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AN OVERVIEW OF INJECTABLE CONTRACEPTIVES WITH SPECIAL APPLICATION TO BANGLADESH

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ABSTRACT

Injectable contraceptives are an increasingly popular method of family planning among women seeking an effective, relatively safe, and reversible method of family planning in many countries, including Bangladesh. Their popularity in Moslem and Hindu societies can largely be attributed to their ease of use and the confidentiality afforded to women who receive them in a domiciliary delivery system.

However, a number of nuisance, short, and long-term side effects have been associated with their use. Extensive research into these side effects and any possible long-term health implications of their use is continuing. Operations research in Bangladesh has, meanwhile, identified a number of issues regarding provision of injectable contraceptive services which are of relevance to planners and implementors of family planning programs.

This paper is divided into two sections. The first section presents an overview of the available international and Bangladesh based medical and biomedical research on injectables; the second focuses on implementation considerations for the injectable program in Bangladesh.

EXECUTIVE SUMMARY

During the 1950's and 1960's injectable contraceptives, as well as the intra-uterine device (IUD) and oral contraceptives, were developed and marketed. All three methods have experienced rapidly growing popularity throughout the world. Noristerat (NET-EN) was the first injectable contraceptive developed, but has been less widely used than Depo Provera (DMPA). Its demand, however, has been increasing in recent years in many countries, including Bangladesh.

Extensive clinical and field research on injectables, oral contraceptives, and the IUD continues, however, and has revealed a number of nuisance, short, and long-term effects from use of each of these methods.

In examining the pros and cons of introducing any contraceptive into a program, consideration should be given to the available information on their safety and effectiveness within the societal context of their use and in relationship to available alternatives. Operations research can also be used to identify implementation problems when introducing a new contraceptive into an existing program and strategies to overcome them. This paper will address both the biomedical and programmatic aspects of injectables and will include recommendations for their use in Bangladesh.

BIOMEDICAL CONSIDERATIONS:

PHARMACOLOGY

DMPA is the injectable form of medroxyprogesterone acetate and is marketed under the name Depo Provera. It is administered in three and six monthly regimens of 150 and 300 mgs., respectively. The length of action of a 150 mg dose is usually three months, but blood levels can persist up to 200 days. Noristerat, Norethindrone enanthate, is prepared in an oily solution, thus it has a more varied rate of absorption than DMPA. Noristerat's administration schedule is bimonthly for the first four injections, then once every three months.

MODE OF ACTION

The primary mode of action of both Depo Provera and Noristerat is inhibition of lutenizing hormone production by the pituitary gland, thus preventing ovulation. They also cause a thickening and decrease in the amount of cervical mucus, acting as a barrier to sperm; supress development of the endometrium, leaving it inhospitable to implantation by a fertilized ovum; and possibly affect the rate of ovum transport through the fallopian tubes.

EFFICACY

Pregnancy rates for the DMPA three month regimen range from 0.0 to 1.4, and for the six month regimen, from 1.58 to 1.73. The rate for NET-EN reported in 1983 in the WHO multinational trials was 1.4 per 100 women years of use.

INJECTABLES IN BANGALDESH

Injectables are used in Bangladesh as a part of the Ministry of Health and Population Control's (MOHPC) cafeteria approach to family planning services. The Bangladesh Fertility Research Program (BFRP) initiated trials on DMPA in 1974 and in 1976 recommended its use to the MOHPC. Noristerat was introduced into Bangladesh by the MOHPC in 1980. Use of injectables in Bangladesh has grown from 58 users in 1975 to 72,679 as of May 1984. According to the Third Five Year Plan for 1985-1990, projected use by 1990 is 490,768 users or 10% of total contraceptive use in a 50:50 ratio of Noristerat to DMPA. DMPA and NET-EN supplies in Bangladesh are donated by the UNFPA and AG Schering of Berlin.

PREVALENCE OF USE

It is estimated that 25% to 75% of eligible women offered a choice of contraceptives world-wide would choose injectables. Several non-governmental organizations in Bangladesh have reported that 34% to 43% of contraceptors choose injectables. Their cultural acceptability in Moslem societies can largely be attributed to their dissociation from intercourse, the ability of the woman to maintain confidentialtiy when they are administered at home, and the fact that injection is a socially accepted mode of drug administration.

CONTINUATION OF USE

World-wide continuation of use rates vary. The WHO multinational trials, reported in 1982, found 63.5% discontinuation of use rates for DMPA and 61.9% and 62.5% for NET-EN 60 and 84-day regimens, respectively, by 18 months of use. However, rates from the Matlab Family Planning Health Service Project (FPHSP) highlight how the use of method switching, as appropriate, can dramatically increase monthly continuation rates. There, when method switching was employed the first method continuation rates for contraceptors was more than 80% compared to only 58.3% for those who used injectables continuously for one year.

Personal, social, and religious concerns, as well as, medical problems have been cited by women as reasons for discontinuation of use. The most common medical reasons are irregular menstrual bleeding and/or spotting and amenorrhea.

These side effects have special social significance in Moslem and Hindu societies as they can interfere with a woman's domestic and social responsiblities. This illustrates the need for close follow-up of injectable users to enable proper side effect management and use of method switching when appropriate.

SIDE EFFECTS

The most commonly reported side effects of injectable use can be classified as short-term and nuisance effects. Several long-term effects have also been associated with their use.

0 MENSTRUAL IRREGULARITIES: Menstrual irregularities are the most prevalently reported short-term or nuisance effects. Included in this category are amenorrhea and intermenstrual spotting and/or bleeding. Amenorrhea lasting 90 days or more may occur in 55% of DMPA and 34% of NET-EN users by the end of the first twelve months of use. This pattern has also been found in Bangladesh based studies. Severe bleeding is uncommon among both Noristerat and DMPA users.

0 METABOLIC EFFECTS: Clinical research has found no significant effects on blood pressure, coagulation, and fibrinolytic factors, or platelet, liver, renal, and thyroid functions from use of injectables. Though there are no reports of diabetes developing among injectable users, clinical research has shown alterations in carbohydrate metabolism which include small increases in fasting glucose and insulin levels and enhanced glucose and insulin response to glucose tolerance tests.

0 CARDIOVASCULAR EFFECTS: Recent research on oral contraceptive users indicates that the increased risk of heart attack and stroke associated with their use is likely attributable to the progestin component of the pills. The progestin in oral contraceptives has also been linked to a reduction in serum levels of high density lipoproteins. Evidence regarding the link between injectable contraceptives and these medical problems is inconclusive.

0 OTHER EFFECTS: A small gain in weight occurs among most women using injectables. Headaches are also commonly reported by both DMPA and NET-EN users. Abdominal discomfort and bloating appear to be more common in users of DMPA than NET-EN.

0 RETURN OF FERTILITY: Delays in return of fertility after discontinuation of use of DMPA of up to two years or longer have been reported. There has not been extensive research into the length of time until return of fertility among Noristerat users; however, NET-EN is metabolized faster than DMPA and blood levels usually cannot be detected after four months post injection.

O LACTATION: There are conflicting reports regarding the effects of injectables on composition of breast milk. Among women on a DMPA regimen of 150 mg every three months, a significant increase in protein and insignificant increase in milk volume have been found. Among those using 300 mg administered every six months a significant decrease in protein, but increase in milk volume have been reported. Studies report no adverse effects on milk volume among Noristerat users.

Infants breastfed by mothers currently using injectables show no significant difference in weight gain from those breastfeeding from mothers who are not. The only significant changes in immune response have been seen in breastfed infants whose mothers used injectables in the first two months post-partum. This suggests it is best to wait at least two months after childbirth before administering injectables.

O TERATOGENICITY AND OTHER EFFECTS ON THE FETUS: Women do not usually ovulate until blood levels of DMPA are less than 0.1 mg/ml or NET-EN levels are approximately 0.4 to 0.8 mg/ml. However, women have become pregnant with blood levels of DMPA as high as 1.8 mg/ml. Some women may take their first injection unaware that they have become pregnant in the month prior to injection, while others seek an injection under tha false assumption that it will induce an abortion. Therefore it is important to consider the possible effects of injectables on the developing fetus. Research evidence to date regarding a teratogenic effect by either DMPA or NET-EN indicates either no risk or possibly a two-fold increase in risk of anomaiies such as cardiovascular defects. Studies conducted in the 1950's and 1960's on women treated with high doses of various progestins for habitual abortion reported occasional masculinization of external genitalia in female children, especially after exposure to progestins derived from testosterone. Because of confliciting findings, this evidence must be considered inconclusive.

O CANCER: There is no evidence from clinical studies of injectable users which suggests a link between Depo Provera or Noristerat and cancer of the breast, ovaries, or endometrium. This is in contrast to studies in which carcinomas were found in laboratory animals administered high doses of DMPA. However, the evidence from these animal studies has not been considered applicable to women as the cancers found in the monkeys developed in a cell layer of the endometrium not found in women and beagle dogs have a species specific response to progestins which is very different from that of humans.

As the findings from these animal studies were viewed as inapplicable to women the U.S.- Food and Drug Administration's (FDA) Obstetrics and Gynecology Advisory Committee recommended approval of DMPA. Nonetheless, the FDA denied approval in 1978 and again in 1983.

PROGRAMMATIC CONSIDERATIONS:

The national family planning program of the Government of Bangladesh provides all contraceptives in a cafeteria approach, but from different service points: pills and condoms are delivered to the doorstep by fieldworkers, the Family Welfare Assistants (FWAs), whereas, all other methods, including injectables, may be obtained at static clinic centers through paramedics, Family Welfare Visitors (FWVs), or medical officers (MOs). Private projects in Bangladesh have found injectables delivered at the doorstep by well-trained female fieldworkers increases their acceptability far beyond that presently achieved in the Government's program. This section of the paper explores the programmatic implications for implementation of the Government's injectable program through the domiciliary and static centers approaches.

MANAGEMENT ISSUES:

0 Worker Density: If a domiciliary delivery system is implemented, administration of both DMPA and Noristerat would require field workers to break from their regular work patterns to administer doses to clients when due. Because of its more frequent dosage regimen in the initial few months of use, Noristerat causes more disruptions than DMPA. Both the disruptions and present field worker density place a ceiling on the number of clients any worker can serve. Also, the present outreach village level worker density in the Bangladesh national program of one Family Welfare Assistant (FWA) per an average 6,000 population does not allow adequate client follow-up for management of side effects, contributing to discontinuation of use. It is recommended that worker density be increased to one per 2,000 population to allow a worker to visit each client on a monthly basis.

0 Record Keeping System and Supervision: Assurance that clients receive injections when they are due is essential to any effective injectable program, whether they are provided at the home or from a clinic. This could be provided if a record keeping system that keeps the service provider informed of due dates were routinely employed. Coverage of clients during worker absences is also necessary and could be improved if supervisors were routinely informed about workers' leaves. The present government system does not provide coverage of field workers on leave. However, the field supervisor, the Family Planning Assistant, could inform the paramedic, the Family Welfare Visitor (FWV), of the nearest static clinic who could then provide coverage of clients due for injections if the domiciliary approach is employed.

0 Ramzan: During the Ramzan month Moslem women usually refuse to take injections during the fasting part of the day. Therefore, clients should be switched to other family planning methods during this time, or if possible, be administered their injections at night. This is carried out more easily in

a domiciliary program, as a clinic program depends on the woman's motivation to come to the clinic to receive the injection.

0 Training: In order to insure proper screening, counseling, education, and follow-up of clients and management of side effects, special training of FWA's, FWV's, and Medical Officers (MO) is required. Successful domiciliary programs demonstrate that FWA's can be trained to perform many of those tasks in the client's home using the FWV and MO for referral and back-up. Where FWV's administer injectables they can provide those services. Other areas requiring special consideration during training include: screening for pregnancy, especially during post-partum amenorrhea and the contraindications to use, ie. cancer of the breast or genital tract, diabetes, and abnormal vaginal bleeding of unknown etiology.

0 Overall Program Considerations: An overview of the administrative and client based considerations involved in the provision of injectables, as well as of oral contraceptives and the IUD, can contribute to the effective administration of a comprehensive family planning programme. Upon making these comparisons it is evident that all three methods share the need for special training of service providers and logisitcal support for obtaining needed supplies. However, there are more client based barriers to effective use of oral contraceptives and IUD's than injectables, suggesting that injectables may be a more socially acceptable method in Bangladesh.

LOGISTICAL SUPPORT:

0 Supplies: Constant and adequate supplies of DMPA and NET-EN and the supporting peripherals are also essential to maintenance of an injectable program. However, the logistics of obtaining needed supplies is complex as they are not always readily available and must be obtained from several different sources in the Bangladesh program. This is time consuming and requires much advanced planning on the part of the upazila official incharge of the family planning program, a task he may not be motivated to do. A workable solution to this would be the provision of all necessary supplies in one kit to the Upazila Health Complex. (The UHC is a 31 bed hospital serving a population of 200,000 and is the administrative headquarters of the family planning outreach program.) These would then be distributed to field workers and paramedics at the union level outpatient clinics within the upazila, the Health and Family Welfare Center (H&FWC).

0 Reusable Versus Disposable Supplies: An insufficient supply of needles and syringes and the fact that autoclaves for sterilization of these supplies and kerosene to run them are not available at all UHC and H&FWC's also contribute to disruptions in service provision. A cost comparison of possible solutions to these problems indicates that the use of disposable needles and syringes by all FWA's or FWV's is less expensive than the installation of autoclaves and maintenance of adequate supplies for the sterilizaiton process of reusable needles and syringes.

0 Use of Both DMPA and Noristerat: Currently, the MOHPC sanctions 50:50 use of Noristerat and DMPA. However, the medical implications of switching clients between these two contraceptives has not been thoroughly researched and can cause confusion for service providers. It should also be noted that different size needles are required for the administration of Depo Provera and Noristerat, further adding to confusion and problems with supply logistics. It is, therefore, suggested that each district receive only one type of injectable with the appropriate peripherals on a continuous basis.

DOMICILIARY VERSUS STATIC APPROACH:

Evidence from several domiciliary programs administered by non-governmental organizations in Bangladesh and the Bangladesh national Management Information System on injectable usage in Bangladesh suggest that a home-based approach to injectable services may encourage greater participation and continuation of use than the current system of the government sector which requires a woman to travel to the UHC for services. The success of domiciliary programs can be attributed to the fact that they allow the client to maintain confidentiality, do not place the burden on her to remember when her next injection is due, or rely on her capability to reach the clinic to receive them or medical attention for any side effects. It suggests that a policy change allowing field workers to provide injectable services is feasible but should only be implemented on a national scale if requisite training, supervision, logistical support, and adequate worker density are provided. The MOHPC should carefully field test injectable strategies in a variety of settings and use sites where carefully conducted injectable programs exist to orient and train service providers before establishing a national domiciliary programme.

INTRODUCTION

The 1950's and 1960's saw tremendous technological advances in the development of contraceptives for women. During this period oral contraceptives, intrauterine devices, and the injectable contraceptives, Depot Medroxyprogesterone Acetate (DMPA) and Norethindrone enanthate (NET-EN), were developed and marketed. Extensive research into the safety and effectiveness of all these methods has continued since then. Findings indicate that injectable and oral contraceptives have nearly 100% use-effectiveness rates, somewhat higher than the rate for the IUD. However, none of these methods are risk free. A number of nuisance and short-term side effects have been reported by users and in research findings. Also, questions regarding possible links to some serious health problems, including certain cancers, have been raised and are continuing to be investigated.

More recently, effort has been directed to making these contraceptives and adequate follow-up available to women who desire them. Packaging and educational materials to accompany each contraceptive were initial considerations. Attention has now shifted to ensuring that delivery systems function to meet and even stimulate demand for contraceptives.

This paper focuses on injectables. It is divided into two parts: the first section will present a broad overview of available international and Bangladesh based medical and biomedical research on injectables in an attempt to provide a background for responsible decision-making regarding their use in Bangladesh; the second section focuses on implementation considerations of the injectable program in Bangladesh. As the first section is just a synopsis of a very large body of information, the interested reader is referred to the attached notes and bibliography of interviews and articles for further reading.

Injectables are increasing in popularity among women seeking an effective, relatively safe, and reversible method of family planning in many countries, including Bangladesh. Much of their perceived desirability can be attributed to their convenience of use, allowing a woman to maintain her privacy, an important consideration in Bangladeshi society.

Operations research, however, has identified several other considerations regarding the provision of injectable contraceptives which are of importance to service providers. These include the need for a continued flow of supplies, adequate training of personnel in screening procedures and counseling techniques and follow-up of side effects, and the need for an adequate worker density to provide these services to clients on a regular basis. All of these are essential to insuring effective operation of any family planning program.

PART - I

STATUS OF INJECTABLES: A REVIEW OF THE MEDICAL AND BIOMEDICAL STUDIES

A. WHAT ARE DMPA AND NET-EN?

DMPA and NET-EN are long acting injectable progestins which vary in structure, preparation, and rate of metabolism in the body. Race, ethnicity, and physique of the woman greatly effect their absorption and metabolism. (fn1)

DMPA is the injectable form of the progestin medroxyprogesterone acetate. It is derived from progesterone, having the chemical structure 17- -acetoxy-6, methyl pregn-4-ene-3, 20 dione and is prepared in a microcrystalline suspension which helps prolong absorption. Plasma levels peak between seven (R 119) and ten days (R170) at 1.0 to 6.8 ng/ml of serum (fn2). Levels can usually be measured for three months, but can either persist up to 200 days, or become negligible after three months post injection(fn3). Serum levels are not cumulative from one dose to the next (R119).

Norethindrone enanthate (NET-EN), 17-Hydroxy-19 nor-17- -pregn-4-en-20 yn-3 one enanthate is derived from testosterone and is prepared in an oily solution. As oily solutions do not have a fixed particle size, the rate of release into the circulation from the injection site varies widely (R119). Blood levels rise rapidly after injection, usually peaking in five to seven days at 4 to 24 ng/ml (fn4). There is then a steady decline with levels generally becoming undetectable within two and one-half to four months (fn5).

NET-EN and DMPA prevent pregnancy through several mechanisms. Their primary mode of action is thought to be the inhibition of ovulation by supressing production of lutenizing hormone by the pituitary gland (fn6). They also cause a thickening and decrease in the amount of cervical mucus, acting as a barrier to sperm (fn7); suppress development of the endometrium, leaving it inhospitable to implantation by a fertilized ovum (fn8); and possibly affect the rate of ovum transport through the fallopian tubes (fn9).

B. EFFECTIVENESS

Pregnancy rates for DMPA ranging from 0.0 to 1.4 (R109, 137, 127; fn10) per 100 woman years after 24 months of use were reported in clinical trials which used regimens of 150 mg every 12 weeks. In a collaborative international study using 300 mg and 450 mg of DMPA administered every six months, Pearl Index pregnancy rates of 1.73 and 1.58, respectively, were found (fn11).

Pregnancy rates for NET-EN are similar to those for the DMPA three-month regimen. In the multinational comparative clincal trials supported by the World Health Organization (WHO), reported in 1983, pregnancy rates for women using a 60-day injection cycle were 0.6±0.3 after 6, 12, and 18 months of use. For those on an 84-day regimen the rate increased over time from 0.3±0.2 at six months to 0.7±0.4 at 12 months and 0.6±0.3 at 18 months of use. The multinational trials, reported in 1983, used an injection regimen of every eight weeks for six months and then every 12 weeks, resulting in a 24-month pregnancy rate of 1.4 per 100 women years of use (fn12).

C. HISTORY AND DEVELOPMENT OF INJECTABLE CONTRACEPTIVES

The first injectable contraceptives were developed by Karl Junkman in 1953. Later, working at AG Schering in Berlin, Junkman and associates derived Norethindrone enanthate, an ester of the progestin norethindrone, in 1957. At approximately the same time medroxyprogesterone acetate (MPA) was developed by the Upjohn Company in the United States (fn13).

NET-EN was the first injectable progestin used as a contraceptive (R 119). Field trials were begun by AG Schering in 1965 and in 1967 it was first marketed in Peru under the brand name Noristerat. Though less widely used than DMPA, its popularity is increasing. Schering reported that 1.4 million doses, enough for 275,000 women years of use, were sold in 1982. Currently, it is approved for use and marketed in 40 countries (R 121), including Bangladesh.

Since the early 1950's Depot Medroxyprogesterone Acetate (DMPA), the injectable form of Medroxyprogesterone Acetate, has been used in the United States and other countries for treatment of a variety of medical problems. These conditions include endometriosis, endometrial carcinoma, renal and breast cancers, threatened abortion, precocious puberty, acromegaly, and premature labor. There is no evidence that women who received DMPA in these treatment regimens have suffered any ill effects (R 171). In the early 1960's it was observed that women who received DMPA as a treatment for premature labor experienced a delay in return of fertility after delivery of from 12 to 21 months (R 50 & 171). It was then that clinical trials of DMPA as a contraceptive agent were begun. These were followed, in 1965, by field trials (R 119).

Today, DMPA is the most widely used injectable contraceptive. Marketed in 84 countries (R 171), including Bangladesh, under the name Depo Provera, distribution is divided between developed and developing countries (fn14). Between 1963 and 1982 an estimated 10 million women had used DMPA as a contraceptive. In 1982 alone, approximately 1.5 million were using it (R 50, 171). In 1983, based on information from sample surveys, manufacturers, and other sources, Population Reports estimated that injectables were most widely used in Jamaica, Thailand, New Zealand, Mexico, Sri Lanka, and Trinidad and Tobago (R 119).

D. INJECTABLE CONTRACEPTIVES IN BANGLADESH

The family planning philosophy of the Bangladesh Ministry of Health and Population Control (MOHPC) has included the use of a cafeteria approach to family planning services - to offer clients a choice of available methods of contraception and to introduce new methods as they become available. Thus, in 1974 the Bangladesh Fertility Research Project (BFRP) decided to initiate trials on Depo Provera at two sites in Bangladesh, the Christian Health Care Project and Gonoshastaya Kendra. In 1976, pursuant to a national conference on the safety and effectiveness of Depo Provera held in Dhaka, the BFRP, headed by Dr. Shafiqur Rahman, recommended that DMPA be used where the services of a physician, or paramedic under a physician's supervision were available. The MOHPC adopted this recommendation, making DMPA available throughout Bangladesh.

Noristerat was approved for domestic use after a 1980 conference sponsored by BFRP, where research conducted in Bangladesh on the safety and effectiveness of Noristerat was discussed. The conclusion of this conference was to recommend approval of NET-EN under the same conditions as those for use of DMPA (R 124).

Use of injectables in Bangladesh has grown from 58 users in 1975 to 72,679 as of May 1984. The target for use of injectables in the Third Five Year Plan for 1985-1990 is 10% of total contraceptive use, or 490,786 users by 1990, an increase from the present level of 3% (R 118).

The United Nations Fund for Population Activities (UNFPA) and AG Schering are the sources of injectables in Bangladesh. Their donations are distributed to district hospitals and upazila health complexes (UHC) by IEMO, the Population Control Warehouse. In most UHCs, injectables are administered by paramedics, the Family Welfare Visitors (FWV) to clients referred by the female family planning field worker, the Family Welfare Assistant (FWA).

E. PREVALENCE OF USE

In clinics around the world, where women were offered a choice of contraceptive methods, Population Reports found that 25% to 75% chose injectables (fn15). Experience in Bangladesh bares this out. At the Matlab Family Planning Health Service Project (Matlab FPHSP) over the period April 1983 through March 1985, injectables were the method chosen by 43.03% of new family planning acceptors (R 2). The Christian Health Care Project reported that 34% of new contraceptive acceptors chose injectables in 1983-1984 (R 11).

The popularity of injectables can largely be attributed to their ease of use; requirement of injection only every two or three months, maintenance of privacy when they are administered at home, and lack of association with intercourse. Privacy and dissociation from intercourse are especially important

considerations in Mosiem societies like Bangladesh where family and social pressures play a large role in use and choice of contraceptives (R 75). They are also well suited for use by women who want to space the birth of their children, or have decided not to have more children but are not yet ready for a permanent method of contraception, ie. tubectomy.

F. CONTINUATION OF USE

Continuation of use rates for injectables vary widely. Based on a number of studies, Population Reports found that 50% to 75% of women who began using three-month injectables were still using them in one year (fn 16). The multinational comparative clinical trials sponsored by the WHO, reported in 1982, found discontinuation rates for DMPA and NET-EN as shown in Table I.

Table-I: CUMULATIVE LIFE-TABLE DISCONTINUATION RATES

	Total Discontinuations		
Months of use	DMPA	NET-EN (60-day)	NET-EN (84-day)
6	32.1% ±1.2	31.1% ±1.2	29.9% ±1.7
12	51.7% ±1.3	49.8% ±1.8	50.1% ±1.8
18	63.5% ±1.2	61.9% ±1.7	62.5% ±1.7 (R 170)

In Phase IV Clinical trials of NET-EN users conducted at six centers throughout Bangladesh in 1984 involving 913 women, overall cumulative life-table continuation rates of 73.7% at 6 months, 62.7% at 12 months, and 57.1% at 18 months were found. Continuation rates varied from center to center. The highest rate was 83.3% at 12 months at the Sir Salimullah Medical College Hospital; the lowest was 48% at 12 months at a Bangladesh Association for Voluntary Sterilization Clinic (R 123).

Another example from a rural Bangladesh setting is the Matlab FPHSP where 58.3% of women using DMPA were found to use it continuously for one year. After 24 months 38% and after 36 months only 27.2% continued first-segment use of DMPA. This is, however, consistently higher than the first method continuation rates for 'Copper T' IUD users. These first-segment rates for DMPA are in contrast to the first year continuation of use rate

of 66.3% and illustrate the added protection afforded by switching women back and forth between contraceptive methods, as appropriate. In this study method switching was found to nearly double the monthly continuation of use rates. When method switching was employed, more than 80% of contraceptive acceptors continued use of a method of contraception for one year, over half used a method for three years. This is double the first method continuation rates for DMPA users. These findings highlight the importance of follow-up and method switching in maintenance of high overall continuation of use rates.

Women cited a number of personal, social, and religious concerns as factors in discontinuing use of injectables in several Bangladesh based studies. Husband's objections were also a significant problem (R 2).

Medical problems were also a major cause of discontinuation of use. The most common problems cited were related to irregular menstrual bleeding and amenorrhea. In the WHO sponsored multinational trials, bleeding and amenorrhea were the most frequently cited medical reasons for drop-out of both DMPA and NET-EN users at 6, 12, and 24 months. A higher percentage of DMPA than NET-EN users of either 60 or 84-day regimens gave these as reasons for drop-out (R 170).

In one study conducted on 19,875 South African women to compare three and six-month DMPA regimens, 0.69% of those on the six-month and 1.39% of those on the three month regimen dropped because of amenorrhea. In the same study 0.62% of women on the six-month and 0.43% of women on the three-month regimen discontinued because of menorrhagia (R 127). Another study on South African women reported reverse findings for three and six-month regimens (R 31).

These side effects are a particular concern in Moslem and Hindu societies where continuous spotting and bleeding can interfere with a woman's domestic and social responsibilities, such as praying, sexual intercourse, fasting during Ramzan, cooking and socializing and can contribute to anemia. Amenorrhea may also be viewed negatively by women in these societies, as there is often the fear that "bad" blood is accumulating in the body and many women miss the monthly break from their domestic duties. This is reflected in the percentage of Bangladeshi women citing bleeding and menstrual irregularities as reasons for discontinuation of use. In the Phase IV Bangladesh study of NET-EN, referred to earlier, heavy and/or prolonged bleeding were the most common reasons given for drop-out, reported by 6.3% of women at 12 months. Amenorrhea was second with 5.1% and irregular bleeding or spotting third with 3.9% of women reporting these reasons (R 125).

At the Matlab FPHSP a different pattern was found among DMPA users. There, menstrual disorders, pain, and headache were the most commonly reported problems (R 2). The Christian Health Care Project found spotting and amenorrhea to be the most prevalent

medical reasons for DMPA drop-outs, while moderate to heavy bleeding was only cited by 3% of drop-outs. Other studies conducted in Bangladesh have reported similar findings for both medical and personal/social/religious reasons for drop-out. For detailed information on other Bangladesh based studies refer to the list of articles (fn 17).

Table II, below, presents a comparison of rates and reasons for discontinuation of use for injectable, oral contraceptive, and intra-uterine device users. As indicated by this comparison, continuation rates for injectables and oral contraceptives are quite similar after 18 months. Injectables have a slightly higher use effectiveness rate than oral contraceptives and the intra-uterine device. There are also similarities in the percentages of women discontinuing use in several of the categories, such as bleeding irregularities for oral contraceptives and NET-EN (Table IIB).

Table II(A): A Comparison of Continuation and Use Effectiveness Rates for Injectable Contraceptives, Intra-Uterine Devices (Copper T), and Oral Contraceptives Using Several Bangladesh Based Studies.

Method		Continuation Rate		Use Effectiveness
INJECTABLE				
DMPA		12 months	53%	
		24 months	39% (R 11)	99.18% (R 33)
NET-EN		12 months	37%	
		18 months	43% (R 123)	99.6% (R 11)
ORAL CONTRA-CEPTIVE		12 months	18 months	
	Field Worker	64.2 (R 126)	42 (R 126)	98.23% overall (R 126)
n=1450	Clinics	60.4 (R 126)	32 (R 126)	
INTRA-UTERINE DEVICE		12 months		
COPPER T n=899		80% (R 90)		92% (R 90)

Table II(B): A Comparison of Discontinuation Reason Rates for Injectable Contraceptives, Intra-Uterine Devices (Copper T), and Oral Contraceptives Using Several Bangladesh Based Studies.

Method	Discontinuation Reasons and Rates: Reasons	% of Dropouts
DMPA		
	Lost to follow-up and unknown	34.22
	Spotting off and on	11.86
	Amenorrhea	10.78
	Method Change	8.95
	Moved away	7.84
	Desired/Planned Pregnancy	6.86
	Husband objected	4.24
	Weakness	3.97
	Moderate to heavy bleeding (requiring some kind of treatment)	3.35
	Medical advice	1.60
	Headache/dizziness	1.54
	Forgot due date for next injection	1.05
	Divorced/Separated/Husband's death	1.02
	Accidental/Unplanned pregnancy	0.82
	Personal reasons	0.48
	Adverse publicity/Bad rumours	0.43
	Over aged (no further need for contraception)	0.30
	Weight gain	0.21
	Heavy bleeding (needing hospitalization with special care)	0.18
		(R 33)

Table IIB. (Contd.)

Method	Discontinuation Reasons and Rates Reasons	% of Users
NET-EN		
	Other personal reasons	9.7
	Other medical reasons	7.1
	Heavy and/or prolonged bleeding	6.3
	Amenorrhea	5.1
	Irregular bleeding or spotting	3.9
	Desire for pregnancy	3.1
	Late for follow-up	2.5
	No further need	1.9
	Pregnancy	0.4
	Lost to follow-up	11.0
	Total	42.9 (R 123)

ORAL CONTRACEPTIVES	% of Users	
	Field Worker	Clinic
Vertigo/nausea	11.76	6.37
Weakness	11.31	11.25
Planned pregnancy	6.06	11.44
Menstrual problem & discharge	6.87	7.25
Accidental pregnancy	2.7	1.77
Fear/Method Change/ Lack of supply	3.4	2.94
Total	42.1	38.08 (R 126)

IUD	% of Dropouts
Discontinuations=175 96% CuT 4% Loops	
Health grounds	43%
Spontaneous expulsion	24%
Wanted to use another method	14%
Husband's dissatisfaction	11%
Accidental pregnancy	8%
	(R 90)

G. SIDE EFFECTS

Side effects from injectable contraceptives can be divided into short and long-term. Short-term side effects only affect the woman during and shortly after use while long-term effects may continue for an indefinite period in either the woman or her off-spring who may have been exposed.

G.1. SHORT-TERM EFFECTS

In the category of short-term effects are included menstrual irregularities, i.e. bleeding, spotting, and amenorrhea, weight gain, effects on milk production during lactation and metabolic effects, i.e. changes in carbohydrate metabolism and delayed return of fertility.

G.1.a. MENSTRUAL IRREGULARITIES:

As reflected in the reasons and statistics for discontinuation of use, bleeding irregularities and amenorrhea, the most common short-term side effects, are experienced by approximately two-thirds of women using DMPA and one-half of the women using NET-EN in the first year (R 3; fn 18). The WHO multinational trials showed that while the incidence of ammenorrhea increases over time for both the Noristerat 60-day regimen and DMPA users, it decreases after 12 months for the NET-EN 60/84 day regimen (fn23). They also showed that episodes of bleeding and/or spotting of 21 or more days of duration decrease with length of use for DMPA and NET-EN 60-day regimens, but fluctuate for the NET-EN 60/84-day regimen users.

Amenorrhea lasting 90 days or more may occur in as many as 55% of DMPA users and 30% of NET-EN users by the end of the first year of use (fn 19). Changes in menstrual patterns for both Depo Provera and Noristerat users are unpredictable. Amenorrhea is more common in DMPA users with greater body weights, but less common in NET-EN and other DMPA users (fn 20). No difference in hormonal profiles was noted in Noristerat users who experienced intermenstrual bleeding and those who did not (fn 21).

Similar patterns of menstrual irregularities were found in studies on Bangladeshi women (R 3, 121, 145, 146). A study conducted jointly by the staff of the Johns Hopkins Fertility Research Project and the Bangladesh Fertility Research Project between 1976-77 on Norethindrone enanthate and Depot Medroxyprogesterone Acetate found that at all follow-up visits the proportion of women reporting amenorrhea was higher for DMPA than NET-EN clients. The proportion of NET-EN users reporting irregular bleeding was consistently higher than DMPA users. By the fourth injection less than 15% of clients in both groups reported having regular cyclic bleeding (R 146). Other Bangladesh based studies report this same pattern. For further information see the annexed list of articles (R 63, 73, 74, 76).

Severe bleeding is uncommon among both Noristerat and Depo Provera users. Studies report that less than 1 in 1000 users require dilation and curettage for treatment (R 110; fn7).

G.1.b. METABOLIC EFFECTS:

Oral contraceptive use has been associated with a variety of metabolic effects such as changes in blood pressure, coagulation, fibrinolytic factors, and platelet, liver, renal, and thyroid function. Effects on these metabolic factors are usually considered to be a consequence of the estrogen component of the pill. Research on DMPA and Noristerat support this conclusion as they have been shown to have little or no effect on these function (R 135, 38, 30, 145, 147; fn 24). The possibility of a relationship between injectable use and alterations in a number of other metabolic functions has been investigated in several studies. Use of hormones, including DMPA, has been linked to change in carbohydrate metabolism, but there have been no reports of diabetes developing among injectable users (fn 25). Reported carbohydrate metabolic changes include a small increase in fasting glucose and insulin levels and an enhanced glucose and insulin response to glucose tolerance tests (R 59).

Protein and vitamin metabolism do not appear to be affected by injectables (fn 32). Blood serum levels of zinc may, however, be lower in NET-EN users than non-users (fn 33).Once again, research on the effects of NET-EN on all these metabolic functions is much less extensive than for DMPA. Findings for NET-IN use have been reported here whenever available.

G.1.c. LIVER FUNCTION:

Bangladesh and other internationally based studies on the effects of injectables on liver function tests indicate no significant changes. An exception is one case in a study by S. Abdul Khaleque which had elevated serum bilirubin, S.G.P.T. and S.G.O.T. levels (R 64, 136; fn31).

G.1.d. WEIGHT GAIN:

Most women using injectable contraceptives gain some weight during use. The average gain, however, is small ranging from one to five kilograms in the first year (fn 34). Weight gain for women using DMPA and NET-EN every 60 days are comparable (fn 35). In the McCormick Program in Chiang Mai, Thailand, mean weight gain was approximately two kilograms after two years. Weight gain did not continue after this period. The WHO multinational trials found that women on 84-day regimens of NET-EN had significantly smaller weight gains than 60-day NET-EN or DMPA users (R 168) Reasons for weight gain are not understood, but the added weight appears to be due to increased body fat, not fluid retention. Researchers have hypothesized that DMPA stimulates the hypothalamic appetite control center, causing women to eat more (fn 36).

A few cases of weight loss have also been reported in several studies (R 119). It is important to consider other possible health factors, such as parasites and tuberculosis in such cases (27).

G.1.e. CARDIOVASCULAR EFFECTS:

Because injectables do not contain estrogen, users of Depo Provera and Noristerat are not subject to the estrogen associated side effects of oral contraceptives use, such as blood clotting (fn 27). However, recent evidence indicates that the increased risk of heart attack and stroke among combination oral contraceptive users is likely associated with their progestin component (fn 28).

Likewise, the reduction of High Density Lipoprotein (HDL) serum levels have also been associated with progestins. Decreased HDL levels are strongly suspected of increasing the risk of cardiovascular disease such as artheriosclerosis (fn 29), but their clinical significance has not been confirmed. There is also no clear evidence of the effect injectables themselves have on HDL levels. One study on 23 women who had used DMPA for one year found a 20% decrease in HDL levels over the control group of IUD users (fn 30). However, the Mymensingh, Bangladesh study found no significant changes in HDL levels among DMPA users (R 4).

There are few reports of cardiovascular complications in women using injections. However, this should not be considered as conclusive evidence since most long-term users live in developing countries where reporting systems are poor and/or other health problems may overshadow these effects.

Most studies report no significant changes in diastolic or systolic blood pressure (R3). The study conducted at Mymensingh Medical College found very small and insignificant blood pressure changes among NET-EN. However, another study comparing the effects of 150mg DMPA given every three months and 450mg. administered every six months found a significant increase in systolic blood pressure among women in both groups after six months use (R 139).

G.1.f. OTHER EFFECTS:

Headache is another side effect reported by a large percentage of injectable users. It has also been reported as a major reason for discontinuing use of injectables. As stated previously, the percentage of women complaining of headaches ranges in various studies from 1% (R 119) to 17% (R 137). In the first WHO trials significantly more DMPA than NET-EN users reported headaches (fn 37). Incidence of headaches was also found to increase with length of use. In the second WHO trial the proportion of NET-EN and DMPA users reporting headaches was similar (fn 38).

Abdominal discomfort and distention appear to be more common among DMPA than NET-EN users (fn 39).

G.1.g. EFFECTS ON REPRODUCTION:

There are several aspects to consider when examining the effects of injectables on reproductive functions: rate and length of time to return of fertility, effects on milk production and the nursing infant, and effects on the developing fetus.

G.1.g.(1). Return of Fertility

Though DMPA is considered only effective in preventing conception for 90 days, a 150 mg dose usually has contraceptive effects for a longer time. Delays in the return of fertility of up to two years or more have been reported in a small number of women (R 121). However, there is no evidence that use of DMPA or NET-EN causes permanent infertility. For women who use injectables as a means to space births, the length of time to return of fertility can be an important factor.

Results of a study by Gray and McDaniel on 796 Thai Women using DMPA found that the median delay in conception for women who had used injectables for more than two years was five months, while women who used them for less than two years experienced a six month delay. The average delay was approximately 5.5 months plus the 15 week duration of action of the drug, or a total of nine months post injection. 7.9± 1.1% of women had not conceived at two years and for oral contraceptive users the rate was 5.7±1.1% at two years. Though the rates for injectable users are somewhat higher, these differences were not found to be statistically significant (R 113). It is thought that the duration of infertility may depend on body weight and rate of metabolism of DMPA (fn 40). Drugs used to stimulate ovulation, such as clomiphene citrate, have restored fertility in women having long periods of ammenorrhea after DMPA use (fn 41). This suggests that there is no permanent effect on fertility (R 119).

Return of fertility following use of NET-EN has not been extensively studied. However, NET-EN is metabolized faster than DMPA and by four months post injection cannot be detected in the blood (fn 42). As with DMPA, the average time from discontinuation to ovulation varies among different populations (fn 43).

G.1.g.(2). Lactation

The safety of administering injectables to breastfeeding mothers has long been questioned and studies on the composition and volume of breast milk of mothers currently using DMPA have reported conflicting findings. A significant increase in protein and a slight, but not significant, increase in milk volume have been observed in women using 150 mg of DMPA every 3 months. However, in women using 300 mg every six months a significant decrease in proteins, fats and calcium, but increase in milk volume has been found (R 87). Other studies confirm the lack of adverse effects of either DMPA or NET-EN on milk volume. This is in contrast to oral contraceptives which, containing estrogens as well as progestin, may reduce milk volume (fn 44). One widely reported study, conducted at Gonoshastaya Kendra, on DMPA contradicts these findings. 147 of the 1020 DMPA users who participated in that study reported a decrease, 37 an increase, in volume, the rest no change in lactation (R 112). Research on the effects of NET-EN on lactation is more limited, but it appears to have no adverse effects.

Another important measure of the effects on lactation is weight gain by infants whose mothers used injectables while breast feeding. A study conducted by Dahlberg in Measareing, Thailand, found no significant difference in weight gain between infants breastfeeding on milk of mothers currently using DMPA and those who were not. Also, no significant change in immunity to infectious disease was found except for a subgroup whose mothers began DMPA use at two days postpartum. This may indicate a decreased transfer of antibodies via breast milk in the first one or two months post partum (R 39).

There are also conflicting reports regarding the quantity of hormone passed by the mother to the nursing infant. Reports for DMPA range from less than 0.5% of the maternal dose (fn 45) to levels equal to maternal plasma levels for 87 days after injection (R 87, 171). MPA levels at one week post injection are approximately 7 mg/liter, decreasing to 0.8 mg/liter at eight weeks. Levels for NET-EN are somewhat less. One study found three mg/liter of breast milk at one week post injection. This would add to a cumulative exposure of 0.2% of the maternal dose of DMPA over three months and 0.05% of the maternal dose of NET-EN over two months time. There is little information available on the effects of these hormones on maturation of hypothalamic and liver function of the neonate. Therefore, it has been recommended that infants should not be exposed to injectables during the first six to eight weeks post partum (R 171).

G.2. LONG-TERM EFFECTS

Long term effects of injectables which will be discussed in this paper include possible teratogenic effects on the fetus, and the possible links to breast and cervical cancers.

G.2.a. EFFECTS ON THE FETUS:

Chances of pregnancy for injectable contraceptive users are very low and women usually do not ovulate until blood levels of DMPA are less than 0.1 mg/ml (fn 46), or for NET-EN levels approximately 0.4 to 0.8 mg/ml (fn 47). Pregnancies, however, have been reported at DMPA serum levels as high as 1.8 mg/ml and women have sometimes become pregnant in the month before their first injection. Some pregnant women also take injections thinking they will induce abortion. Therefore, possible teratogenic and other effects on the fetus need to be considered.

A study conducted by Dahlberg at Maesareing Christian Hospital, Thailand on 118 babies whose mothers had used DMPA at some time prior to birth, found an average birth weight of 2948 grams. This is compared to an average birth weight for the 428 controls of 2889 grams. Fifteen infants who had experienced in utero exposure had an average birth weight of 2813 grams (R 39).

In this same study there were two cases of major anomalies (1.7%), one of cleft palate and lip and one with mental retardation and blindness among offspring of ever-users. There were five cases of anomalies (1.1%) among the controls, offspring of women who had never used DMPA. The fifteen infants with in utero exposure had no anomalies (R 39).

In another Thai Study the incidence of congenital anomalies to offspring of women who had formerly used DMPA was 2.3% compared to a 2.2% incidence for non-users. There were no differences in the rates of still or multiple births, in sex ratio, or birth weights in children of former users compared to nonusers (R 119).

Studies based on women treated for habitual abortion with high doses of various progestins in the 1950's and 1960's, found occasional masculinization of external genitalea (enlarged clitoris and/or labial fusion) in female children. This occured when women received progestins, especially those derived from testosterone, in the first trimester of pregnancy (fn 48). Some cases were also found in neonates whose mothers took oral doses of MPA, derived from progesterone (fn 49). Results of other studies suggest either no risk, or approximately a two fold increase in the risk of anomalies, such as cardiovascular defects.

G.2.b. INJECTABLES AND CANCER:

At the heart of the controversy regarding the use of injectables is their possible association with the development of breast, cervical, and endometrial cancers. However, evidence from epidemiological and clinical studies suggests no significantly increased risk of cancer among DMPA and NET-EN users. In fact, studies conducted on oral contraceptive users suggest there may be a protective effect of progestins against ovarian and

endometrial carcinomas. One study of DMPA conducted from 1967-1980 on 5,000 Black women in the United States found fewer cases of breast cancer than expected, but approximately the same number of uterine and ovarian cancer cases as expected. The relative risk for breast cancer was 0.69, for uterine cancer 1.20, and for ovarian cancer 0.86 (R 88).
Preliminary analysis of the data from a recent WHO case-control study conducted at 11 centers in nine countries showed no relationship between DMPA use and either invasive or in situ cervical cancer and no increased risk of breast cancer and perhaps even a slight protective effect. There were too few cases of endometrial cancer to make an analysis. Data for these preliminary results were obtained from three centers in Thailand where DMPA has been used for over 20 years, enabling the possible detection of effects from long term-use (fn 50).

Other evidence against a link between DMPA and cancer comes from studies on women using large doses of DMPA or MPA for treatment of endometrial cancer or postmenopausal symptoms. In a study of 100 women taking one gram of MPA orally per week, about 80 times the contraceptive dose, for several years there were no signs of breast dysfunction or dysplasia (fn 51). Oral MPA or DMPA used to treat breast cancer leads to partial remission in about one-third of the cases (fn 52). Occasionally, symptoms have been found to worsen (fn 53). The addition of progestins, including MPA, to estrogens used for treatment of symptoms of menopause reduces the incidence of hyperplasia and endometrial cancer associated with these therapies (fn 54). When large doses have been used for treatment of metastatic or recurrent endometrial cancer complete or partial remission has occured in 18% to 57% of the cases (fn 55).

This evidence stands in contrast with animal studies which have reported development of these cancers in laboratory animals administered high doses of DMPA. Animal studies were conducted in accordance with the United States Food and Drug Administration's (US-FDA) regulations for approval and marketing of new medications. Data from these studies was monitored by the FDA's Toxicology Review Panel which discusses the significance of results of animal studies.

In these studies beagle dogs who were administered doses 16 and 25 times the human dosage died of pyometra. Pyometra developes in beagles given any progestogen. However, in this study they did not develop in those dogs who had received ovariectomies, suggesting that estrogen may play a role in their development. No pyometra has been found among women using DMPA.

Mammary gland nodules also developed in all beagles that lived past the first few years of treatment, except for two in the control group. However, it is important to note that the breasts of healthy beagles contain a reservoir of microscopic neoplasms that may grow and possibly become malignant, especially if over-stimulated by progestogens (fn 56). Reservoirs of this type have never been seen in healthy women. The susceptibility of beagles

to mammary tumors and their species specific response by progesterone receptors in the myometrium led the Toxicology Review Panel to conclude, in 1978, that the beagle was not a suitable model for studying possible long-term effects of DMPA use in women (fn 57).

The results of studies conducted on monkeys, as part of these trials, reported the development of endometrial carcinoma in two monkeys out of 12 receiving 50 times the human dose of DMPA. These findings have, however, questionable relevance to humans because endometrial carcinomas in women originate in a hyperplastic endometrium, whereas, tumors in the monkeys were found in an atrophic endometrium. The tumors apparently arose from a cell type not found in women. Interestingly, DMPA in relatively high doses has been successfully used to treat endometrial cancer in women (R 171).

A ten-year study on the effects of NET-EN on monkeys revealed only one case of endometrial cancer in a monkey in the high dose group. No cases of endometrial carcinoma have been reported among women using Noristerat (R 4). In light of the findings from these animal studies, a controversial article by Stephen Minkin was published in Mother Jones Magazine raising concerns over the safety of injectables and pointing to the need for caution and further investigation into their possible long-term effects on users and their offspring before granting approval for use. (R 102).

In 1975, the US-FDA's Obstetrics and Gynecology Advisory Committee recommended approval of DMPA for use by women who were not able to use other methods of family planning or had experienced contraceptive failures (R 119). However, in 1978 the US-FDA formally denied approval of DMPA for contracptive use based on four reasons:

1. Questions raised by the development of breast nodules in beagles given DMPA were not resolved.

2. There was a potential risk of birth defects in cases of contraceptive failure.

3. Estrogens would be used to control irregular menstrual bleeding caused by DMPA, reducing the benefits of progestin-only contraception.

4. A significant need for DMPA in the US had not been demonstrated (fn 58).

The FDA's decision was reviewed in 1983 by a Public Board of Inquiry at the request of the Upjohn Company. Recommendations of this board were reviewed by the commissioner of the US-FDA (R 152) who, once again, did not grant approval.

PART - II

CONSIDERATIONS FOR PROGRAM IMPLEMENTATION

The national family planning program of the Government of Bangladesh delivers contraceptive methods to women through a system of static clinics, facilities staffed by medics and paramedics, and in the household through fieldworkers. However, not all methods are available at all service points. According to Government orders, fieldworkers, the Family Welfare Assistants (FWA), carry pills and condoms with them during their routine visits for distribution in the household; they refer clients for IUD insertions to the union level clinics where para medics, the Family Welfare Visitors (FWV), provide such services, and to medics at the Upazila Health Complex (UHC) for sterilization. Union level outpatient clinics cover an average population of 20,000, whereas a UHC provides for a population of 200,000 and is the administrative unit for the family planning field program. Injectables are presently provided to clients coming to the UHC by paramedics under the supervision of a medic. However, in a collaborative study with the International Center for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), the Government is experimenting with providing injectables at the doorstep through its system of female fieldworkers, the FWA's. To date, injectable acceptors of the Government program only make up approximately 3% of all users of contraceptives. In contrast to this, are the domiciliary programs run by private groups who find injectable users to be 30-40% of their clientele. This section of the paper explores the implications for implementation of the Government's injectable program through the domiciliary and static centers approach.

A. MANAGEMENT ISSUES

A.1. WORKER DENSITY

The first injection of both DMPA and Noristerat must be administered during the first five to seven days of a woman's menstrual cycle (R 119). Follow-up injections of DMPA, in most programs, are given every 90 days. For Noristerat the regimen is an injection bimonthly for the first four injections and then every 90 days. If a domiciliary delivery system is implemented, these regimens require the field worker to break from her work cycle to give injections at the appropriate time. Disruptions of routine will occur more frequently with use of Noristerat than the DMPA three month regimen. In the ICDDR,B Family Planning and Health Services Project in the upazila of Matlab, DMPA clients who experience no or few side effects are switched from a three to six month injection cycle, minimizing these disruptions.

However, present worker density in both the Matlab program and government sectors implicitly places a ceiling on the number of injectable clients any one worker can serve. In Matlab each field worker is responsible for a population of approximately 1,200. She is able to visit each household every two weeks, allowing her to give frequent and consistent follow-up services to clients and to screen for and manage side effects. Clients with medical complications, such as bleeding, are referred to the clinic for treatment(R 2). This has been a particularly successful program, as 40% of contraceptive users in the Matlab FPHSP choose injectable contraceptives (Matlab FPHSP Monthly Reports).

The Matlab Community Health Workers (CHW's) serve a function comparable to that of the female field worker, the Family Welfare Assistant (FWA's) in the Government of Bangladesh program. However, the density of FWA's in the government sector of one per average population of 6,000 only allows them to complete a work round, on average, once every three months. This creates a problem by not allowing enough time to provide adequate follow-up and management of clients using injectables. Increasing the worker density to one per 2000 population would allow a worker to visit each client on a monthly basis providing more frequent follow up.

A.2. RECORD KEEPING SYSTEM AND SUPERVISION

The need for a record keeping system which will keep the service provider informed about clients due for injections and supervisors who will insure that due dates are met, and coverage is provided during times when the provider is on leave, are of particular importance. Currently, within the government system there are no provisions for coverage of workers on leave. However, if the field supervisor, the Family Planning Assistants (FPA) were routinely informed of fieldworker leaves they could, in turn, inform the paramedics, the FWV's of the union or UHC who could provide coverage to clients due for injections if a domiciliary approach is implemented.

A.3. RAMZAN

The Ramzan month also presents special administrative problems as fasting women will not accept injections during the fasting hours. During this period clients can either be temporarily switched to alternative family planning methods or be given their injections at night. In the Sirajganj Upazila, one of the sites of the MOHPC-ICDDR,B collaborative study, injectables were administered by several FWA's at night during the Ramzan of 1985, greatly reducing the expected number of drop-outs during that time. In the static clinic approach, women must be motivated to come to the clinics on their own; during Ramzan it is unlikely that clients would be motivated to do so.

A.4. TRAINING

The reasons cited by clients for discontinuation of use, such as spotting, bleeding, and amenorrhea and the fact that some pregnant women inappropriately seek injections of DMPA and Noristerat to induce abortions, point to the need for special training of workers in screening and follow-up procedures, client education, counseling techniques, and management of side effects. While there is a need for medical supervision of workers by a physician, the FWV's and FWA's can be trained in these basic skills. This type of training is provided to female village workers in the Matlab FPHSP. In a domiciliary program, FWA's can provide most of the education, screening, and follow-up, using the FWV and Medical Officer for back-up and referral. Women could consult with the FWA about side effects and the FWA could provide appropriate counseling on how to cope with these problems, by switching the client to another method of contraception or referring her to the UHC when needed. This type of system is used successfully in the Matlab FPHSP.

Other areas that require special consideration during training include: screening for pregnancy, especially during post-partum amenorrhea, and for the contraindications to use, ie. cancer of the breast or genital tract, diabetes, and abnormal vaginal bleeding of unknown etiology (R 119). Screening for breast cancer could be done in the home if the FWA were trained in performing a breast examination. An FWA could also screen for genital tract carcinoma by history taking and refer clients to the UHC if further screening was needed. Where FWV's administer injectables, they could perform the necessary screening and examinations. Pap smears would also be a valuable tool in screening for cervical carcinoma.

A.5. OVERALL PROGRAM CONSIDERATIONS

These are just a few of the considerations necessary for implementation of a domiciliary injectable program service. As each service and method of contraception has its own administrative implications, it is informative to have an overview of programatic considerations for all methods of contraception to enable effective administration of a comprehensive family planning program. Table III., below, presents a brief comparison of the implementation problems of oral contraceptives, the intra-uterine device, and injectables.

Table III

A COMPARISON OF IMPLEMENTATION PROBLEMS

ORAL CONTRACEPTIVES

CLIENT ORIENTED CONSIDERATIONS

1. The need for a high level of motivation on the part of the woman to remember to take a pill each day.

2. The cultural implications of the common side effects of decreased menstrual bleeding and/or amenorrhea. (R 121)

ADMINISTRATIVE CONSIDERATIONS

1. Training of workers to provide adequate screening, counseling of clients in daily pill taking, follow-up, and management of side effects.

2. Provision of proper storage facilities so that the pills do not decompose.

3. Insuring a constant supply of pills is in the hands of service providers. (R 121)

Table III (Contd.)

INTRA-UTERINE DEVICE

CLIENT ORIENTED CONSIDERATIONS

1. The need for the woman to be highly motivated to seek out clinic services for IUD insertion. Constraints against her doing so include cost of transportation, time involved for travel and the insertion, and lack of confidentiality.

2. The health implications of heavy and prolonged menstrual bleeding, a common side effect of IUD use (R 119).

3. The cultural implications of heavy and/or prolonged menstrual bleeding.

4. Cultural inhibitions against inserting a foreign object into the body.

6. Cultural inhibitions against a woman touching herself to regularly check the IUD string to insure that the IUD is properly in place.

7. Husbands may feel the IUD string and find this unsatisfactory.

8. The increased risk of contracting pelvic infections among IUD users. (R 120)

ADMINISTRATIVE CONSIDERATIONS

1. Special training of staff in providing this service at home or in the clinic, follow-up, and management of side effects.

2. Maintenance of an adequate supply of IUD's and supporting peripherals.

3. Both special training and adequate peripherals to allow for aseptic techniques to be maintained. (R 120)

Table III (Contd.)

INJECTABLES

CLIENT ORIENTED CONSIDERATIONS

1. Health implications of prolonged bleeding.

2. Cultural implications of spotting or amenorrhea.

ADMINISTRATIVE CONSIDERATIONS

1. Maintenance of an adequate supply of DMPA, NET-EN, and the supporting peripherals to insure continuity in an ongoing program and the possibility for program expansions.

2. Coverage of service providers during leave.

3. Special training of workers in screening, follow-up, and side effect management.

4. Disruptions of field worker routines to provide injections.

From this comparison it is apparent that all three methods share the need for special training of workers, with the IUD requiring the most training to acquire the requisite skills, and the logistical problems of maintaining adequate supplies of the contraceptives and supporting peripherals. However, there are more client based barriers to effective use of oral contraceptives and intra-uterine devices than injectables, suggesting that injectables may be a more suitable method in Bangladeshi society.

B. LOGISTICAL SUPPORT

B.1. SUPPLIES

Constant and adequate supplies of DMPA, Noristerat, and the supporting peripherals are also essential to maintenance of an injectable program. This is illustrated by the problems which resulted from the disruption in the supply of DMPA which occured between 1981-1982 in Bangladesh. During this time the Christian Health Care Project reported that 40% of their DMPA users dropped out because they refused to use another method of contraception. Likewise, 75% of Family Planning Association of Bangladesh injectable users dropped during the period of 1982-1983 when supplies were delayed because of bureaucratic problems (R 11).

The logistics of obtaining needed supplies are complex in the Bangladesh program as they are obtained from several different sources. DMPA and Noristerat are supplied by the central warehouse through the district stores to the Upazila Health Complex (UHC). However, many of the essential peripherals, such as spirit, cotton, savlon, and soap are not always available from the family planning stores. Others, linens for wrapping sterilized needles and syringes, registers and forms for recording clients,, plastic bags for carrying the needles and syringes, and kerosene, must all be purchased with the very limited contingency funds of the upazila level Family Planning Officer (FPO). One solution to these problems would be the provision of all necessary supplies in one kit to the UHC and then to the union clinics, the Health and Family Welfare Centers (H&FWC), if a domiciliary approach is implemented.

B.2. REUSABLE VERSUS DISPOSABLE SUPPLIES

Another problem is the often insufficient supply of appropriate and sterilized needles and syringes. Also, autoclaves for sterilization and kerosene to fuel them are not available in all UHC's and HFWC's. This creates disruptions in service provision, as well. Possible options for dealing with these supply problems include:

1. The use of disposable needles and syringes by all FWA's involved with home administration, or FWV's in the UHC.

2. If a domiciliary approach is implemented or injectables are provided at the union level clinics, installation of functioning autoclaves or pressure cookers at each H&FWC for sterilization of needles and syringes. Then sterilized equipment could be transported by the field supervisor between the H&FWC to the FWA for household services.

3. Increasing the supply of needles and syringes for each FWA or H&FWC to insure an adequate monthly supply. Sterilization could then be done at the UHC on a monthly basis.

Appendix I provides an analysis of the comparative costs of reusable and disposable needles and syringes. It shows that the costs of using disposable needles and syringes are less than those for using equipment that must be resterilized, when considering all the expenses incurred in the sterilization process and for the transportation between site of sterilization and field worker.

B.3. THE USE OF BOTH DMPA AND NORISTERAT

At present, the Government of Bangladesh sanctions an injectable program with 50:50 DMPA and Noristerat. If the two types of injectables are distributed randomly a number of field problems may arise:

1. As there have been no clinical studies of switching clients from one injectable to another, it is unknown what side effects may be experienced. Each individual client should, therefore, be continued on the same injectable compound.

2. Different peripherals are needed for the two types of injectables. Noristerat, a viscous, oily solution, requires a larger gauge needle, whereas a smaller gauge can be used for DMPA. Noristerat, given with the smaller gauge needle is slow and sometimes painful for the client.

3. The different initial regimens of Noristerat and DMPA can create confusion for the service deliverers, the paramedics or fieldworkers, if they are provided with both.

Therefore, it is suggested that each district receive only one type of injectable with the appropriate peripherals. Once a pattern is established in a district, it should be continued.

C. DOMICILIARY VERSUS STATIC APPROACH

Evidence from the Christian Health Care Project, Matlab FPHSP, and the MOHPC-ICDDR,B collaborative MCH-FP Extension Project, suggests that a domiciliary approach to injectable services may encourage greater participation and continuation of use of injectables than the current approach used in the Government system where women must travel to the UHC to receive their injections and follow-up. Statistics provided by the national Management Information System office for 1983-1985 further reflect clients' preference for home based services. In 1983-1984 and 1984-1985 non-governmental organizations, which largely provide domiciliary injectable services, administered 63.2% and 54.3% of injectables used in Bangladesh, respectively. The domiciliary system is popular because it allows the woman to maintain confidentiality, does not place the burden on her to remember when her next injection is due, or rely on her ability to reach the clinic to receive it or medical attention for any side effects.

Another example of a successful domiciliary program is in Thailand, where injectables have been used since 1965 by the McCormick Family Planning Program of Chiang Mai. There, mobile teams made up of a physician, nurses, midwives, and aides provide

injectable contraceptives and other family planning services in the rural areas. Reportedly, they are reaching approximately 90% of the rural population with this method of distribution (R 119).

Successful domiciliary programs suggest that a policy change allowing field workers (FWA's) to provide home based injectable services is feasible in the future only if requisite training, supervision, logistical support, and adequate worker density are provided. Government program officials should, however, carefully field test injectable strategies in a variety of settings before embarking on a national domiciliary program. Field sites where carefully conducted injectable programs exist can serve as demonstration areas for orienting all service providers to program needs.

III. CONCLUSION

Evidence to date strongly suggests that Depot Medroxy-progesterone Acetate and Norethindrone enanthate are safe and effective methods of birth control. Results from studies on their metabolic effects indicate that they have no more side effects than other widely used methods of family planning, such as oral contraceptives and the IUD. They may also be more popular and acceptable to Bangladeshi women than these other methods.

Certainly, no one would argue that any of these methods are risk free, but it is all too easy to look only at the problems associated with any drug or prophylactic when considering its use. It is important, however, to place the use of injectables within the broader context of both the associated risks and the benefits from their use and other available choices. Bangladesh, as well as most developing countries, is experiencing rapid population growth along with very high maternal and child mortality rates. While not being the only solution necessary to solving these problems, a reduction in the overall fertility rate and child spacing are essential components. Women in Bangladesh find DMPA and Noristerat acceptable because they have the same relative safety as other available family planning methods, are easy to use, and are provided in a manner found culturally acceptable. For women who desire future children and are not yet ready for a permanent method of contraception they offer an effective means of birth control. In these ways they may be more desirable than either oral contraceptives, IUD's or sterilization.

While it is important to continue research into the possible links between injectables and side effects, including cancer, it has been noted that no deaths have been directly associated with their use. Estimates of maternal mortality in Bangladesh range from 5.4 to 12.7 per 1000 live births (R 151). Juxtaposing these two facts while considering the acceptability of injectables in Bangladeshi society points out the positive impact they can have as one element in reducing maternal deaths.

The success of NGO domiciliary injectable programs in Bangladesh, likewise, highlights the importance of a family planning program which includes adequate worker density, supervision, logistical support, and staff training to provide patient education, screening, and follow-up of side effects. These components will help ensure that those women who can use injectables will continue to do so.

Appendix I

DISPOSABLE vs. REUSEABLE NEEDLES AND SYRINGES: Supplies, Management and Costs

It has been noted in the text that both management issues and logistics can present major barriers to effectively implementing an injectable program. One means of decreasing the extent of these barriers is to use disposable needles and syringes rather than reuseable supplies now in use in the Bangladesh national program. The agrument against this, however, is always one of expense. In this appendix, we shall examine the effect of using disposable versus reuseable needles and syringes on the cost of the program.

A list of the required supplies for an injectable program using either reuseable of disposable needles and syringes may be found in Figure 1. The major difference between the two is that reuseable needles and syringes require that the equipment and supplies are sterilized after once used and that the logistics are in place to transport the needles and syringes between the site of sterilization and the site of service delivery. Field observations of the present government program utilizing only reuseable needles and syringes indicate that the stock of necessary supplies at the H&FWC and often at the UHC is rarely complete, especially of those materials needed to sterilized the needles and syringes. Supplies frequently in short supply include kerosene, autoclave tape and wraps. The kerosene is

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FIGURE 1. Supplies and Equipment Required for an Injectable Program: Reuseable vs. Disposable Needles and Syringes

REUSABLE	DISPOSABLE
Needle	Needle
Syringe	Syringe
Cotton	Cotton
Spirit	Spirit
Plastic Bags	Plastic Bags
Sharpening Stone	Wire Clipper
Wash Basin	
Test Tube Brush	
Autoclave	
Burner	
Kerosene	
Matches	
Autoclave Wraps	
Autoclave Tape	

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essential for the heating of the autoclave unit and the tape for the labelling and dating of the sterilized needle and syringe packages. This is important because each set is good for only

one month from the time of sterilization. Further, it has been reported that a sharpening stone does not exist in any of the clinics. This means that the needles which are being used are in poor condition (i.e., they are dull or have burrs) and/or they must be discarded far sooner than a maintained needle would be. The condition of the needle has many implications. If the needle condition is poor, the injection may be extremely painful to the client; so painful that she may decide to stop using injectables and contraceptives altogether.

Another supply problem with the present system is that often the quality of the goods is less than optimal. For instance, the autoclave wraps should optimally be made of a double layer of tightly woven material. Instead, they are usually a single, loosely woven layer allowing contamination of the sterilized needle and syringe. Once again, it is essential to overcome barriers such as these to ensure a safe and efficient injectable program.

However, the lack of proper management of the sterilization process of the reuseable needles and syringes may be the most serious problem for implementation of an injectable program. It usually takes a week for the small supply of needles and syringes to be cleansed and sterilized; this may cause an operational shortage of equipment. Due to the oily-based solution of the prophylactic, cleansing requires extra scouring with a test tube brush. Further, operation of the autoclave requires special technical skills in addition to several hours of direct supervision for monitoring pressure and heat. Problems at any stage of this process create repercussions for the entire injectable program. For example, a needle which has not been properly cleansed and which may also have burrs, may lead to abcesses, infection and other blood born diseases. The frequency with which this occurs is not known. It is problems such as these which must be mitigated in a successful injectable program.

The cost of reusable equipment for injectable contraceptives can be based on different assumptions. Although the use of reuseables mandates a strict sterilization process, for the purpose of analysis we could examine the costs incurred assuming the costs of the sterilization procedure are absorbed elsewhere. One may, for example, assume that the autoclave procedure is already operative and, therefore, requires no additional inputs for the sterilization of needles and syringes. Unfortunately, in practice, this assumption does not hold and the purchase of an autoclave unit is very expensive, as is the use of kerosene. Without these two factors, however, the price per injection would be US$0.04005 compared to the total cost (including the autoclave and kerosene) of US$0.20690 per injection as is shown in Figure 2. Even this lower cost is still approximately US$0.016 more that the total cost of the disposable equipment.

Further, the use estimates in Figure 2 (column 3) are based on ideal conditions such as the proper maintenance of reuseable needles and syringes. The need or use of more needles and

syringes would add to the costs of reuseables. It is important to note also that the costs of transportation and logistics are excluded from this analysis. In practice, these costs can be quite high and would be higher for the reuseable than the disposeable system.

Disposable needles and syringes alleviate many of the logistics and management problems associated with reuseable supplies. On the supply side, there are far fewer items on which the entire process depends. From a management perspective, disposables are easier to manage than reuseables as they do not require the sterilization process or the attendant logistics scheme to transport them between sites of sterilization and service delivery. After the injection, the FWA must discard the used needle and syringe in a plastic bag and return this to the clinic for clipping and proper disposal. This entails the use of a wire clipper to snip the needles. These needles and syringes, like many other medical supplies, require special disposal facilities which should already be operative at the H&FWC and the UHC. With regard to transportation of supplies to the field, disposables require much less effort (and frequency of trips) than reusables. Provided a dependable monitoring system is in place, it would be feasible to equip the field workers with supplies for several months.

On the cost side, United Nations sources cite US$0.023 for the cost of the disposable needle and syringe. Including the purchase of a wire clipper, the fee per injection (excluding cotton, spirit, plastic bags and the contraceptive serum which are constant in both the reuseable and disposable cases) is approximately $0.02388. As Figure 2 indicates, this is nearly one-tenth of the cost of reuseable equipment.

With the use of either reuseables or disposables as presented herein, the problem of wastage of the prophylatic remains to be addressed. That is, the DMPA presently in use is packaged in ten dose vials. It is estimated that 1 per every ten doses is wasted. More important than wastage, however, is the potential for contamination. Should an improperly cleansed needle be inserted in a 10 does vial of DMPA, the entire vial is susceptable to contamination, hence clients who receive injections from that vial are at risk to infection or unforeseen complications. As of September, 1985, UNFPA has made one dose ampules of DMPA available in Bangladesh. Noristerat is packaged in one dose ampules.

While the problems of wastage and contamination can be alleviated with the implementation of one dose ampules, an ideal solution would be the use of individual prepackaged doses. (i.e.: one disposable needle and syringe which already contains one dosage of the drug in the syringe.) This would be the optimal use of disposable equipment. Although desirable, the viability and

costs of this option are unknown. A second-best solution, however, is the use of disposable for they appear to be less expensive and to entail fewer management problems than reuseables.

This appendix has identified some of the problems associated with the use of reuseable and disposable needles and syringes for injectable contraceptives. Whichever method policy-makers decide to implement in a project it will be necessary to recognize the potential shortcomings and ways to overcome these.

FIGURE 2. Costs of Equipment for Reuseable and Disposable Needles and Syringes

REUSEABLES: Costs per Use

(1) Item	(2) Unit Cost	(3) # uses per unit	(4) Adjusted Unit Cost (in US$)	(5) Remarks and Assumptions
Needle	(a) $0.02779	30	0.00093	Based on proper sharpening of needles
Syringe	(a) $0.33350	250	0.00133	Based on 250 uses with proper cleansing and handling
Test Tube Brush	(b) Tk. 20	200	0.00345	Based on life expectancy of 200 uses/brush
Sharpening Stone	(a) $0.98900	1300	0.00076	Based on life expectancy of 1300 uses/stone
Wash Basin	(b) Tk. 1500	3900	0.01326	Based on 1 washing of 15 needles and syringes/wk for 5 yrs with no maintenance
Matches	(c) $0.00025	0.25	0.00006	Based on the use of 10 matches per usage of autoclave
Burner	(b) Tk. 90	260	0.00080	same as autoclave
Kerosene	(b) Tk. 10	0.5	0.09195	Based on need of 2 liters per 1 usage of autoclave for 15 needles and syringes
Autoclave	(d) $292.100	260	0.07[illegible]0	Based on 1 use/wk for 5 yrs with no maintenance for 15 needles and syringes/weekly
Autoclave Wraps	(b) Tk. 20	50	0.01379	Based on price of linen where 1 meter of fabric makes four autoclave wraps
Autoclave Tape	(c) $1.70000	300	0.00567	Based on the use of 3 inches for each wrap
TOTAL COST		in US$	0.20690	
		in BGD Tk	6.00010	

DISPOSABLES: Costs per Use

Item	Unit Cost	# uses per unit	Adjusted Unit Cost (in US$)	Remarks and Assumptions
Needle	(a) $0.01150	1	0.01150	Based on one use only
Syringe	(a) $0.01150	1	0.01150	Based on one use only
Wire Clippers	(b) Tk. 100	3900	0.00088	Based on usage once weekly for 5 yrs
		in US$	0.02388	
		in BGD Tk	0.69252	

NB: All prices are in current prices. The US$-Taka conversion rate is US$1=29Taka. None of these costs include expenditures which remain constant over injection type (i.e., cotton, spirit, plastic bags and the DMPA and/or Noristerat). These figures also do not include labor costs which are much greater for reuseables than they are for disposables. These prices also include shipping and handling charges where necessary.

Sources [as noted in column (1)]:
(a) UNIPAC; UNICEF Procurement and Assembly Centre; Copenhagen, 1985.
(b) Current Market Prices; based on cost estimates from the Bioengineering Cell of the ICDDR,B, Dhaka, July 1985.
(c) ICDDR,B; Detailed Cost Report, Office of Budget and Finance, Dhaka, May 1985.
(d) ICDDR,B; Purchase Order for ICDDR,B MCH-FP Extension Project; Noapara, March 1985.

FOOTNOTES

1. See reference number 54 as cited in Fraser, reference number 52; see reference numbers 35, 70, 107, and 137 as cited in Nash, reference number 110.

2. See reference numbers 46, 47, 48, 66, and 160 as cited in Population Reports, reference number 119.

3. See reference numbers 46, 80, and 110 as cited in Population Reports and "Facts About Injectable Contraceptives", reference numbers 119 & 171; reference number 47 as cited in reference number 119.

4. Reference numbers 54, 132, 158, and 160 as cited in reference number 119.

5. Reference number 115 as cited in number 171; reference numbers 44, 45, 48, 158, and 160 as cited in number 119.

6. Reference number 115 as cited in number 17; reference numbers 103, 104,and 105 as cited in number 109; reference numbers 45, 54, 55, 103, 157, and 160 as cited in number 119.

7. Reference numbers 92 and 104 as cited in number 119.

8. Reference numbers 92, 93, and 104 as cited in number 119.

9. Reference number 93 as cited in number 119.

10. Reference number 156 as cited in number 119.

11. Reference number 153 as cited in number 127.

12. Reference number 170 as cited in number 119.

13. Reference numbers 15, 41, 68, and 69 as cited in number 119.

14. Reference number 152 as cited in number 119.

15. Reference numbers 20, 34, 61, 74, 94, 114, 138, and 143 as cited in number 119.

16. Reference numbers 41, 74, 85, 96, 137, 167, and 173 as cited in number 119.

17. See reference numbers 11, 32, 76, 123, 147, and 148.

18. Reference numbers 30, 31, 78, 148, and 168 as cited in number 119.

19. Reference numbers 152 and 168 as cited in number 119.

20. Reference numbers 90, 167, and 171 as cited in number 119.

21. Reference number 170 as cited in number 119.

22. Reference number 82 as cited in number 171.

23. NET-EN 60/84 day regimen refers to clients who were given the first four injections every 60-days and subsequent injections every 84 days.

24. Reference number 61 as cited in number 171; reference numbers 4, 12, 21, 23, 24, 60, 63, 107, 131, 142, 155, 168, and 181 as cited in number 119.

25. Reference number 166 as cited in number 119.

26. Reference numbers 149 and 154 as cited in number 119.

27. Reference number 1 as cited in number 119.

28. Reference numbers 49, 73, 144, and 145 as cited in number 119.

29. Reference numbers 101 and 56 as cited in number 119.

30. Reference number 86 as cited in number 119.

31. Reference numbers 8, 10, 42, 57, 75, 92, 107, 128, and 141 as cited in number 119.

32. Reference numbers 6, 8, 75, 139, and 162 in number 119.

33. Reference numbers 51 and 122 in number 119.

34. Reference numbers 7, 31, 36, 62, 72, 106, 168, and 173 as cited in number 119.

35. Reference number 173 as cited in number 119.

36. Reference number 9 as cited in number 119.

37. Reference number 168 as cited in number 119.

38. Reference number 173 as cited in number 119.

39. Reference numbers 170 and 173 as cited in number 119.

40. Reference number 17 as cited in number 119.

41. Reference numbers 177 and 178 as cited number 119.

42. Reference numbers 46 and 49 as cited in number 119.

43. Reference number 49 as cited in number 119.

44. Reference numbers 71, 122, and 125 as cited in number 119.

45. Reference numbers 133, and 165 as cited in number 119.

46. Reference numbers 48, 80, 110, and 159 as cited in number 119.

47. Reference numbers 54 and 158 as cited in number 119.

48. Reference numbers 133, 163, adn 164 as cited in number 119.

49. Reference numbers 29, 152, and 153 as cited in number 119.

50. Reference number 175 as cited in number 119.

51. Reference number 22 as cited in number 119.

52. Reference number 89 as cited in number 119.

53. Reference number 81 as cited in number 119.

54. Reference numbers 27, 53, 59, 108, and 146 as cited in number 119.

55. Reference numbers 25 and 117 as cited in number 119.

56. Reference number 25 as cited in number 171.

57. Reference number 26 as cited in number 171.

58. Reference numbers 5 and 37 as cited in number 171.

59. Reference numbers 149 and 154 as cited in number 50.

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