
NET-EN	Norethisterone oenanthate
RD	Risk difference
RevMan	Review Manager
UN	United Nations
UNFPA	United Nations Population Fund
WHO	World Health Organisation
WMD	Weighted mean differences

Chapter 1: Background & Literature review

There are two injectable progestogen-only contraceptives (IPCs) available for use. These are depot medroxyprogesterone acetate (DMPA) and norethisterone oenanthate (NET-EN).

It was discovered in 1953 that esterifying a progestogen produced a drug with a long lasting effect. IPCs are now available in many countries in the world (Lande 1995) and play an important role in many national family planning and health programs (Sapire 1990). They are extensively used in some developing countries (e.g. Indonesia, Thailand and South Africa) and are currently used in more developed countries. In 2004, approximately 7 million doses of DMPA were distributed in the United States (IMS 2005). Donor agencies have reported that use of IPCs has increased across the world in the last decade (DoH 1999). For instance, the United Nations Population Fund (UNFPA) provided 12 million doses of injectables in 1992, and about 20 million in 1994 (Lande 1995). By 2000, more than 30 million women worldwide were using contraception in the form of an implant or injection (UN 2003), and by 2002, injectable contraceptives constituted 18.5% of global donor support for contraceptives (UN 2002). The use of injectable contraception remains higher in less developed countries (UN 2001), and in countries where IPCs are widely used, they account for a substantial share of expenditure on drugs (Smit 2000). In South Africa, they are by far the most commonly used contraceptive method in the public sector (DoH 1999) and provide a safe, convenient, effective and reversible method of fertility regulation (Sapire 1990).

DMPA is a synthetic 17-hydroxyprogesterone derivative with progestational activity, providing contraceptive protection for three months; and NET-EN is a long chain ester of norethisterone, effective for two months. They are both highly effective contraceptive agents and 12-month pregnancy rates are generally lower than with oral contraceptives (Sapire 1990). The mechanism of action of the IPCs is primarily the prevention of ovulation, supplemented mainly by contraceptive actions at the endometrial and cervical mucus level (Guillebaud 1993). The commodity cost of DMPA is considerably lower than that of NET-EN (DoH 1999, Smit 2000). For example in South Africa in 2005, the annual cost ratio of NET-EN:DMPA is 2.3:1(DoH 2005). DMPA is the predominant product used world-wide (Lande 1995), but there appears to be increasing use of norethisterone

oenanthate (NET-EN) in at least one country (South Africa) where IPCs are extensively used (Smit 2000). Given the cost implications of the increasing use of NET-EN, a careful and systematic comparison of these preparations is required in order to ensure their rational use, particularly in less developed countries.

To this end, the best evidence comparing DMPA and NET-EN will indicate whether these contraceptives differ significantly regarding their clinical efficacy and adverse effects. Evidence-based medicine is based upon the assimilation and evaluation of data gathered from the cumulative experience of others in the field, and making the best use of that evidence in clinical practice (Sackett 1995). Once a clearly defined question has been formulated, it should be answered through the process of a search for the relevant evidence which should then undergo a critical appraisal for its validity and usefulness (Sackett 1995). The search for evidence requires a systematic approach by an explicit and pre-determined method. This will identify all available published and unpublished literature on a specific topic that will then be appraised, synthesised, and, if relevant statistically aggregated (Moher 1999). A good systematic review addresses a clearly defined question, details the search strategy and explains how studies were selected and excluded (Cochrane Library 2006). Research synthesis is the process whereby two or more research studies may be combined to summarise the evidence relating to a particular question. Meta-analysis is a statistical procedure that integrates the result of two or more independent studies considered to be "combinable" (Egger 1997).

A Cochrane review is a systematic review that is produced by the Cochrane Collaboration. This is a non-profit organisation that prepares, maintains and disseminates up-to-date systematic reviews of health care interventions. These reviews are produced in a standardised format and undergo extensive external peer review (Cochrane Library 2006). Once completed, a systematic review is published electronically in the Cochrane Library and indexed in Medline. This presentation of evidence-based medicine offers a robust scientific method to aid clinical decision making, and may further assist expert clinicians in making evidence-based decisions outside their fields (Burch 2003).

Chapter 2: Objectives and Criteria for Inclusion

2.1. Objectives

To determine if there are differences between depot medroxyprogesterone acetate (DMPA) given at a dose of 150 mg IM every 3 months and norethisterone oenanthate (NET-EN) given at a dose of 200mg IM every 2 months, in terms of contraceptive efficacy, reversibility and discontinuation patterns, and adverse effects.

2.2. Criteria for considering studies for this review

2.2.1. Types of studies

All randomised controlled comparisons of DMPA given at a dose of 150 mg IM every 3 months versus NET-EN given at a dose of 200mg IM every 2 months, used for contraception.

2.2.2. Types of participants

Healthy women of reproductive age, of all ethnic groups who are using either of the IPCs i.e. DMPA or NET-EN.

2.2.3. Types of interventions

DMPA given at a dose of 150 mg IM every 3 months versus NET-EN given at a dose of 200mg IM every 2 months, used for contraception.

2.2.4. Types of outcome measures

- Cumulative discontinuation rates: overall risks and risks due to specific menstrual and non-menstrual adverse effects.
- Contraceptive efficacy: accidental pregnancy as a risk of reason for discontinuation.
- Risk differences of specific menstrual and non-menstrual adverse effects.

Adverse effects

These were classified as menstrual or non-menstrual

Menstrual

- Amenorrhoea
- Menorrhagia
- Spotting
- Irregular bleeding
- Dysmenorrhoea

Non-menstrual

- Headache
- Clinically significant weight change of 2 kg or more.
- Decreased libido
- Mood swings and/or depression
- Nausea
- Dizziness
- Vaginal discharge

Chapter 3: Methods

3.1. Search strategy for identification of studies

We searched the computerized databases Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE using PubMed, EMBASE, POPLINE, Biblioline, LILACS, and PASCAL for randomised controlled trials of DMPA versus NET-EN for long-acting progestogenic contraception. Studies were included regardless of language, and all databases were reviewed from the time that injectable progestogens have been in use, namely 1963.

We searched Cochrane Controlled Trial Register using the search strategy:
(injectable contraceptives OR contraceptive agents) AND (medroxyprogesterone acetate-17 OR medroxyprogesterone acetate OR 17-medroxyprogesterone acetate OR depot medroxyprogesterone acetate OR depo provera OR depot provera OR DMPA) AND (norethindrone OR NET-EN OR NET-ENT OR NET-OEN OR nuristerate OR norethisterone oenanthate.

We searched PubMed using the search strategy:
((contraceptive agents, female OR contracept*) AND ((medroxyprogesterone acetate-17 OR medroxyprogesterone acetate OR 17-medroxyprogesterone acetate OR depot medroxyprogesterone acetate OR depo provera OR depot provera OR DMPA) AND (norethindrone OR NET-EN OR NET-ENT OR NET-OEN OR nuristerate OR norethisterone oenanthate))) AND (clinical trials OR random allocation or random*) NOT (menopaus* OR post menopaus* OR HRT OR "hormone replacement")

We searched EMBASE using the search strategy:
(contraceptive agent or contracept?)
AND
((DMPA or depot medroxyprogesterone or depot medroxyprogesterone acetate or medroxyprogesterone acetate or depo provera or depot provera) AND (NET EN or norethindrone or norethisterone or norethisterone enanthate))
AND
(clinical trial or random(w)allocation or random)

We searched POPLINE using the search strategy:
((medroxyprogesterone acetate/depo provera/DMPA) & (NET-EN/norethindrone/norethindrone acetate/norethindrone enanthate))/ (contraceptive agents progestin & inject*)) & (clinical trial*/random*)

We searched Biblioline using the search strategy:
1. contraception, hormonal OR contraception, injectable OR family planning, hormonal
2. medroxyprogesterone acetate-17 OR medroxyprogesterone acetate OR 17-medroxyprogesterone acetate OR depot medroxyprogesterone acetate OR depo provera OR depot provera OR DMPA
3. NET-EN OR NET-ENT OR NET-OEN OR nuristerate OR norethisterone oenanthate
4. clinical trials OR random allocation OR random

We searched LILACS using the search strategy:
medroxyprogesterone acetate or depo or depot provera or dmpa or depo provera or DMPA or acetado de medroxiprogesteronade de deposito or injectivo de solo progestageno [Words] and norethindrone or noretindrona or noretindrona or net-en or net-ent or en-net or noristerat inyectable or enantato de norestistero or anticonceptiva noristerat inyectable [Words] and (contraceptive or contraceptives or agentes anticonceptivos or anticoncepcionais) [Words]

We searched PASCAL using the search strategy:
(Contraceptive OR contraceptive agent OR contracept OR contraception)
AND
(DMPA OR depo OR depo provera OR depo-provera OR depo-provero OR depo-medroxyprogesterone acetate OR medroxyprogesterone OR medroxyprogesterone acetate OR medroxyprogesteroneacetate OR medroxyprogesterone(17-0-acetyl)-ana OR medroxyprogest) AND
(NET EN OR NET-EN OR norethisterone OR norethisterone enanthate OR norethindrone OR norethynodrel OR noretisterona)
AND
(clinical trial OR comparative study)

The variation in search strategies for the different computerised databases may be explained by the process of initial searches of the databases that gave indication of the key words each one contained that pertained to the search topic. Boolean links and

grouping of the keywords were then inserted under advisement of the search strategist of the Cochrane Fertility Regulation Group. Hence the Pubmed search strategy was wider than that for EMBASE or POPLINE. The databases that contained considerable literature that was not in English, namely LILACS (Spanish) and PASCAL (Spanish and French) were accessed with the relevant language key words, in addition to the English terms. The abstracts that were in Spanish were translated by the Cochrane Fertility Regulation Group search strategist from Family Health International.

We searched the reference lists of all identified studies for eligible trials and additional, previously unidentified trials. Relevant book chapters and review articles were searched for all relevant trials. In addition, we attempted to find unpublished randomized controlled trials through personal communication with experts and the manufacturers of both contraceptives.

We accessed conference proceedings and health organisations including:
World Health Organisation
Family Health International
Population Council
U.S. Food and Drug Administration
Evidence on adverse effects / Medicines Control Council

3.2. Methods of the review

The primary reviewer and a second reviewer evaluated the titles and abstracts obtained through applying the search strategy as described previously and applied the eligibility criteria. The reviewers performed this independently using a standardised study validity form (Appendix A), and differences were resolved through discussion. If there was the possibility for inclusion, we obtained the full article. We focused on the types of intervention and method of randomization. The primary reviewer made numerous attempts to contact the authors of the trials and the centres where they were performed, in studies where randomization was unclear. Details about the methods used were requested, but no responses were received, presumably because a considerable length of time had elapsed since these studies were executed. The reasons for excluding studies are stated in Table 1 (Characteristics of excluded studies).

The only suitable study for inclusion was the WHO multinational trial which was conducted in 13 centres. The primary reviewer and the same reviewer abstracted the data. The large WHO multinational study did not supply discontinuation rates for the total study. Only the individual discontinuation rates for each of the thirteen centres where the study had been performed were published in the study results. It was agreed to use the results individually from all thirteen centres in order to obtain a more accurate result. Therefore these centres were entered as separate studies for this purpose. For all other results of the WHO study, we used the total outcomes of the multinational study.

3.3. Analysis

We used the software package RevMan 4.2. to analyse the data.

Meta-analysis was applied to analyse the discontinuation rates according to the 13 centres in the trial. Another reviewer who is a statistician assisted with the statistical analysis of the abstracted data. For the dichotomous outcomes, such as discontinuation rates, episodes of bleeding and spotting, and amenorrhoea, cumulative rates per 100 women were converted to risks. These were compared by calculating risk differences (RD) with 95% confidence intervals (CI) assuming random effects models. Numerical data such as duration of bleeding and spotting episodes, and changes in body weight and blood pressure were summarised using weighted mean differences (WMD) assuming random effects models. Subgroup analysis included results at 12 months and at 24 months.

3.4. Potential conflict of interest

No conflict of interest exists in the research for this review.

Chapter 4: Description of Studies

4.1. Description of studies

Initially fifty six articles were accessed for assessment and consequently short-listed to nine randomised controlled trials. Four of these trials were initially included because they were thought to meet the inclusion criteria for the study. They were WHO 1983, Salem 1988, Swenson 1980 and Janjua 1983(WHO multinational, Salem HT, Swenson I, Janjua S). Those of Salem, Swenson and Janjua were later excluded. For characteristics of excluded trials (Table 1).

Table 1: Characteristics of excluded studies

Study	Reason for exclusion
Abdel-Sayed WS	Randomisation is not specified. The outcomes are metabolic and hormonal changes that are not the outcomes for this review. Gonadotrophin inhibition is discussed as the mechanism for ovulation inhibition, but no conclusions are drawn.
Aly FA	The study subjects were not randomised into the two treatment groups. A random sample was selected of two groups who used either depot medroxyprogesterone acetate or norethisterone oenanthate, and data collected from each group. Efforts to contact the researchers were unsuccessful.
Beksinska M	The study subjects were not randomised on recruitment. The users all had at least one year of use of contraceptive on commencement of the study.
Fotherby K	It is not clear whether randomisation took place. The authors were contacted with no success. Furthermore, the outcomes were not applicable to the review. Return to ovulation function was recorded but did not apply to discontinuation, because pregnancy as a reason for discontinuation did not necessarily coincide with return to ovulation.
Gray RH	It does not specify in which country this study was conducted. Publication was in 1981 around the time of the WHO study to which it refers. The interventions are not the same as the review for norethisterone. This study looks at norethisterone administration every 12 weeks, the same time interval as the depot medroxyprogesterone intervention, instead of every 2 months as specified by this review.
Janjua S	It is unclear whether randomisation took place at the outset of this study. Mean variables of the two study groups indicate that this was not accomplished. Attempts to contact the researcher to establish whether randomisation was in fact applied, were not successful.
Salem HT	The loss to follow up was 27% in the DMPA group and 40% in the NET-EN group after one year. This was too large to include without resulting in bias from high loss.
Swenson I	The intervention in the Norethisterone group differed from the type of intervention stipulated in this review. The dose intervals were inconsistent. The second Norethisterone dose was given at 10 weeks after the initial injection, and the subsequent doses were given at 12 week intervals.

In addition to the four trials, a study by Beksinska 2001 (Beksinska M) was considered. It compared women aged 40-49 years using DMPA, NET-EN or combined oral contraceptives for contraception. However, the users all had at least one year of use on commencement of the study, some of whom had been using an injectable contraceptive method for a number of years. The second part of the trial includes younger women initiating IPCs (Beksinska M part 2) and analysis of the data is still pending. Thus this study was not included in the review.

Table 2 : Characteristics of ongoing study

Study	Trial name or title	Participants	Interventions
Beksinska M part 2	Bone mineral density in women using depot-medroxyprogesterone acetate, norethisterone enanthate or combines oral contraceptives for contraception	Not known at this stage	Injectable & Oral contraception

The current review thus includes one randomised controlled trial with 2376 women at the commencement of the types of interventions stipulated for this review. These participants were observed for a total of 30,911 women-months. This study was the multinational study conducted by the WHO Special Programme of Research, Development and Research Training in Human Reproduction. It was conducted from 1977 to1982 at thirteen centres throughout the world, nine from developing countries and four from developed countries. There were in fact three treatment groups: DMPA given at 90 day intervals, NET-EN given at 60 day intervals, both for the entire period of the study, while a third group were given NET-EN at 60 day intervals for 6 months and at 84 day intervals thereafter. The study results comparing DMPA given every 90 days and NET-EN given every 60 days only were included in this review. The objective was to recruit 200 participants on each drug in each centre, but because of slow recruitment in some centres and premature closure in others, this could not ultimately be attained.

The countries in which this study was conducted were Brazil, Chile, Egypt, Italy, Luxembourg, Mexico, the Netherlands, Nigeria, Pakistan, Philippines, Thailand, Yugoslavia and Zambia. In total 10,331 women participated in this study. There was variation of some outcomes according to the different centres in which the trial was conducted.

The number of participants according to country and details of the study are shown in Tables 3 and 4.

Table 3: WHO study centres

Study centre	***No of participants***
Alexandria	292
Bangkok	170
Ibadan	252
Karachi	292
Ljubjana	193
Lusaka	108
Luxemborg	70
Manila	297
Mexico City	242
Milan	27
Salvador	299
Santiago	115
Utrecht	19
WHO multinational	**2376**

Table 4 : Characteristics of the included study

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation conceal-ment
WHO multinational	Trial conducted by the WHO Special Programme of Research, Development & Research Training in Human Reproduction. It was a clinic based multicentred Phase III trial of 3 regimens at 13 centres, in 9 developing and 4 developed countries. The participants were non-breast feeding women who were randomly allocated and followed up for 2 years. Loss to follow up is listed as 10.7% in the DMPA group & 8.9% in the NET-EN group	Women who were not breast feeding and chose IPC as contraceptive of choice. Their mean age was 27.4 +/- 5.2 years; mean parity was 3.3; mean interval since last birth was 4.4 +/- 1.7 months; mean body weight 55.5 +/- 12.1 kg. All participants underwent a medical history and examination, and cervical cytology on entry into the trial	There were 3 treatment groups: 1. DMPA every 90 days 2. NET-EN every 60 days 3. NET-EN every 60 days for 6 months, then every 84 days for the rest of the 2 years of follow up. Only the results for 1. & 2. are included in this review. Injection was given within 5 days of the menstrual cycle. Follow up was done over two years The DMPA group consisted of 1587 participants, and the NET-EN group of 789 participants.	* Discontinuation rates: Total rates and reasons for discontinuation: (1) Accidental pregnancy (2) Amenorrhoea (3) Bleeding problems (4) Other medical reasons, including - abdominal distension or discomfort - weight gain - anxiety/depression - fatigue - dizziness - headaches - decreased libido - hypertension (5) Cervical neoplasia discontinuation rates * Number & duration of menstrual bleeding / spotting * Changes in blood pressure * Changes in body weight	The sample comprised a total of 3172 women. The two study arms included in this review consisted of 2376 participants. There was local variability of discontinuation rates, according to different centres. This may have been related to culturally determined tolerance of menstrual disturbances, and attitudes of clinic staff towards injectable contraception. It is stated that logistic and economic advantage must be considered when viewing the results of the individual centres. There were 2 cases of cervical neoplasia and 4 deaths, that could not be related to drug use	Adequate

The outcomes that were measured in the study were risks for discontinuation. These risks for discontinuation were given as a total as well as subdivided according to reasons for discontinuation. These reasons for discontinuation are given as pregnancy, menstrual and non-menstrual reasons. The outcome relating to fertility is stated as accidental pregnancy, reported by the study as a reason for discontinuation. The menstrual reasons for discontinuation included amenorrhoea as well as bleeding irregularities. The non-menstrual effects of abdominal distension or discomfort, weight gain, anxiety/depression, fatigue, dizziness, headache, decreased libido and hypertension were presented as medical reasons for discontinuation and expressed as rate per 100 women-years. Discontinuation for personal reasons was also stated in the results. The study gives data collected on amenorrhoea and the duration and proportions of bleeding and spotting episodes occurring in the participants. Changes in blood pressure and body weight were also recorded in the study. Vaginal discharge was not an outcome of the included study.

4.2. Methodological quality of included studies

Participants in the WHO study were randomly allocated to the treatment groups after being recruited into the study. Use was made of a randomisation table prepared by the WHO Special Program of Research, Development and Research Training in Human Reproduction. Women were assigned to one of the two contraceptive methods through the allocation of a sealed envelope containing a random number.

The time intervals between administrations of the injection differed between DMPA and NET-EN. Therefore once the women were allocated into one or other of the study arms, it would not have been possible to blind the participants to the method of contraception. The study is not clear as to whether there was assessor blinding. The data processing of the study was carried out by the WHO in Geneva. In this analysis, the data were analysed according to counts of events and the use of life-tables procedures to estimate the duration of events.

Loss to follow up in the WHO study is reported as 10.7% in the DMPA group and 8.9% in the NET-EN group after 2 years. Patient follow up times were the periods of time that elapsed between each administration of the contraceptive.

Chapter 5: Results

The results of the WHO trial comparing DMPA and NET-EN are shown in the review. (WHO multinational 1983). The WHO data on discontinuation rates is published only according to the 13 centres, with no single rate for the whole study. For this reason the results for the individual centres were combined by meta-analysis to give single rates for frequency of discontinuation, overall and for each medical reason (see Figures 1-7 and Table 5) There was a non-significant difference between the two treatment groups for the frequency of discontinuation at 12 months (Risk difference (RD) 0.01; 95%CI -0.04 to 0.07 p=0.62) and at 24 months (RD 0.03; 95% CI -0.04 to 0.09 p=0.42) (Figure 1).

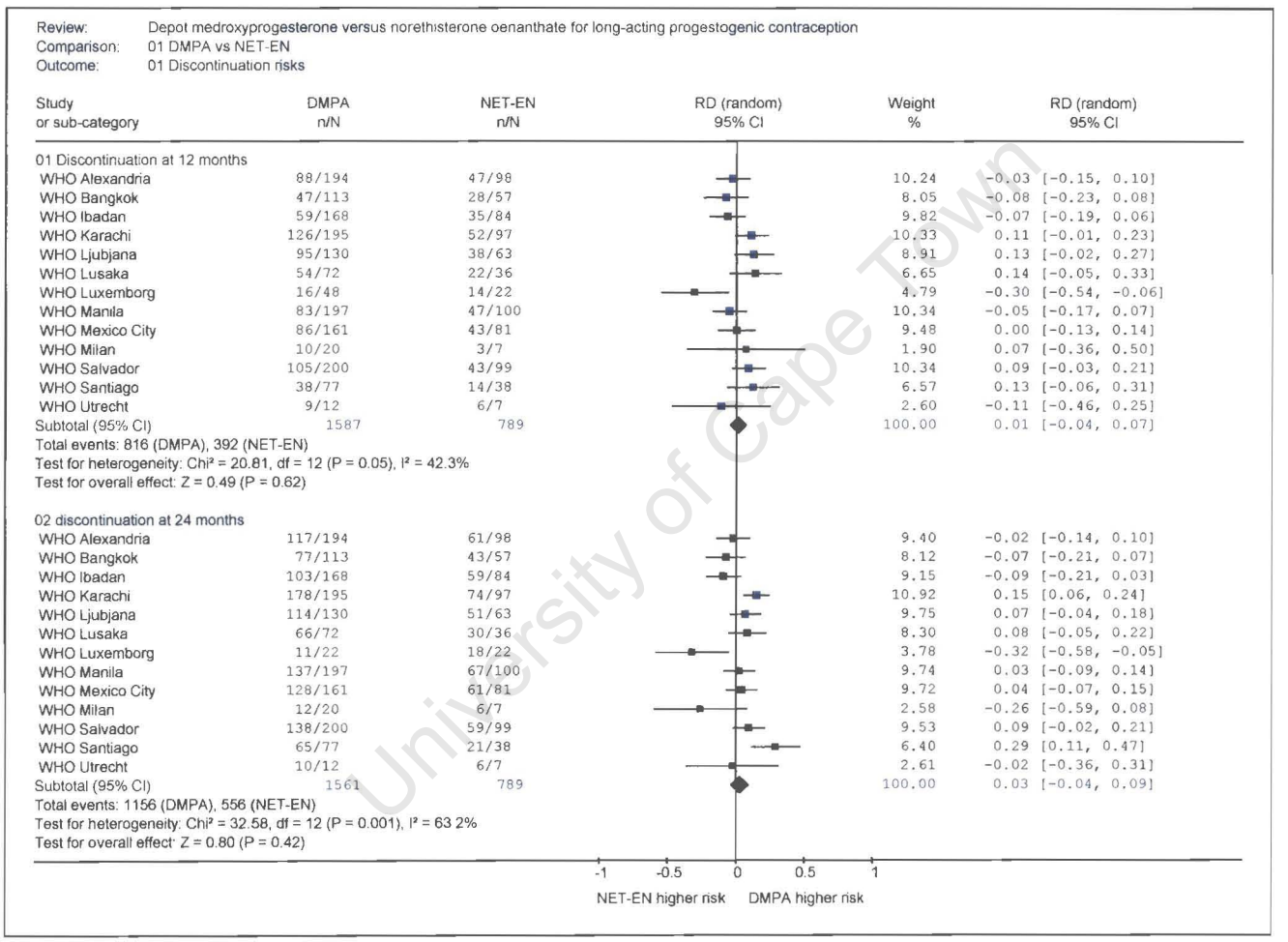

Figure 1: DMPA vs NET-EN: Discontinuation risks

The reasons for discontinuation at 12 months were similar for both groups regarding accidental pregnancy (RD 0.00; 95%CI -0.01to 0.00), bleeding problems (RD 0.01; 95%CI -0.02 to 0.04) and other medical reasons (RD -0.01; 95%CI -0.03 to 0.02). However, there was a significant difference between the groups for women who discontinued for the reason of amenorrhoea. Those on DMPA were 5% more likely to discontinue because of amenorrhoea (RD 0.05;

Those on DMPA were 5% more likely to discontinue because of amenorrhoea (RD 0.05; 95%CI 0.03 to 0.07). If discontinuation was for personal reasons, on average there was a statistically significant 4% difference (RD -0.04; 95%CI -0.07 to 0.00) showing that women on NET-EN were **4%** more inclined to discontinue treatment for personal reasons (Figure 2). Discontinuation for selected medical reasons was expressed as rate per women years. There were no significant differences between the groups. These results were collectively reported as other medical reasons for discontinuation. The selected non-menstrual reasons are recorded in Table 5.

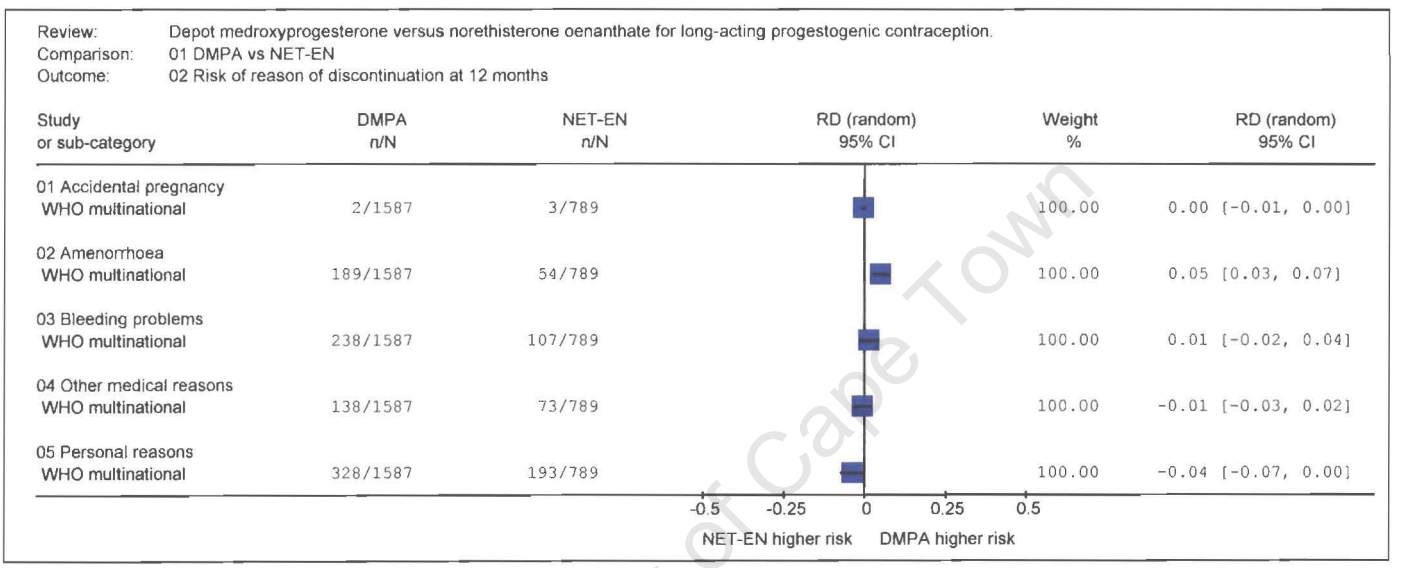

Figure 2: DMPA vs NET-EN: Reasons for discontinuation

Table 5: Selected medical reasons for discontinuation over two years observation

Other medical reasons	**DMPA**	**NET-EN**
	Rate per 100 woman-years	Rate per 100 woman-years
Abdominal distension or discomfort	1.1	0.6
Weight gain	2.1	1.6
Anxiety/depression	0.7	0.9
Fatigue	0.9	0.9
Dizziness	1.2	1.6
Headaches	2.3	2.0
Decreased libido	0.9	0.6
Hypertension	0.5	0.7

The proportions of women experiencing episodes of bleeding/spotting indicated a significant difference of 2% between the groups at 12 months (RD 0.02; 95%CI 0.01 to 0.04) and of 1% by 24 months (RD 0.01; 95%CI 0.00 to 0.02) (Figure 3). The weighted mean difference (WMD) between the groups in the duration of bleeding and spotting episodes similarly showed no significant dissimilarity between the groups at 12 months (RD 0.40; 95%CI -0.43 to 1.23) and at 24 months (RD 0.20; 95%CI -0.51to 0.91) (Figure 4). Results for the study of the percentage of women with bleeding and/or spotting episodes after 6 months, 12 months, 18 months and 24 months are recorded under additional tables. Both groups showed a decrease over time in the proportion of women who experienced episodes of bleeding/spotting.

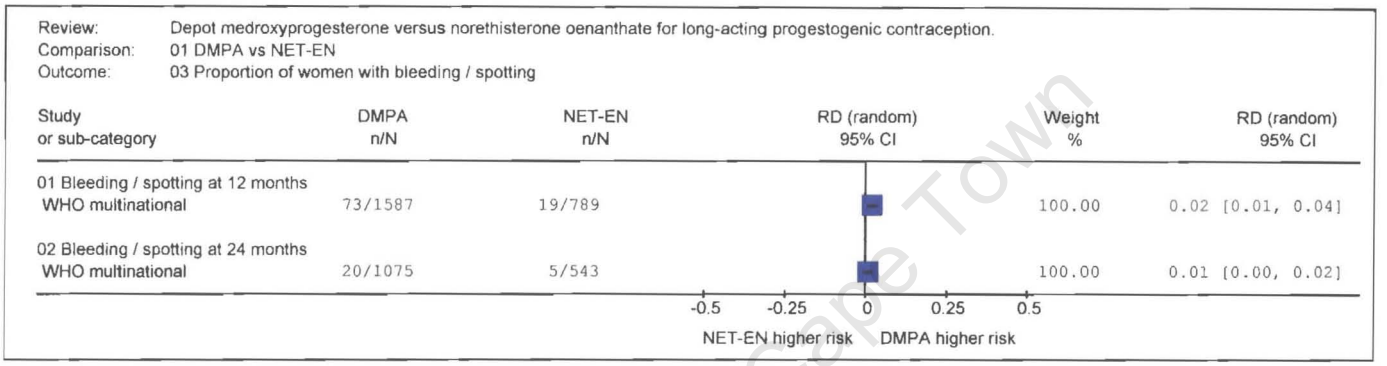

Figure 3: DMPA vs NET-EN: Proportion of women with bleeding or spotting

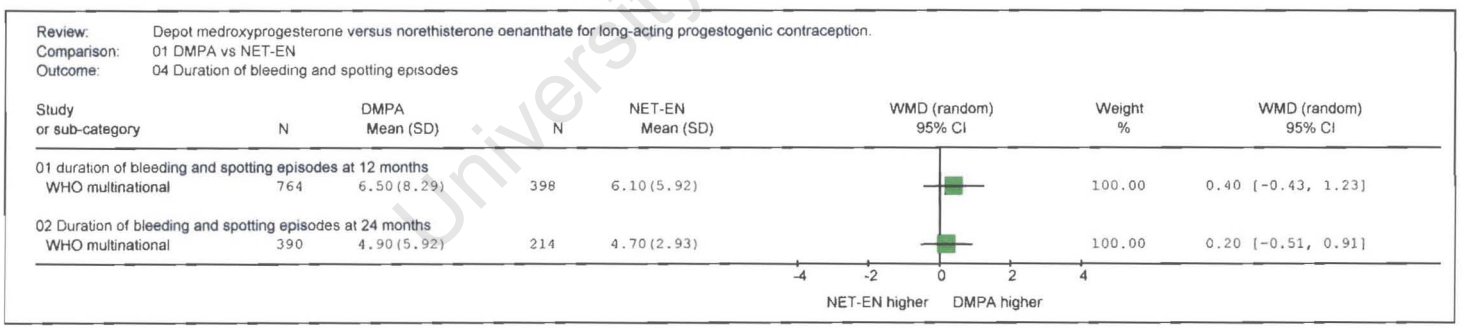

Figure 4: DMPA vs NET-EN: Duration of bleeding or spotting

The analysis of amenorrhoea (Figure 5) showed a highly significant difference between groups at both 12 and 24 months. Amenorrhoea was defined in the study as lasting more than 90 days. The risk of discontinuation for amenorrhoea was on average 27% higher in women on DMPA than those on NET-EN at 12 months (RD 0.27; 95%CI 0.21to 0.32) and 21% higher at 24 months (RD 0.21; 95%CI 0.14 to 0.29).

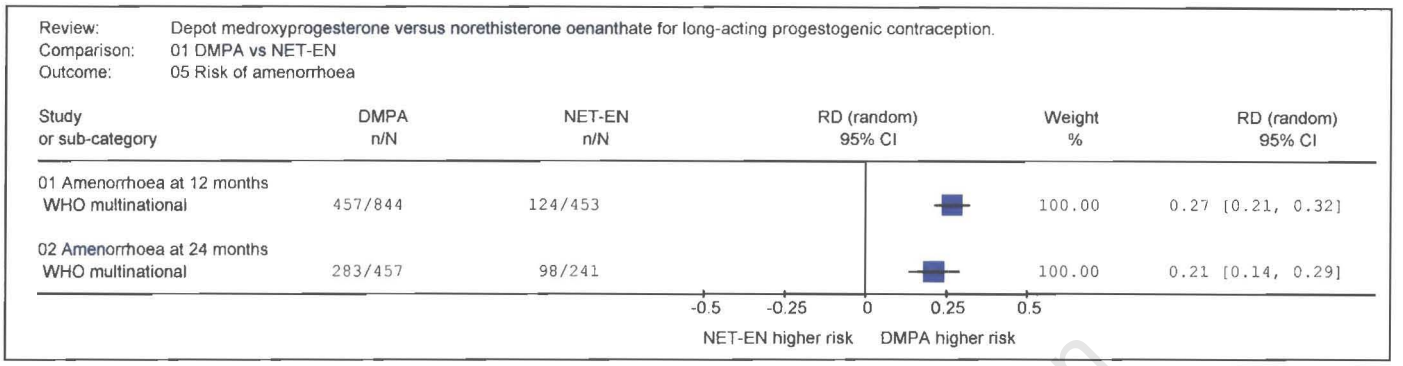

Figure 5: DMPA vs NET-EN: Risk of amenorrhoea

The results for mean changes in body weight (Figure 6) showed that on average at 12 months, the DMPA group gained 0.2 kilograms more than the NET-EN group, but this was not statistically significant (WMD 0.20; 95% CI -0.63 to 1.03). By 24 months results showed equal increases in body weight in women in the two groups, resulting in no difference between groups (WMD 0.00; 95%CI -1.39 to 1.39). Mean changes in blood pressure (Figure 7) did not differ significantly between the groups. There was a difference of 0.8 mm Hg for systolic blood pressure (WMD 0.80; 95%CI -1.16 to 2.76) and 0.2 mm Hg for diastolic blood pressure (WMD -0.20; 95%CI -1.61 to 1.21)

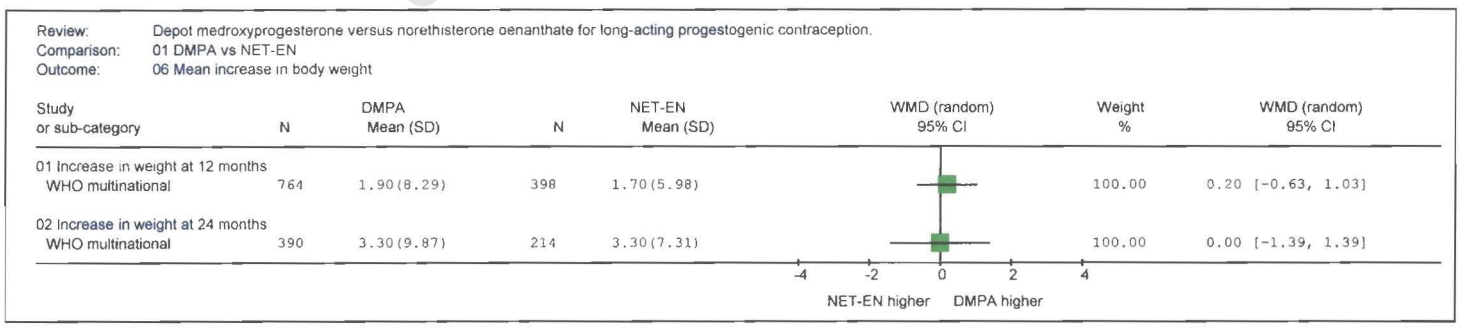

Figure 6: DMPA vs NET-EN: Changes in body weight

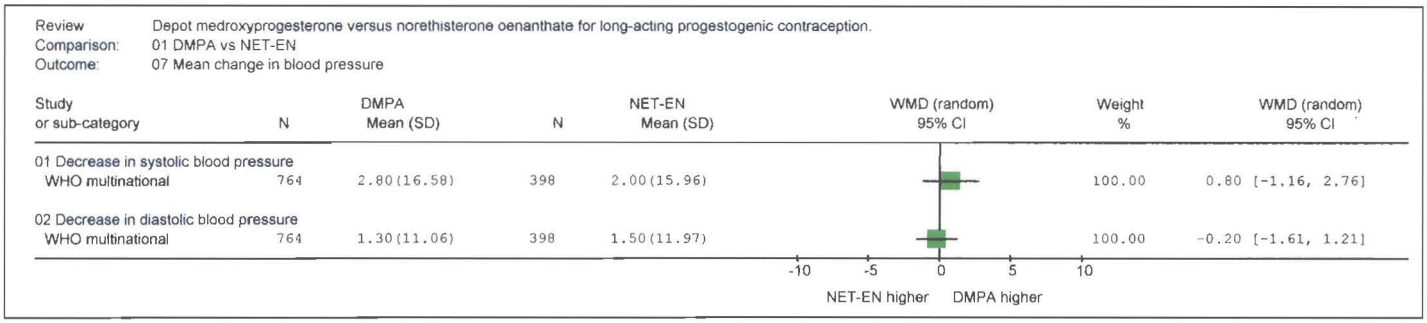

Figure 7: DMPA vs NET-EN: Changes in blood pressure

Chapter 6: Discussion

After assessing fifty six studies identified in the initial search, only one randomized controlled trial qualified for inclusion in this review. The WHO multinational study was a large trial with a sample size of 2376. Although indications are that the included study was well conducted with appropriate randomization and record keeping with menstrual diaries, it was performed over a decade ago. Both contraceptive methods were similarly effective, but a larger sample size would be needed to observe a sufficient number of pregnancies to estimate effectiveness.

Results showed no difference in the risk of discontinuation between the groups of IPC users after one year. After two years, there was a non-significant 3% difference, the DMPA group being more likely to discontinue. The DMPA group were, however, 5% more likely to discontinue for the reason of amenorrhoea, which is in keeping with the finding of this study that those women on DMPA were far more likely to experience amenorrhoea. However, amenorrhoea may in fact be viewed by contraception users in certain circumstances as an advantage, and absence of bleeding seen as a reason to continue the method, as in the case of use of the levonorgestrel intrauterine system (Backman 2005).

The NET-EN group were significantly 4% more likely to discontinue for personal reasons. These results should be viewed in the context that the WHO multinational study was performed in 13 centres, with differences between the groups according to social and cultural practices. One must consider that discontinuation rates are dependant on many factors, and should be interpreted with caution (Gallo 2005). Deviations from normal menstrual bleeding patterns may exert influence on women's lives in certain cultural and religious groups (Best 1998). Menstrual experiences and beliefs may influence choices of family planning methods (Severy 1993). A difference of menstrual bleeding patterns between the two IPCs could therefore influence the reason for discontinuation due to amenorrhoea. Cessation of menstrual bleeding might be culturally unacceptable in certain groups of women, where menstrual bleeding may be viewed as proof of continued fertility. Personal reasons for discontinuation may also be associated with the demographic profiles of the study subjects from the various centres. This could have influenced the risk of discontinuation after 2 years.

Provider attitudes towards amenorrhoea may also well have influenced discontinuation. If providers' perception was that menstruation served no excretory function nor was it connected to any side effects, for example bone density, then they may have been more inclined to

discourage the women on DMPA to discontinue use on the grounds of amenorrhoea alone. Unfortunately there was no data in the study that indicated centre-specific rates of discontinuation for the reason of amenorrhoea, that may have reflected a variability in provider attitudes.

Both intervention groups of DMPA and NET-EN experienced episodes of menstrual bleeding and spotting. There was a significant difference between the groups in the proportion of women who did experience bleeding and/or spotting after 12 months, and at the onset of use, women on DMPA appear to bleed more. However, this decreased over time, showing a very small difference after 2 years of use. There was no difference between the groups in the actual duration of the bleeding and spotting episodes. This may have affected discontinuation, if women in one group had experienced longer periods of bleeding that caused them to discontinue use (d'Arcangues C 2000).

With the commencement of use, women in both groups equally experienced some bleeding and spotting and did not differ in the actual duration of these episodes. The most important finding, though, relates to outcomes after one to two years of use, in that the DMPA group were found to have significantly more amenorrhoea than the NET-EN group. There was little change from one year to two years. This finding regarding amenorrhoea is in fact the only significant clinical difference that was found on analysis. The implication of this is that if injectable progesterone contraceptives are the method of choice, then the long term effects of DMPA and NET-EN on menstrual patterns need to be considered rather than the short term effects, which are similar.

While changes of mean body weight and blood pressure are often considered as undesirable factors in hormonal contraception (El Mahgoub 1980), analysis showed no statistically significant differences between the groups after one year of use. The included study showed that even after two years there was no difference at all in weight gain between the groups, and implies that clinically significant weight gain need not be considered in the choice of method. There were no significant differences between the groups regarding changes in either systolic or diastolic blood pressure. In addition, the mean changes in blood pressure were very small. Furthermore, the rate of hypertension as a selected medical reason for discontinuation did not differ between the groups. The groups also did not differ regarding other non-menstrual adverse effects, expressed as selected medical reasons for discontinuation. Therefore, only differences in menstrual effects, and possible personal reasons for discontinuation were shown to be significant.

The outcome of vaginal discharge could not be compared in this study. Research subsequent to this study has demonstrated significant association between the use of DMPA and vaginal shedding (Mostad 1997), some vaginal infections (Morrison 2004) and an increased incidence of HIV-1 infection (Martin 1998). There was no data to compare DMPA and NET-EN regarding these effects.

Chapter 7: Conclusions

The main conclusion of the study was that DMPA is more likely to lead to amenorrhoea than NET-EN in women using injectable progestogen-only contraceptives. There was no difference in discontinuation rates between the groups. Women who were on DMPA were 21% more likely to stop vaginal bleeding altogether, and discontinue use for this reason.

7.1. Implications for practice

Both DMPA and NET-EN are highly effective contraceptive agents (Sapire 1990). The risk of discontinuation between the groups of DMPA and NET-EN users was similar. However, users may differ in their discontinuation of these injectable contraceptives for amenorrhoea or personal reasons. Although the duration of episodes of spotting or bleeding is the same for both groups, DMPA carries a higher risk of amenorrhoea than NET-EN and may be recommended to women who prefer minimal menstrual bleeding. Changes in body weight and blood pressure as well as other non-menstrual adverse effects do not differ between the two groups.

The evidence of this review indicates that there is little to differentiate between these two methods of contraception. This should influence the decision regarding which of these injectable contraceptives to prescribe. Product cost and patient convenience should be borne in mind.

7.2. Implications for research

There are no recent trials comparing injectable progestogen-only contraceptives, although they remain in wide use in some less developed countries. Further research may be indicated in the following areas:

- *Transmission of HIV*. Further research on association of IPCs and the transmission of HIV is needed. Studies have demonstrated that women who use DMPA had an increased incidence of HIV-1 infection (Martin 1998). It would be important to compare the effect of DMPA with NET-EN on this incidence.

- *Bone mineral density.* The World Health Organisation has acknowledged the current research on the effect of DMPA on bone mineral density. (WHO 2005).

- *Health provider and user attitudes.* Little is known about whether health provider attitudes towards the use of either DMPA or NET-EN contribute to a variation of use. This information would be of considerable assistance in health systems planning.

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Appendix A:
Study validity form

DATA EXTRACTION FORM **NUMBER:**_____

Reviewer	BD	CM

Title of paper_____

_____

_____

Reference_____

_____

STUDY DESIGN AND CONDUCT:

	Yes	No	Unclear
Subject blinded			
Provider blinded			
Assessor blinded			

Date trial was initiated:_____

Total duration of trial : _____

Duration of follow-up:_____

Type of follow-up: _____

Frequency of follow-up: _____

Overall loss to follow up: _____

STUDY POPULATION:

Country in which trial was done: _____

Setting (general): Rural Urban Unclear

Community based Clinic based Hospital based

Unclear

Numbers of persons in trial:

	TOTAL	DPMA	NET-EN
Number			
% of total	100%		

Definitions: Exposure _____

Inclusions _____ (specify or state unclear)

Exclusions _____

QUALITY ASSESSMENT

		Adequate	Inadequate	Unclear
1. Study criteria	**Exposure**			
	Inclusion / exclusion criteria			
2. Selection bias	**Randomisation**			
	Allocation concealment			
	Outcome / success of randomisation			
3. Performance bias - Blinding	**Subjects**	Blind at allocation	Not blind	Unclear
	Providers	Blind at allocation & outcome assessment	Not blind	Unclear
	Outcome assessors	Blind at outcome assessment	Not blind	Unclear
4. Attrition bias – differential loss of subjects from groups		Loss to follow up completely recorded	Loss to follow up incompletely recorded	Not clear or not done
5. Intention to treat		ITT analysis performed	ITT analysis not performed	Not clear
6. Detection bias		Adequate	Inadequate	Unclear
	Detection bias acknowledged			
	Detection bias evident			
7. Cluster randomization & level of analysis	**Did cluster randomization occur?**			
	Was statistical analysis carried out at the same level of randomization			
	Did statistical analysis take account of the level of randomization			
	Was statistical analysis carried out at a different level to randomization			

OUTCOME MEASURES

			Was it measured?	If yes, definition of outcome	Results (e.g. %s, RR, OR, etc
Contraceptive efficacy					
Reversibility					
Minor effects	Menstrual	Amenorrhoea			
		Menorrhagia			
		Spotting			
		Irregular bleeding			
		Dysmenorrhoea			
	Non-menstrual	Headache			
		Clinically significant weight change			
		Decreased libido			
		Mood swings &/or depression			
		Nausea			
		Dizziness			
		Vaginal discharge			

		Was it measured?	If yes, definition of outcome	Results (e.g. %s, RR, OR, etc
Major effects	Risk of breast cancer			
	Risk of cervical cancer			
	Effect on bone mineral density			
	Cardiovascular disease			
	Increased vaginal shedding			
	Susceptibility to HIV or other sexually transmitted infections			

Extra notes:

Appendix B:
Cochrane Review details

Title of Cochrane Review:

Depot medroxyprogesterone versus norethisterone oenanthate for long-acting progestogenic contraception.

Reviewers:

Draper BH, Morroni C, Hoffman M, Smit J, Beksinska M, Hapgood J, Van der Merwe L.

Dates

Protocol first published: February 2005
Review first published: Accepted for publication February 2006

Contribution of reviewers

Beverly Draper wrote the protocol for the review, performed the search, identified the studies and written up the final review

Chelsea Morroni served in an advisory capacity in writing the data analysis for the protocol and for changes to the protocol after the first distribution for comment. She has assisted in identifying outcomes for analysis.

Margaret Hoffman initiated the review from her current research, compiled the review team and advised on protocol and review changes. She supplied the information on local research and findings on the use of injectable contraceptives that has provoked interest in the research.

Jennifer Smit was the original initiator of the review during the writing of her PhD on this topic and contacted Professor Hoffman in this regard. She supplied some of the original references for the protocol background.

Mags Beksinska served in an advisory capacity on the research question, on the strength of her research on injectable contraceptives. She has performed a study including injectable contraceptives.

Janet Hapgood provided the biochemical information on the differences between the injectable progestogen contraceptives, and thereby aided the identification of major and minor effects to be included in the protocol.

Lize van der Merwe assisted with the extraction of data, statistical analysis of the outcomes of the identified studies, both in the conversion of the published data and in the meta-analyses, and commented and assisted with the final draft of the review.

Internal sources of support

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External sources of support

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