EXPERIENCES OF IMPLANON NXT® USERS AT PUBLIC HEALTH FACILITIES IN SOUTH AFRICA

Submitted by:

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November 2018

DECLARATION 1: DISSERTATION SUBMISSION

This is to certify that the contents of this dissertation are the original work of:

Student's Name: S Prosad

Signed: 

Date: March 2019

As the student's supervisor, I have approved this dissertation for submission.

Supervisor's Name: Dr E Ojewole

Signed: 

Date: March 2019

DECLARATION 2: PLAGIARISM

I, S Prosad declare that:

1. The work reported in this dissertation is my original work except where otherwise specified in the relevant sections of this dissertation.
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DECLARATION 3: PUBLICATION/MANUSCRIPTS

The details of contributions to publication/manuscripts that form part, and/or include the research presented in this dissertation are listed below:

1. **Prosad, S**., Mashamba-Thompson, T. P. & Ojewole, E. 2018. Evidence of patients' challenges and barriers related to usage of Implanon®: scoping review protocol. *Systematic reviews* 7/1: 157. doi: 10.1186/s13643-018-0827-1. (***The publication has attained an Altmetric Attention Score of 6***)

   S Prosad performed all literature searches and prepared the first draft of the manuscript. The student, together with the supervisor (Dr E Ojewole) and Dr T Mashamba-Thompson, designed the protocol and finalized the manuscript for journal submission. The manuscript titled **"Evidence of patients' challenges and barriers related to usage of Implanon®: scoping review protocol"** was accepted and published in Systematic reviews.

2. **Prosad S**, Ojewole E, Dheda M & Tlou B 2018. Adverse drug reactions and discontinuation of Implanon NXT® among users at public health facilities in South Africa. The European Journal of Contraception and Reproductive Health Care. *Submitted manuscript (DEJC-2018-0138.R1)*

   S Prosad designed the research project, performed all literature searches, extracted the data, and performed statistical analysis and interpreted results with the assistance of the supervisor (Dr E Ojewole) and statistician (Dr B Tlou). The student together with the supervisor and the statistician, prepared the manuscript for journal submission. The manuscript titled "**Adverse drug reactions and discontinuation of Implanon NXT® among users at public health facilities in South Africa"** was submitted to The European Journal of Contraception and Reproductive Health Care.

   *Dr M Dheda (the Director, Pharmacovigilance Centre for Public Health Programmes at the National Department of Health) and his team granted gatekeeper permission and data used in this study. He also reviewed and approved the manuscript for journal submission.

   *Dr B Tlou (the Statistician) also reviewed and approved the manuscript for journal submission.

   *Dr E Ojewole (the Supervisor) directed the research and contributed to the overall research process, manuscript and dissertation writing.

3. **Prosad S**, Ojewole E, Dheda M, Tlou B. Comparisons of experiences of Implanon NXT® users between provinces in South Africa.

S Prosad, (together with the assistance of the supervisor and statistician) designed the research project, performed statistical analysis and interpreted results for manuscript drafting. The manuscript titled "**Comparisons of experiences of Implanon NXT® users between provinces in South Africa"** was prepared and is to be submitted to the South African Medical Journal for publication.

*Dr M Dheda (the Director, Pharmacovigilance Centre for Public Health Programmes at the National Department of Health) and his team granted gatekeeper permission and data used in this study. He also reviewed and approved the manuscript for journal submission.

*Dr B Tlou (the Statistician) also reviewed and approved the manuscript for journal submission.

*Dr E Ojewole (the Supervisor) directed the research and contributed to the overall research process, manuscript and dissertation writing.

DECLARATION 4: ETHICS APPROVAL AND GATEKEEPER PERMISSION

1. This study titled **EXPERIENCES OF IMPLANON NXT® USERS AT PUBLIC HEALTH FACILITIES IN SOUTH AFRICA** was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE266/17). A copy of both the ethical approval letter and subsequent amendment letter are attached as Annexure 1.

2. Gatekeeper permission letter from the National Pharmacovigilance Centre for Public Health Programmes at the National Department of Health (dated 11/08/2017) is attached as Annexure 2.

RESEARCH OUTPUTS

1. **Prosad, S**., Mashamba-Thompson, T. P. & Ojewole, E. 2018. Evidence of patients' challenges and barriers related to usage of Implanon®: scoping review protocol. *Systematic reviews* 7/1, 157. doi: 10.1186/s13643-018-0827-1.

   The PROSPERO registration (CRD42017072926) and the scoping review protocol publication are attached as Annexes 3 and 4 respectively.

2. **Prosad S**, Ojewole E, Dheda M & Tlou B 2018. Adverse drug reactions and discontinuation of Implanon NXT® among users at public health facilities in South Africa. The European Journal of Contraception and Reproductive Health Care. Submitted manuscript (DEJC-2018-0138.R1).

   The manuscript was drafted using the data generated in this study and submitted to international ISI journal. The submission confirmation letters are attached as Annexure 5.

3. **Prosad S**, Ojewole E, Dheda M, Tlou B. Comparisons of experiences of Implanon NXT® users between provinces in South Africa.

   This manuscript is to be submitted to the South African Medical Journal.

4. **Prosad S**, Ojewole E, Dheda M & Tlou B. Discontinuation of Implanon NXT® among users at public health facilities in South Africa. ***Presented at an International Conference****, 2nd AFREhealth Symposium, 6-8 August 2018, ICC Durban, Durban, South Africa.*

   The conference proceeding page 128 is attached as Annexure 6.

5. E Ojewole, **S Prosad,** B Beemath, A Haniff, N Mpanza, K Naidoo, B Shaik. Awareness, attitude and knowledge of modified release contraceptives among women attending public family planning clinics in eThekwini KwaZulu-Natal. ***Presented at an International Conference****, 2nd AFREhealth Symposium, 6-8 August 2018, ICC Durban, Durban, South Africa.*

   The poster presentation is attached as Annexure 7.

6. **Prosad S**, Ojewole E, Dheda M & Tlou B. Discontinuation of Implanon NXT® among users at public health facilities in South Africa, *College of Health Sciences Research*

Symposium, 11-12 October 2018, KRITH, University of KwaZulu-Natal, Durban, South Africa.

The research symposium book of abstract page 31 is attached as Annexure 8.

DEDICATION

This dissertation was possible through the guidance and blessings from God and support of my immediate family. This dissertation is dedicated to my parents Mr and Mrs Prosad, my sister Dr Nikita Prosad Singh and my fiancé, Mr Akash Singh. Thank you for giving me strength throughout this journey and helping me to conquer my obstacles.

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
ALT	Alanine Aminotransferase
ARV	Antiretroviral
BMI	Body mass index
CDC	Centre for Disease Control
CHC	Community Health Centre
CI	Confidence Interval
COC	Combined oral contraceptive
DVD	Digital versatile disc
EC	Eastern Cape
FDA	Food and Drug Administration
FS	Free State
Gt	Gauteng
HCV	Hepatitis C virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HIV/AIDS	Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome
IUD	Intra-Uterine Device
IUS	Intra-Uterine System
IQR	Interquartile range
KZN	KwaZulu-Natal
LDL	Low-density lipoprotein
Lmp	Limpopo
Mp	Mpumalanga
NC	Northern Cape
NNRTI	Non-nucleoside reverse-transcriptase inhibitor
NPC	National Pharmacovigilance Centre

NW	North West
PHC	Primary Health Care
POC	Progestogen-Only Contracepti
RP	Reference period
SA	South Africa
SSA	Sub-Saharan Africa
SOP	Standard operating procedure
STATSSA	Statistics South Africa
STI	Sexually Transmitted infection
TB	Tuberculosis
TC	Total Cholesterol
USA	United States of America
UK	United Kingdom
WC	Western Cape
WHO	World Health Organisation

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ABSTRACT

Background and aim:

Implanon NXT® was introduced in South Africa (SA) in the public health sector in February 2014. There exist concerns with premature Implanon NXT® user discontinuation in SA however, the true extent remains unknown due to delayed monitoring systems and limited empirical data. This study aimed to evaluate the experiences of Implanon NXT® among users in the public health sector in SA.

Methods:

A retrospective study was conducted and entailed analysis of secondary data attained from the National Department of Health Pharmacovigilance Centre for Public Health Programmes using reports submitted from 1 April 2015 to 11 September 2017. A total of 3743 cases were extracted and analysed using SPSS®. Tests of association were performed using demographics, adverse drug reactions and discontinuation variables. Chi square test and Mann Whitney U-Test were performed to test differences between Gauteng and KwaZulu-Natal (KZN).

Results:

The 20-24-year olds were the most frequent Implanon NXT® users (25.70%; 962/3743). Of the 36.57% (1369/3743) cases which reported adverse drug reactions (ADRs), menorrhagia (52.01%;712/1369), headache (20.45%;280/1369) and dizziness (11.18%;153/1369) were the most frequent ADRs. Discontinuation was reported by 63.56% (2379/3743) of case reports and premature discontinuation was reported by 81.1% (1210/1492). The common reasons for discontinuation were menorrhagia (34.27%;728/2124), expiry (29.57%;628/2124) and headache (10.26%;218/2124). Overall, ADRs were found to be the main reason for discontinuation (83.99%; 1784/2124). Pregnancies reported with Implanon NXT® occurred in 4.97% (68/1369) of case reports and efavirenz-based therapy was suspected to be associated with pregnancy in Implanon NXT® users ($p<0.001$). The common ADRs and reasons for discontinuation of Implanon NXT® reported in Gauteng was consistent with the national data while drug interaction and pregnancy were commonly reported in KZN. Premature discontinuation of Implanon NXT® was higher in Gauteng (82.6%, 252/305) than KZN (76.7%, 23/30).

Conclusion:

Young women were frequent users of Implanon NXT®. Menorrhagia was the predominantly reported ADR among all the users. A high frequency of discontinuation was identified, and ADRs were mainly responsible for discontinuation. The frequency of failure was small and efavirenz was suspected to be associated. The experiences of Implanon NXT® users differed between KZN and Gauteng which emphasizes tailored strategies need to be considered. Users' counselling,

adverse drug reaction treatment and management, monitoring and evaluation are recommended to address high discontinuation in SA.
Keywords: Contraception, Implanon NXT®, Adverse drug reactions, Discontinuation, Failure, Pharmacovigilance. experiences, South Africa, Provinces

CHAPTER 1: INTRODUCTION

1.1 Introduction

This chapter provides a background to the study and contextualizes Implanon NXT® use in South Africa (SA). A description of the problem statement is provided, which includes the challenges with Implanon NXT® in the post-introductory phase in SA, particularly in KwaZulu-Natal (KZN) and Gauteng Provinces outlined. User discontinuation with Implanon® and Implanon NXT® is discussed in the background and problem statement, as it is relevant in both sections. The research questions, aims and objectives are stated, a brief description of the methodology is provided, followed by definition of terms, and the chapter concludes with an outline of the dissertation.

1.2 Background and context

Subdermal contraceptive implants are devices that provide a sustained release of sex steroids in vitro (Association of Reproductive Health Professionals, 2008), with the first implant being licensed in 1983 in Finland (Rowlands & Searle, 2014). There are two main types of implants currently on the market, levonorgestrel (e.g. Jadelle® and Sino-implant (II)®) and etonogestrel (e.g. Nexplanon® and Implanon NXT®) (2014). Implanon® is one of the etonogestrel contraceptive implants (2014), having been initially released in 1998 in Indonesia (Darney, Patel, Rosen, Shairo, & Kaunitz, 2009) and approved by the United States of America's (USA) Food and Drug Administration in 2006 (Creinin et al. 2017). In Africa, Implanon® was introduced in Ethiopia in 2009 (Gebre-Egziabher, Medhanyie, Alemayehu, & Tesfay, 2017) and in Nigeria in 2006 (Madugu, Abdul, Bawa, & Kolawole, 2015).

The successor, Implanon NXT®, was approved by the European Medicines Agency as well as by the United Kingdom (UK) Medicines and Healthcare Products Regulatory Agency in 2010 (Reproductive Health Supplies Coalition, 2013; Mansour, 2010). Implanon NXT® is reportedly bioequivalent to its predecessor Implanon® (Schnabel et al. 2012). The difference between Implanon® and Implanon NXT® is the addition of barium sulphate to make it radiopaque as well as changes to the applicator to facilitate one handed insertion of the implant (Schnabel et al. 2012; Mansour, 2010). The efficacy, pharmacokinetic characteristics and safety profile observed with Implanon® is comparable to Implanon NXT® (Schnabel et al. 2012).

Nexplanon® is another brand of Implanon NXT® and the two products are equivalent (Park, Bae, Lee, Bae, & Park, 2017; Darney, 2015; Reproductive Health Supplies Coalition, 2013). Nexplanon® was launched in 2010 by Merck (Rowlands and Searle, 2014) and is available for use in several countries, including the USA. Implants (including Nexplanon®, Implanon® and

Implanon NXT®) have been registered for use in more than 100 countries and Implanon NXT®/Nexplanon® are registered in 80 countries (WHO, 2015; Rowlands & Searle, 2014). Implanon® or Implanon NXT® are registered in 44 of the world's poorest countries, and in 2016, were registered in Egypt, Nepal and Sri Lanka (Merck Sharp & Dohme Corp., 2018). It appears that there is a phase-out process of Implanon®, as the Reproductive Health Supplies Coalition (2013:2) stated that "*Implanon NXT® will progressively replace Implanon® in all countries in the next few years.*" Lince-Deroche et al. (2016) remarked that the "*introduction of the implant in South Africa in 2014 was relatively late compared with other countries on the continent"* (Lince-Deroche et al. 2016:102). Implanon NXT® and Jadelle® are registered in SA, "*but only Implanon NXT was made available in public health clinics as part of the national contraception programme*" (Pleaner et al. 2017:933; Republic of South Africa, National Department of Health, 2015). The purpose of the Medicines Control Council in SA, now South African Health Products Regulatory Authority, is to "*register every medicine before it may be sold/marketed*" (Republic of South Africa, National Health Department, 2008:3), with Implanon NXT® being under review for registration by the Council in 2013 (Republic of South Africa, National Department of Health, 2013c). Implanon NXT® was introduced into South African public health sector facilities in February 2014 (Mullick, Chersich, Pillay, & Rees, 2017).

The London Summit on Family Planning in 2012 aimed to mobilize commitments to provide family planning services that are easily accessible, acceptable and affordable (Family Planning 2020, 2012b). The Family Planning 2020 initiative was formed to address issues related to accessibility to contraceptives by the world's poorest countries by 2020 (Scoggins & Bremner, 2016). Of the 57 countries committed to this initiative, many were developing nationals, including Democratic Republic of Congo, India, Madagascar, Malawi, Mozambique, SA, Tanzania, Zambia and Zimbabwe, which pledged to strengthen its family planning services (Family Planning 2020, 2012a). The commitment stipulated that a complete range of family planning methods must be made available at public health facilities (Family Planning 2020, 2012a), hence SA released contraception policies that added contraceptive implants to their existing methods (Republic of South Africa, National Department of Health, 2013a, 2013b).

The public health sector in SA is government funded and provides health care services to all South Africans (Young, 2016). There are 4200 public health facilities in SA (Jobson, 2015) and they serve the majority of the SA population (Statistics South Africa, 2017b). The public health care system in SA runs as a district-based health system with a Primary Health Care (PHC) approach (Dookie & Singh, 2012). Family planning and contraception is an integral component of the PHC comprehensive services. The National Contraception and Fertility Planning Policy and Service

Delivery Guidelines 2013 state that implant services must be accessed at community health centers (CHC), district hospitals, tertiary hospital and academic and quaternary centers (Republic of South Africa, National Department of Health, 2013b). However, another report indicated that implants should be available at all service levels, including the PHC facilities (Lince-Deroche et al. 2016). Most implants insertions (76.2%) are performed at the main PHC facilities (Massyn et al. 2016).

1.2.1 Prevalence of implant usage

The prevalence of implant usage ranges from 0.1% to 18.1% among 113 countries worldwide, based on the latest available survey data for individual countries (United Nations, Department of Economic and Social Affairs, Population Division, 2018). The demographics of the women using the implants are those aged 15-49 years old and married (2018). The United Nations reported low implant prevalence in high income countries (range: 0.1%-5.6%), with an increase in several countries (2018). A notable increase in prevalence was observed in Australia from 0.8% in 2002 to 4.3% in 2016, in France from 0.1% in 2008 to 2% in 2011, and in the USA from 0.6% in 2013 to 1.3% in 2015. This document did not offer any explanation for the increase in prevalence, however, an Australian study identified younger age and those living outside major cities as factors influencing higher prescription of the etonogestrel implant (Bingham et al. 2016).

Particularly for BRIC countries (Brazil, Russia, India and China), the implant prevalence was unchanged from 0.3% in China in 2001 to 2006 and from 0.1% in Brazil in 2006 to 2013 in married women aged 15-49 years old (United Nations, Department of Economic and Social Affairs, Population Division, 2018). No data was reported for India and Russia in the United Nations report (2018) in 2015/2016 despite it being in use (Scoggins & Bremner, 2016). Additionally, some studies have alluded that Implanon® is used in India (Bhatia, Nangia, Aggarwal, & Tewari, 2011; Singh, Gupta, Nigam, & Nigam, 2015). A trend of increased implant prevalence has been found in Sub-Saharan Africa (SSA) countries across almost all socio-demographic categories (Jacobstein, 2018). The prevalence ranges from 0.4 % to 16.1% in married women aged 15-49 years old based on data from 2015 and 2016 (Tsui, Brown, & Li, 2017). Jacobstein (2018:1) suggests the following key factors for increased prevalence rates in SSA:

> "*sizeable reductions in commodity cost, much increased commodity supply, greater government commitment to expanded method choice, and wider adoption of high-impact service delivery practices that broaden access and better reach underserved populations"*

In SA, implant usage among currently married and sexually active unmarried women was 3.9% in 2016 (Statistics South Africa, 2017c). Implant usage varied across all provinces in SA, with a range of 2.6%-6.6%, the Western Cape and Northern Cape Provinces reporting the highest use, and Limpopo and North West provinces reporting the lowest (Statistics South Africa, 2017c). KZN's implant users (4.1%) are reportedly higher than Gauteng (3.1%) among the currently married and sexually active unmarried women (2017c). However, the overall highest users (6.6%) were reported in the Western Cape.

1.2.2 Implant discontinuation

Although implant use is reportedly increasing in several countries worldwide, user discontinuation is simultaneously occurring. Hence, discontinuation and the reasons for discontinuation are briefly discussed in this section and a comprehensive overview of discontinuation in international and local studies is described in Chapter 2.

1.2.2.1 Global studies on etonogestrel implant discontinuation

Discontinuation is defined as "*a breach or interruption of continuity*" (Dictionary.com, 2018) and specifically refers to termination of etonogestrel implant use in this dissertation. Discontinuation is occurring, which ranges from 10.3% to 26.8% within 12 months of etonogestrel implant use internationally (Law, Liao, Lin, Yaldo, & Lynen, 2018; Apter et al. 2016; Grunloh, Casner, Secura, Peipert, & Madden, 2013). Discontinuation has also been reported in studies conducted in some BRIC countries (Bhatia et al. 2011; Singh et al. 2015; Shu-Rong, Huai-Mei, Snao-Zhen, Guo-Wei, & Kaper, 1999) and in Egypt, Ethiopia and Nigeria (Asaye, Nigussie, & Ambaw, 2018; Ezegwui, Ikeako, Ishiekwene, & Oguanua, 2011; Aziz, El-Gazzar, & Elgibaly, 2018).

Adverse drug reactions (ADRs) were the main reason for Implanon® discontinuation in several global studies including in India and Africa (Teunissen, Grimm, & Roumen, 2014; Bahamondes et al. 2015; Asaye et al. 2018; Bhatia et al. 2011; Aziz et al. 2018; Ezegwui et al. 2011). ADRs are unintended noxious effects of a drug (Waller & Harrison-Woolrych, 2017) and in this dissertation specifically related to etonogestrel implants. Menstrual bleeding pattern changes is the most frequently reported ADR and reason for discontinuation, these changes being experienced by 11.5% to 26.7% of etonogestrel implant discontinuers (Harvey, Seib, & Lucke, 2009; Apter et al. 2016; Asaye et al. 2018). To a lesser degree, non-menstrual ADRs such as

emotional lability (2.3%), weight increase (2.3%), headache 1.6%), acne (1.3%) and depression (1%) also led to discontinuation (Darney et al. 2009).

1.2.2.2 South African studies on implant discontinuation

The South African Health Review reported 820 implant discontinuations during the period February 2014 to December 2014, and an estimated 0.1% implant discontinuation rate (Lince-Deroche et al. 2016). In a short space of time, discontinuations increased with an estimated 5 000 implant discontinuations recorded by April 2015 (Pillay et al. 2017b).

In the Western Cape, a hospital recorded 239 Jadelle®/Implanon NXT® discontinuations in 2015 (Western Cape Government, 2016) and 231 discontinuations in 2016, with the discontinuation frequency calculated at 11.03% in 2015 and 16.99% in 2016 using numbers from the report (2016). There were no reasons suggested for the discontinuations or increase in percentage of discontinuations from 2015 to 2016 in Western Cape. The KZN Annual report 2014/15 Vote 7 reported 3884 discontinuations in 2014/15 (Province of KwaZulu-Natal, Department of Health, 2015a), with the proportion of user discontinuations being calculated as 1.67%. The report went on to state that discontinuations were on the rise (2015a). Implanon NXT® associated menstrual bleeding and religious influences were some reasons for discontinuation offered by Ugu district in KZN (Province of KwaZulu-Natal, Department of Health, 2015b). Empirical data on Implanon NXT® discontinuation in governmental reports in Gauteng Province was unavailable, but an online 2015 newspaper article (Komane, 2015) suggested 250 Implanon NXT® discontinuations, with the proportion being calculated at 0.5%. Forty percent of participants discontinued Implanon NXT® in a study conducted in Gauteng and North West Province, with 90% discontinued due to intolerable ADRs across both provinces with menstrual pattern changes cited as a frequent reason (Pillay et al. 2017a).

According to a study conducted in the Eastern Cape Province (Mrwebi et al. 2018), 67.3% discontinued within the first year of Implanon NXT® use. ADRs were reported to be the reason that over 70% of participants discontinued Implanon NXT® in the Eastern Cape and menorrhagia was the most reported ADR (Mrwebi et al. 2018). Pregnancy is a notable ADR associated with Implanon NXT® and reports of pregnancy while using Implanon NXT® have resulted in discontinuation of the device (Mrwebi et al. 2018).

1.2.3 Adverse drug reactions due to drug interactions with etonogestrel implants

Etonogestrel implants such as Implanon®, Implanon NXT® and Nexplanon® are the common therapeutic implants that are used as contraceptives. While these implants have been reported as

highly efficacious contraceptives (WHO, 2018), pregnancy is one of the serious ADRs particularly due to drug interactions with Implanon® (Creinin et al. 2017; Simon et al. 2016) and Nexplanon® (Simon et al. 2016). These studies that reported pregnancy during Implanon® and Nexplanon® are discussed further in Chapter 2 in addition to other studies such as method failure, untimely insertion and technique failure.

A common reason for failure is due to drug interactions between Implanon® and concomitant enzyme-inducing drugs, such as antiretrovirals (ARV) (Patel et al. 2015), antituberculosis drugs (Gbolade, 2010) and antiepileptics (Schindlbeck et al. 2006). Contextually, failure of Implanon NXT® due to drug interaction is problematic as a large portion of the SA population rely on efavirenz, rifampicin and carbamazepine, to treat Human Immunodeficiency Virus (HIV), Tuberculosis (TB) and Epilepsy respectively. According to Statistics South Africa (STATSSA), the estimated overall SA HIV prevalence rate is approximately 12,6%, and the number of people living with HIV is approximately 7.06 million as of 2017 (Statistics South Africa, 2017a). In adults of reproductive age (aged 15–49 years), approximately 18,0% of the population is HIV positive (2017a). SA is one of the top 20 countries with the highest estimated TB incidence, this being estimated to be 438 000 as of 2017 (WHO, 2017). Although there is limited data on the prevalence of Epilepsy in SA, one study reported the prevalence of active convulsive Epilepsy to be 7.0/1,000 in a rural SA population (Wagner et al. 2014). While the prevalence of Epilepsy in SA is lower than HIV and TB, women taking Antiepileptics will possibly be affected if they use Implanon NXT®.

Policy changes have occurred in SA regarding the prescription of Implanon NXT® in patients using concomitant enzyme inducing drugs, such as efavirenz, rifampicin, carbamazepine, phenytoin and phenobarbital. In October 2014, the circular specified that these patients should not use Implanon NXT® and those already on Implanon NXT® should be offered discontinuation (Lince-Deroche et al. 2016). A recent commentary remarked that findings suggest implants could possibly be removed as a contraceptive option for HIV-positive women in SA (Patel et al. 2017). They also claimed that policy advising against the use of implants in women using efavirenz-based therapy was guided by limited evidence in SA (2017). Research on use of enzyme inducing drugs and implants continues, with new findings having influenced Implanon NXT® policy in the public health sector (Republic of South Africa, National Department of Health, 2014a; Republic of South Africa, National Department of Health, 2014b).

1.3 Problem statement

Globally, it was reported that approximately a quarter of users discontinue their etonogestrel implant within 12 months (Law et al. 2018; Apter et al. 2016). While challenges with etonogestrel implants have been identified as premature discontinuation, drug interactions and failure, ADRs remain the primary reason for discontinuation among users (Apter et al. 2016; Teunissen et al. 2014). There has been growing concern about the number of women returning for premature discontinuation of Implanon NXT® in SA. Studies from SA have reported the introduction of Implanon NXT® (Mullick et al. 2017), experiences of users (Mrwebi et al. 2018; Petro, 2017; Adeagbo et al. 2017; Pillay et al. 2017a), challenges of using Implanon NXT® (Pillay et al. 2017b; Mullick et al. 2017) as well as the way forward with the use of Implanon NXT® in SA (Mullick et al. 2017; Pleaner et al. 2017; Rees et al. 2017). A delayed monitoring system for Implanon NXT® has posed a challenge in determining the true extent of the discontinuation in SA (Lince-Deroche et al. 2016). Furthermore, limited recording of user discontinuation, ADRs and other pharmacovigilance data (Pillay et al. 2017b), especially in patients using enzyme inducing drugs (Pleaner et al. 2017), were identified as challenges in SA.

While experiences of Implanon NXT® users have been reported in the literature, there is limited publicably available national empirical data on Implanon NXT® in SA and uncertainty on its use in those also taking enzyme inducing drugs (Mullick et al. 2017). Additionally, at the initiation of the study, there was a lack of understanding of the experiences of Implanon NXT® users in the public health sector in under researched provinces such as KZN and in provinces with no available published discontinuation data such as Gauteng. The demographic profile of the provinces differs hence a provincial depiction of experiences of Implanon NXT® users in different provinces in SA is necessary to provide a comprehensive understanding. With few studies providing a comprehensive overview of the extent of Implanon NXT® discontinuation, ADR, frequency of failure as well as reasons for its discontinuation, this gap needs to be addressed as an evaluative exercise. An investigation on these factors will assist in identifying and quantifying problems of Implanon NXT®. This information will assist in policy making and have an impact on the practice and rational use of the device.

1.4 Research questions

The main research question was “what are the experiences of the Implanon NXT® users?”
The secondary research questions are as follows:

1.4.1 What are the demographics of Implanon NXT® users?

1.4.2 What ADRs of Implanon NXT® are reported among users?

1.4.3 What is the frequency of discontinuation of Implanon NXT® and what are the reasons for discontinuation of Implanon NXT®?

1.4.4 What is the frequency of failure with the use of Implanon NXT®?

1.4.5 How do the experiences of Implanon NXT® compare between users from KZN and Gauteng Provinces?

1.5 Aim and objectives of the study

The study aimed to evaluate the experiences of Implanon NXT® among users in the public health sector in SA.

The objectives of the study were:

1.5.1 To identify the demographic profile of Implanon NXT® users

1.5.2 To identify ADRs of Implanon NXT® reported among users

1.5.3 To determine frequency of discontinuation of Implanon NXT® and reasons for discontinuation

1.5.4 To determine frequency of failure of Implanon NXT®

1.5.5 To compare experiences of Implanon NXT® between users in KZN and Gauteng Province.

1.6 Research methodology

This retrospective study entailed the analysis of secondary quantitative data from a national pharmacovigilance data set. Secondary analysis is when "*the researcher takes previously collected and analyzed data from one study and reanalyzes the data or a subset of the data for a secondary purpose*" (LoBiondo-Wood & Haber, 2018:516). This "*secondary purpose*" may be to answer "*new research questions*" (Polit-O'Hara & Beck, 2006:509). The advantages of secondary data analysis are the cost-effectiveness and volume and scale of available data that is a representative sample of the population (Boslaugh, 2007). Additionally, Boslaugh (2007) stated that data collected on a national scale are particularly important in epidemiology and public health fields that focus primarily on the health of populations. However, there are key disadvantages with secondary analysis such as deficient data sets and no control over variables collected (Polit-O'Hara & Beck, 2006).

1.6.1 Process of data collection by the National Department of Health Pharmacovigilance Centre for Public Health Programmes

Although there was delayed monitoring of Implanon NXT®, there is some monitoring data available. A closed data set containing monitoring information on Implanon NXT® in SA is housed by the National Department of Health Pharmacovigilance Centre for Public Health Programmes and is referred to as the National Pharmacovigilance Centre (NPC) in this dissertation. The purpose of the NPC is discussed in Chapter 2. The NPC is carrying out an ongoing surveillance reporting programme since 2015, where Implanon NXT® data reporting forms were completed by health practitioners across the country at public sector facilities where implant services were offered. It is within the scope of practice of professional nurses, midwives and doctors to provide implants to patients (Republic of South Africa, National Department of Health, 2013b). According to the Standard Operating Procedure (SOP) for Subdermal Contraceptive Implants Data Collection (Annexure 9), the form should be completed by any health practitioner prior to insertion, discontinuation and upon reporting ADRs of Implanon NXT® (Republic of South Africa, National Health Department. n.d.). The form collected some of the following categories of information: demographics, clinical data, ADRs, and discontinuation (Annexure 9). Once completed, provincial co-ordinators facilitated their collection and conducted data quality assurance. The successfully examined forms were forwarded to the Maternal Child and Women's Health co-ordinator at the nine provinces various District Offices and were thereafter sent to the Provincial Health Departments, where they were finally transferred to the NPC.

The data collection tool i.e. surveillance form, belongs to the NPC, and its validity and reliability was therefore not tested by the principal investigator of this study. The data was screened by the Department of Health at various stages, from data collection by the provincial coordinators to data capturing at the NPC for confirmability, validity and reliability. All nine provinces in SA provided data, with 36 of the country's 52 districts submitting forms for analysis.

1.6.2 Study area

Over half (51%) of SA's population were female in 2016 (Statistics South Africa, 2016), with the highest number of females in reproductive age range (15-49) being 20-24 years (Statistics South Africa, 2016). According to the Demographic and Health Survey of 2016, 58.3% of the married and sexually active unmarried women were contraception users of any method (Statistics South Africa, 2017c).

The demographic profiles of the provinces differ, with KZN and Gauteng Provinces being chosen as examples in the comparative analysis to represent different demographics in SA. Table 1-1 illustrates the difference in demographics between KZN and Gauteng.

Table 1-1: Demographics of KwaZulu-Natal and Gauteng Provinces

Variable	KZN %	Gauteng %
Number of women (Statistics South Africa, 2016)	52.0	49.6
Females of reproductive age (Statistics South Africa, 2016)	50.9	56.5
Currently married and sexually active unmarried contraception users (Statistics South Africa, 2017c)	61.2	57.2
Residing in urban areas (Housing Development Agency, 2013a, 2013b)	47.0	97.0

KZN=KwaZulu-Natal

1.6.3 Cases

All case reports from the nine provinces submitted to the surveillance programme at the NPC were included in the analysis of the study. The data date ranged from 1 April 2015 to 11 September 2017. The following number of cases were reported per province: Eastern Cape (n=1011), Free State (n=792), Gauteng (n=717), KZN (n=84), Limpopo (n=547), Mpumalanga (n=31), North West (n=219), Northern Cape (n=264) and Western Cape (n=78). All variables related to counselling, laboratory test results and health practitioners on the case reports were excluded, as they fell beyond the scope of this study.

1.6.4 Data extraction

A Microsoft Excel® spreadsheet was designed to extract the quantitative data from the raw data provided by the NPC. The extraction sheet included the following additional variables that was not on the raw data set: health facility type, level of health care, level of urbanization and Body Mass Index (BMI). The name of the health facility, which appeared on the raw data set, was used to search for the health facility type, level of health care and level of urbanization using online governmental sources and STATSSA (National Department of Health, South Africa, 2018; Province of KwaZulu-Natal, Department of Health, 2014; Republic of South Africa, National Department of Health, 2016; Statistics South Africa, 2011). The weight and height data, which

appeared on the raw data set, was used to calculate BMI (Centers for Disease Control, 2017). The tool was designed to address the five objectives:

Objective 1. Demographics: age, health facility visited, district and province.

Objective 2. ADRs: specified ADR including additional information, date of onset of reaction and date of report of ADR.

Objective 3. Discontinuation: Date of insertion, date of discontinuation, reason for discontinuation. Case reports with discontinuation date or a reason for discontinuation were considered to have discontinued, these variables being used to calculate the frequency of user discontinuations. Premature discontinuation was calculated using less than 36 months' duration of treatment as an indicator.

Objective 4. Failure: unwanted pregnancy was interpreted as failure of the product.

Objective 5. Comparative experiences: Compared ADRs, discontinuation and failure between KZN and Gauteng

It must be noted that the following clinical history variables were also included in the extraction tool: para, gravida, weight, height, concomitant conditions, concomitant drugs, name of drug, pregnancy test performed and results, previous contraception method and breastfeeding status. These were considered to be relevant in addition to the other variables and therefore extracted.

The raw data set was received via email in the form of a Microsoft Excel® sheet from the NPC on 11 September 2017. The principal researcher and a data extractor assistant extracted data from the raw data set from 12 September 2017 to 2 November 2017, which was thereafter cleaned by identifying and correcting incomplete and inaccurate data. Validation and accuracy of extracted data was performed by randomly selecting 10% of cases to cross-check with the raw data.

1.6.5 Data analysis

The 3743 case reports were entered into Microsoft Excel® from where they were exported to SPSS® (version 25) for analysis. As majority of the data was quantitative, descriptive analysis was performed for all relevant variables described in the data extraction section using the following methods: frequencies, percentages, measures of central tendency and variability. Inferential statistics were performed to relate the cases to the population for objective 1-5, with a 95% Confidence Interval (CI) being used. Tests of association were performed using the Chi square test and Fischer's Exact Test, and a p-value of less than 0.05 was considered statistically significant. Univariable and multivariable analysis using binary logistic regression was performed to identify factors associated with Implanon NXT® discontinuation as an additional statistical test. Odds ratio was calculated to measure the association between variables and the

discontinuation of Implanon NXT® as an additional statistical test. In the comparative analysis of objective 5, Chi square test was performed using an online calculator to compare the ADRs, discontinuation and reasons for discontinuation between the Gauteng and KZN groups (Social Science Statistics, 2008), and the Mann Whitney U-test was performed to compare their users' discontinuation.

1.6.6 Data management

The electronic data, including the original data set, will be deleted upon successful submission and completion of the degree, and all disseminations in the form of publications and reports to the Department of Health have been completed.

1.6.7 Ethical considerations

Full ethical approval was obtained from the University of KZN Biomedical Research Ethics Committee (BE266/17) (Annexure 1). Permission to use the raw data set was obtained from the NPC (Annexure 2).

1.7 Definition of terms

ADR: "*a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man"* (WHO, 2002:5).

Contraception: "*a process or technique for preventing pregnancy by means of a medication, device, or method that blocks or alters one or more of the processes of reproduction in such a way that sexual union can occur without impregnation*." (Mosby's Medical Dictionary, 2009)

Discontinuation: "*a breach or interruption of continuity*" (Dictionary.com, 2018). In this study, 'discontinuation' was determined using case reports that reported a discontinuation date or a reason for discontinuation.

Experience: "*the fact or state of having been affected by or gained knowledge through direct observation or participation"* (Merriam-Webster.com, 2018). In this study, experiences encompass ADRs, discontinuation experiences, reasons for discontinuation and failure of Implanon NXT®.

Failure: *"the fact of not doing something that you must do or are expectedto do*" (Cambridge Dictionary, 2018). In this study, failure was defined as unwanted pregnancy reported during Implanon NXT® use.

Implanon NXT®: is a subdermal progestin contraceptive implant which contains etonogestrel (Rowlands & Searle, 2014).

Pharmacovigilance: "*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem"* (WHO, 2004:1).

Premature discontinuation: In this study, premature discontinuation is defined as the discontinuation of Implanon NXT® before 36 months post-insertion.

Public health facilities: These include PHC clinics, CHCs, district hospitals, regional hospitals, provincial tertiary hospitals, specialised hospitals and central hospitals (Province of KwaZulu-Natal, Department of Health, 2014).

1.8 Outline of dissertation

In addition to chapter one, the dissertation comprises of the following chapters:

Chapter 2: Literature review. This chapter presents international and local literature available on pharmacovigilance, contraception practices and guidelines, description of etonogestrel implants, experiences of etonogestrel implants and challenges in the SA context. Experiences include: ADRs of etonogestrel implants, drug interactions, user discontinuation of etonogestrel implants, reasons for etonogestrel implant discontinuation and failure of etonogestrel implants.

Chapter 3: Submitted Manuscript. This chapter consists of the first manuscript from the data extracted in this study and addressed objectives 1 - 4. The manuscript is titled: **Adverse drug reactions and discontinuation of Implanon NXT® among users at public health facilities in South Africa** and was submitted to The European Journal of Contraception & Reproductive Health Care on 29 June 2018. This article reported on the findings of ADRs amongst Implanon NXT® users, discontinuation and the associated reasons and factors.

Chapter 4: Manuscript for submission. This chapter presents the second manuscript from the data extracted in this study and addressed objective 5. The manuscript is titled: **Comparisons of experiences of Implanon NXT® users between provinces in South Africa.** The manuscript includes the demographic profile of the Implanon NXT® discontinuers and provides a descriptive overview of ADRs, discontinuation and reasons for discontinuation on a provincial level in SA and includes a comparative analysis of the experiences of Implanon NXT® among users from Gauteng and KZN Provinces. This manuscript is to be submitted to the South African Medical Journal.

Chapter 5: Synthesis. This chapter concludes on the main objectives of the study, mentions the significance of findings and highlights the limitations of the study. Recommendation for policy, clinical practice and future research are also provided.

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CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter provides a background and the description of etonogestrel implants. This chapter expands on studies on discontinuation of etonogestrel implants, and other associated problems regrading the use. It must be noted that there are several published studies from the initial clinical trials of Implanon® that were retracted in 2004 (Rekers & Affandi, 2004), this being due to errors in data collection in Indonesia (Adams & Beal, 2009). The chapter highlights various sections including pharmacovigilance, contraception and experiences of etonogestrel implants.

2.2 Background

2.2.1 Pharmacovigilance

The concept of pharmacovigilance emanated during the investigation of drug safety associated with Thalidomide at the World Health Assembly in 1963 (WHO, 2002a). Pharmacovigilance is a process of monitoring and evaluating ADRs (Jeetu & Anusha, 2010), which are considered detrimental to health, and rank among the top leading causes of mortality and morbidity in many countries (Najafi, 2018). There are numerous contributors to pharmacovigilance programmes, namely: international pharmacovigilance bodies, continental pharmacovigilance authorities, NPCs, pharmaceutical companies and manufacturers, health facilities, health practitioners and patients (Jeetu & Anusha, 2010).

The World Health Organisation (WHO) Programme for International Drug Monitoring is responsible for the collection of global reports of ADRs from contributing countries (WHO, 2004). Their collaborating centers are responsible for maintaining a global ADR database (2004). Some continents and countries also have local pharmacovigilance coordinators and regulatory bodies e.g. European Medicines Agency and USA Food and Drug Administration (FDA). There are 33 national pharmacovigilance centers in Africa that are full members of the WHO Programme for International Drug Monitoring (Dodoo & Ampadu, 2014). SA has been engaged in pharmacovigilance activities for 40 years and is the first country in Africa to become a member of the WHO International Drug Monitoring Programme in 1992 (Mehta et al. 2014; Mehta et al. 2017) In particular, the Medicine Control Council in SA, now South African Health Products Regulatory Authority, is responsible for the safety, efficacy quality and post-marketing safety of drugs, the pharmacovigilance programme being coordinated by the NPC (Mehta, 2011).

The National Adverse Drug Event Monitoring Centre in the NPC is responsible for maintaining and managing the national ADR database (2011).

The process for gaining pharmacovigilance data starts with health care practitioners, patients and the pharmaceutical industry reporting ADRs to the national pharmacovigilance centres (Delaney, 2017). The national pharmacovigilance centres submit data to the WHO international database at the Uppsala Monitoring Centre (VigiBase) where they can analyse their data using VigiLyze (2017). Additionally, the Uppsala Monitoring Centre conducts analysis to detect signals which are reported to the national pharmacovigilance centre (2017).

The success of a national post-marketing surveillance programme is therefore dependent on the active participation of health practitioners (WHO, 2002b). They are integral to drug monitoring programmes, as they are involved in conducting drug reviews, aid in drug and dosage selection, and are a part of developing therapeutic monitoring plans for patients (Karpa et al., 2015). They are the first point of contact with patients and are therefore in a position to recognize and report drug issues (Najafi, 2018; WHO, 2002b). According to the WHO, all healthcare practitioners should report ADRs as part of their professional responsibility, even if they are unsure of the direct relationship between the drug and a suspected ADR (WHO, 2002b). The degree to which health practitioners are informed about the principles of pharmacovigilance has an impacted on their quality of patient health care (WHO, 2002a). Patients also play a significant role in ADR reporting (Härmark & van Grootheest, 2008), with patient-reported concerns contributing to detecting drug safety issues (Härmark et al. 2016). They are provided with the opportunity to report ADRs to spontaneous reporting system in some regions e.g. European (Härmark & van Grootheest, 2008). Pharmacovigilance is conducted through surveillance methods. Surveillance is defined as a:

> *"form of non-interventional public health research, consisting of a set of processes for the continued systematic collection, compilation, interrogation, analysis, and interpretation of data on benefits and harms (including relevant spontaneous reports, electronic medical records, and experimental data)" (Aronson, Hauben, & Bate, 2012:347).*

A spontaneous case reporting system is a "*systematic collection, collation and analysis of reports of suspected ADRs" (WHO, 2015a:3).* When an ADR is suspected, a case report form is completed. It contains patient information and a description of the ADR, or problem detected and drug information (WHO, 2002b). The completed forms are forwarded to the

relevant health authorities (2002b), the advantage of spontaneous reporting systems being that they detect signals of drug safety issues, which need to be confirmed by formal studies (van Grootheest, Harmark, & van Puijenbroek, 2011).

Pharmacovigilance does not only involve spontaneous reporting but includes conducting various types of research using both quantitative and qualitative methods (Mehta et al., 2014). It is expanding to include quantifying event rates and the severity of known ADRs, identifying risk factors and their incidence (Mehta et al., 2017). The scope of pharmacovigilance includes: ADRs or adverse events, drug errors, counterfeit or substandard medicines, lack of efficacy of medicines, misuse and/or abuse of medicines, and the interaction between medicines (WHO, 2015a). The pharmacovigilance approaches adopted in SA are active surveillance, targeted spontaneous reporting for specific drugs or population groups and regulatory spontaneous reporting for all drugs (Mehta et al. 2017). The pharmacovigilance methods adopted link post-marketing research with pre-marketing data, and also include use cohort studies and registries (2017).

An example of pharmacovigilance in hormonal contraception was the detection of thrombo-embolism associated with the use of Yasmin (ethinylestradiol/drospirenone) (van Grootheest et al. 2011), and the association between Mirena (levonorgestrel containing intrauterine device) and uterine perforation (2011). International studies conducted on pharmacovigilance and post-marketing research and data on etonogestrel implants has been released in the form of publications (Creinin et al. 2017; Simon et al. 2016; Harrison-Woolrych & Hill, 2005). These studies emphasize safety and efficacy issues reported with Implanon® (Creinin et al. 2017; Simon et al. 2016; Harrison-Woolrych & Hill, 2005) and Nexplanon® (Simon et al. 2016), as well as complications with insertion and discontinuation of the implants.

2.2.2 Contraception

The WHO maintains that:

> *"Family planning allows people to attain their desired number of children and determine the spacing of pregnancies. It is achieved through use of contraceptive methods and the treatment of infertility" (WHO, 2018).*

Hence, contraception "*prevents pregnancy by interfering with the normal process of ovulation, fertilization, and implantation"* (Encyclopedia of Children's Health, n.d). Family planning/contraception prevents pregnancy related health risks, reduces infant mortality and the risk of unwanted pregnancy, empowers females and slows population growth (WHO, 2018). There are several modern contraception methods in use e.g. contraceptives pills, implants and

injectables, as well as traditional methods which includes the calender method and withdrawl technique (WHO, 2018). Family planning/contraception methods vary in effectiveness to prevent pregnancy, with implants, sterilization and IUDs being some of the most effective forms of contraception (WHO, 2018).

In 2015, 64% of married or in-union women of reproductive age were using some form of contraception method globally, with contraception use being 40% in the least developed countries, especially in Africa (33%) (United Nations, Department of Economic and Social Affairs, Population Division, 2015b). A modern contraceptive is "*A product or medical procedure that interferes with reproduction from acts of sexual intercourse*" (Hubacher & Trussell, 2015:420). The United Nations Department of Economic and Social Affairs Population Division reported that modern contraception methods were used by most married and in-union women of reproductive age (57%) in 2015 (2015b). The 2015 United Nations Trends in Contraceptive Use Worldwide also found that more than one in three married or in-union women globally use long-acting or permanent methods, namely sterilization, intrauterine device and implants (2015b). Short-term and non-hormonal methods i.e. the pill and male condom, are popular methods in Europe whereas the pill and sterilization are popular in North America (United Nations, Department of Economic and Social Affairs, Population Division, 2015a). In SSA, injectables and implants are frequently used methods (Tsui, Brown, & Li, 2017). In SA, the three monthly injectable is the most commonly used method (17.7%) in currently married and sexually active unmarried women (Statistics South Africa, 2017). As mentioned in Chapter 1, the implant is used in 3.9% of currently married and sexually active unmarried women in SA (2017), which is low compared to other SSA countries (Tsui et al. 2017).

2.2.3 Accessibility and affordability of implants in developing countries

The Implanon Access Initiative was launched in 2011 (Reproductive Health Supplies Coalition, 2013), its aim being to improve affordability through public sector price agreements (2013). In 2013, Merck and partners announced an agreement that will expand contraceptive access and options for millions of women in some of the world's poorest countries. Merck will reduce the cost of Implanon® and Implanon NXT® or Nexplanon® by approximately 50% for the next six years in specific countries (Merck, 2013). Merck has extended this initiative to these same targeted countries through till 2023 (IFPMA, 2012). Sixty four countries, including SA, are part of this initiative in the following regions: East Asia and Pacific, Europe and Central Asia, Latin America & Caribbean, Middle East & North Africa, South Asia and SSA (2012). The unit price of Implanon NXT® in SA is R 2 137.62 as of 1 April 2018, however, is it dispensed free of charge

by public health facilities (Republic of South Africa, National Department of Health, 2018a; Lince-Deroche et al. 2016). This section provides some insight for understanding the background to Implanon NXT® and this study. Implanon NXT® will hereafter be discussed in detail.

2.3 Implanon NXT®

2.3.1 Description of Implanon NXT®,

Implanon NXT® is an etonogestrel subdermal implant, 4cm in length with a 2mm diameter, and is packaged inside a preloaded applicator (Kolawole et al. 2018; Mommers et al. 2012). The product contains "*68 mg etonogestrel with 3% barium sulphate [37% ethylene vinyl acetate (EVA) copolymer;3% barium sulphate (15 mg); 60% ENG (68 mg)]"* (Mansour, 2010:187). A summary of some of the Implanon NXT® product characteristics is provided in Table 2-1.

There are several advantages of implants, including Implanon NXT®, which include: high efficacy, long-term effect, oestrogen-free, rapid return to fertility and is a non-user dependant contraceptive (Adams & Beal, 2009; Ladipo & Akinso, 2005). However, there exists some disadvantages which includes: ADRs, insertion and discontinuation complications, requires surgical procedure for insertion and discontinuation and practitioner dependence (Adams & Beal, 2009; Grentzer, McNicholas, & Peipert, 2013).

2.3.2 Timing of Implanon NXT® insertion and procedures for placement and discontinuation

The appropriate timing of Implanon NXT® insertion depends on the previous contraception method used e.g if progestogen injectable was used then it can be inserted on the following due date (Palomba et al. 2012). If no previous contraception was used, Implanon NXT® can be inserted between day 1 and 5 of the cycle (2012). Insertion should be performed on the same day if it is post-first trimester abortion or between day 21 and 28 of the cycle if post-second trimester abortion (2012). Pregnancy must be ruled out prior to Implanon NXT® insertion, with the SA Standard Treatment Guidelines 2018, indicating that it can be inserted anytime in the menstrual cycle as long as pregnancy has been excluded (Republic of South Africa, National Department of Health, 2018b). Implanon NXT® is inserted subdermally on the non-dominent arm at 8-10cm above the medial epicondyle of the humerus (Palomba et al. 2012). The procedure is outlined in the product information leaflet (Merck Sharp & Dohme, Australia, 2010) as well as the SA Standard Treatment Guidelines (Republic of South Africa, National Department of Health,

2018b). Complications such as: pain, swelling, redness and wound infection are possible (Rowlands & Searle, 2014).

Table 2-1: Summary of some Implanon NXT® characteristics

Name	Etonogestrel implant
Brand/ manufacturer	Implanon NXT® by Merck (Reproductive Health Supplies Coalition, 2013:2).
Therapeutic category	Contraceptive, etonogestrel implant (Mansour, 2010).
Use	Prevention of pregnancy for at least three years (Palomba et al. 2012).
Mechanism of action	Primary: Inhibition of ovulation (Kolawole et al. 2018). Secondary: Prevents sperm penetration and implantation (2018).
Pharmacokinetic and pharmacodynamic properties	Etonogestrel is the active metabolite of desorgestrel (Palomba et al. 2012). Etonogestrel is partially bound to sex hormone-binding proteins. Serum levels of etonogestrel >90pg/ml prevent ovulation (Hohmann, 2009). Serum etonogestrel concentraction levels increase to a mean of 265.9± 80.9 pg/ml 8 hours post-insertion (Palomba et al. 2012). "*Serum levels reach maximum values after about 4 days from the insertion of the device reaching a stady-state (200 pg/mL) after 4–6 months."* (2012:711). The serum concentrations decline from a mean of 196pg/ml after 1 year to a mean of 156 pg/ml after 3 years of use (Hohmann, 2009). The half-life elimination is approximately 25 hours (Palomba et al. 2012).
Return of fertility	The serum etonogestrel level is undetectable one week post-discontinuation (Hohmann, 2009). Ovulation has been reported 2-6 weeks post-discontinuation (Palomba et al. 2012).
Dosage	68 mg of etonogestrel (Schnabel et al. 2012).
Efficacy	The three-year Pearl Index is 0.00 (Mommers et al. 2012).

Implanon NXT® must be located prior to discontinuation, and an X-ray or ultrasound may be performed if its presence cannot be verified (Palomba et al. 2012). Palomba et al. describes the discontinuation procedure as follows:

"*Once the device has been located, it is necessary to press the proximal end in order to cause a lifting of the distal end. Identified the distal portion, after local anesthesia, a small skin incision is practiced on this zone."* (2012:713)

The discontinuation procedure is also outlined in the product information leaflet (Merck Sharp & Dohme, Australia, 2010) as well as the SA Standard Treatment Guidelines (Republic of South Africa, National Department of Health, 2018b). The serum etonogestrel levels will decrease rapidly and be undetectable within four days post-discontinuation (Rowlands et al. 2017). Complications that arise from discontinuation include: implant breakage, implant attached to fibrous tissue and difficulty locating implants (Palomba et al. 2012). ADRs, which include complications arising from insertion and discontinuation, are reasons for discontinuation and the next section details their profile.

2.4 Contextualization of experiences of etonogestrel implants

2.4.1 Adverse drug reactions

Adverse drug reactions (ADRs) associated with etonogestrel implants include menstrual-related ADRs as shown in Table 2-3 and non-menstrual related ADRs, such as headaches, weight gain and acne as displayed in Table 2-4.

2.4.1.1 Menstrual-related adverse drug reactions

Menstual bleeding patterns have been inconsistently defined across studies as highlighted in Table 2-2, but most people have used or adapted the WHO assessment of bleeding patterns experienced while using progestin-only contraceptive methods (Belsey, Machin, & D'Arcangues, 1986). A 90-day reference period (RP) is used to asses bleeding patterns (Belsey et al. 1986).

Table 2-2: Summary of etonogestrel implant studies outlining definitions of menstrual bleeding patterns over a 90-day reference period

Bleeding pattern	Definition	Reference
Normal	3 to 5 bleeding/ spotting episodes	• Darney, Patel, Rosen, Shapiro, and Kaunitz (2009)
	Normal menstrual bleeding	• Laban, Abd Alhamid, Ibrahim, Elyan, and Ibrahim (2012)
Amenorrhoea	No bleeding or spotting	• Darney et al.(2009) • Guazzelli, De Queiroz, Barbieri, Torloni, and De Araujo (2010) • Laban et al.(2012)

		• Singh, Gupta, Nigam, and Nigam (2015)
	No bleeding	• Bitzer, Tschudin, Alder, and Group, S.I.S. (2004) • Zheng, Zheng, Qian, Sang, and Kaper (1999)
	Absence of menstruation	• Chaovisitsaree et al. (2005) • Gezginc, Balci, Karatayli, and Colakoglu (2007)
Infrequent bleeding	< 3 episodes of bleeding/spotting	• Darney et al.(2009) • Chaovisitsaree et al. (2005) • Gezginc et al. (2007) • Singh et al. (2015)
	Bleedings that occurred at intervals were more than 6 weeks apart	• Bitzer et al. (2004)
	1-2 bleeding episodes	• Guazzelli et al. (2010)
	< 2 bleeding-spotting episodes	• Zheng et al. (1999)
	1 or 2 bleeds or spotting episodes	• Laban et al. (2012)
Frequent bleeding	> 5 episodes of bleeding	• Darney et al. (2009) • Laban et al. (2012) • Singh et al. (2015)
	> 4 bleeding-spotting episodes	• Guazzelli et al. (2010) • Zheng et al. (1999)
	> 5 bleeding or spotting episodes	• Chaovisitsaree et al. (2005) • Gezginc et al. (2007)
Prolonged bleeding	≥ 1 bleeding lasting > 14 consecutive days	• Darney et al. (2009) • Laban et al. (2012)
	Bleeding longer than seven days	• Bitzer et al. (2004)
	≥ 1 bleeding-spotting episode lasting > 14 days	• Guazzelli et al. (2010) • Chaovisitsaree et al. (2005) • Gezginc et al. (2007) • Singh et al. (2015)
	≥1 bleeding-spotting episode lasting ≥ 10 days	• Zheng et al. (1999)
Irregular bleeding	3-5 bleeding episodes & < 3 bleeding-free intervals of ≥ 14 days	• Guazzelli et al. (2010)
	Experiencing frequent, infrequent, and prolonged bleeding	• Chaovisitsaree et al. (2005) • Gezginc et al. (2007)
Regular	Periodic withdrawal bleeding within 28 ± 7 days	• Chaovisitsaree et al. (2005)
	Recurring bleeding at 28 ± 7 days intervals	• Gezginc et al. (2007)
Acceptable	None of the above	• Guazzelli et al. (2010)

Table 2-3 displays the frequency of bleeding patterns reported with etonogestrel implants globally. It must be noted that it may be difficult to compare findings across studies due to use of different definitions for bleeding patterns. The following quote from Adams and Beal (2009:144) explains the difference in interpretation of bleeding patterns using various definitions:

> *"Infrequent bleeding is the most common pattern under the older, more inclusive WHO standards …and is reported by 35% to 51% of users at 3 months, declining to approximately 25% to 34%at the end of year two. In studies using the stricter, revised WHO definition, the incidence generally drops to 10% or less for all time periods."*

The interpretation of bleeding patterns in this section will include all studies in Table 2-3 regardless of their definitions. It must be noted that Darney et al. (2009) provided proportions of bleeding patterns based on total RPs and not total women. Hence, they reported the following results: amenorrhoea (21.4% of RPs), infrequent bleeding (33.3% of RPs), frequent bleeding (6.1% of RPs) and prolonged bleeding (16.9% of RPs).

Amenorrhoea ranges from 2.4% to 61.2% across studies with those from high income countries on the lower half of the scale i.e. 7.0% - 33%, however, 7.0% was an outlier. Amenorrhoea was considered a favourable bleeding pattern by users in international studies (Casey, Long, Marnach, & Bury, 2011; Beligotti, Mommers, & Marintcheva-Petrova, 2012; Flore et al. 2016; Inoue et al. 2016). A study conducted in high income countries found that 77.7% of those who experienced amenorrhoea were very satisfied with their bleeding pattern, which could explain the lower proportion of reports (Apter et al. 2016). Additionally, a scoping review found that amenorrhoea was preferred in North America and Europe (Polis, Hussain, & Berry, 2018).

Under half of the studies reported prolonged bleeding, which ranged from 2.2%-56.2%, with a review of Implanon® clinical trials reporting that this occurred in a small number of women (Mansour, Korver, Marintcheva-Petrova, & Fraser, 2008) and the Implanon® prescribing leaflet stating that 17.7% reported prolonged bleeding. Prolonged bleeding appears to be poorly tolerated in several studies (Polis et al. 2018), which potentially could explain the increased reporting. Unmet expectations of menstrual ADRs could have impacted on satisfaction levels as found in a study of Implanon NXT® users, prolonged bleeding occurred more often than expected (Beligotti et al. 2012), which could have increased the number of reports.

In studies conducted in Africa, menorrhagia and amenorrhoea were more frequently reported than other bleeding patterns. One reason for frequent reporting of amenorrhoea was explored in a scoping review, which found that amenorrhoea was viewed negatively by some women, as they were suspicious of its occurrence and viewed menstruation as a natural process (Polis et al. 2018). Mrwebi et al. (2018) described that menorrhagia was the top ADR experienced by SA women.Although menorrhagia was frequently reported, the study also revealed higher

proportions of menorrhagia in the global literature i.e. 56.2% in Australia and 62% in the UK. Generally, users from Nigeria reported a low proportion of bleeding patterns (range: 1.2-14.8). Roberts, Morhason-Bello, Okunlola, and Adekunle (2015:51) argued that:

> *"None of the clients manifested any complication of excessive bleeding clinically or through their haematological parameters. The amenorrhoea following Implanon® insertion has been associated with increased haematocrit level amongst clients; this is of clinical benefit in settings where maternal anaemia remains a public health concern"*

This quote suggests that menstrual ADRs were tolerable and beneficial, with the reporting of bleeding possibly having been low in Nigeria.

Normal bleeding appears uncommon among users and ranged from 8%-11%. Infrequent bleeding was reported in 50% of studies (range: 3.2%-56.0%), while half reported frequent bleeding (range: 2.3%-36.4%). Mastor, Khaing, & Omar (2011) and Booranabunyat & Taneepanichskul. (2004) conveyed that infrequent bleeding was the most commonly reported bleeding pattern. Other bleeding patterns reported in studies included: regular (Mastor et al. 2011), vaginal haemorrhage (Mommers et al. 2012), prolonged spotting and polymennorhagia (Bhatia, Nangia, Aggarwal, and Tewari, 2011) as well as spotting and intermenstrual bleeding (Ojule, Oranu, and Enyindah, 2012; Roberts et al. 2015). Spotting, irregular and frequent bleeding were viewed as unfavourable bleeding patterns, which could explain the increased reports (Casey et al. 2011; Beligotti et al. 2012; Yonan, Borzutzky, Olson-Kennedy, Tanaka, & Iverson, 2018).

It must be noted that menstrual bleeding appears to be varied across age groups, with age therefore probably not influencing bleeding patterns. López del Cerro et al. (2018) found no statistically significant differences for amenorrhoea, frequent, infrequent and prolonged bleeding according to age. Additional variables, such as BMI, postpartum and breastfeeding, were also not predictive of bleeding pattern (Casey et al. 2011). The range in bleeding patterns is extreme across studies and the reason for breakthrough bleeding in implants was proposed by Ramdhan et al. (2018:3) who observed that:

> *"Women can experience a variety of bleeding patterns despite similar hormonal levels. For example, low estradiol levels and an absence of luteal activity can be associated with amenorrhea, frequent or prolonged bleeding"*

Summarizing the findings of various studies, bleeding patterns appear to be unpredictable and fluctuate over time (Guazzelli et al. 2010; Apter et al. 2016; Aisien & Enosolease, 2010). Women

have also experienced changes in bleeding pattern from their initial pattern (Darney et al. 2009; Bitzer et al. 2004). Studies suggest that there is no long-term trend in bleeding pattern associated with etonogestrel implants, these being patient specific.

Table 2-3: Summary of studies reporting percentage of menstrual bleeding patterns with etonogestrel implants

Bleeding pattern	Percentage (%)[1]	Region	Reference
Amenorrhoea	61.2	Ecuador	Medina, Bahamonde, Endara, & Leon, (2015)
	41.3	Turkey	Gezginc et al. (2007)
	40.2	Thailand	Chaovisitsaree et al. (2005)
	38.9	Brazil, Chile, Zimbabwe, Dominican Republic, Hungary, Thailand	Bahamondes et al. (2015)
	38.6	Brazil	Guazzelli et al. (2010)
	10.1-35.3	Bangkok	Thamkhantho, Jivasak-Apimas, Angsuwathana, Chiravacharadej, and Intawong (2008); Booranabunyat and Taneepanichsku (2004)
	33.0	Switzerland	Bitzer et al. (2004)
	24.4-32.0	Turkey	Şahİn et al. (2009): Duvan, Gözdemir, Kaygusuz, Kamalak, and Turhan (2010)
	27.9	Spain	López del Cerro et al. (2018)
	11.8-24.0	India	Singh et al. (2015); Bhatia et al. (2011)
	22.9	Malaysia	Mastor et al. (2011)
	2.4-9.4	Nigeria	Ojule et al. (2012); Balogun, Olaomo, Adeniran, and Fawole (2014); Roberts et al. (2015)
	7.0	Australia, Germany, France, UK, Norway and Sweden	Mommers et al. (2012)
Infrequent bleeding	56.0	Spain	López del Cerro et al. (2018)
	50.7	Malaysia	Mastor et al. (2011)
	39.1	Thailand	Chaovisitsaree et al. (2005)
	38.2	India	Singh et al. (2015)
	28.0	Switzerland	Bitzer et al. (2004)
	3.2-24.4	Turkey	Duvan et al. (2010); Gezginc et al. (2007); Şahİn et al. (2009)
	23	Ecuador	Medina et al. (2015)
	15.9	Brazil	Guazzelli et al. (2010)
Frequent bleeding	36.4	India	Singh et al. (2015)
	22.9	Malaysia	Mastor et al. (2011)
	6.5-17.5	Turkey	Duvan et al. (2010); Şahİn et al. (2009); Gezginc et al. (2007)
	16.4	Spain	López del Cerro et al. (2018)
	9.8	Thailand	Chaovisitsaree et al. (2005)
	2.3	Brazil	Guazzelli et al. (2010)

Prolonged bleeding	56.2	Brazil, Chile, Zimbabwe, Dominican Republic, Hungary, Thailand	Bahamondes et al. (2015)
	10.0-21.0	Turkey	Gezginc et al. (2007); Şahİn et al. (2009); Duvan et al. (2010)
	15.0	Switzerland	Bitzer et al. (2004)
	13.6	India	Singh et al. (2015)
	2.3	Brazil	Guazzelli et al. (2010)
	2.2	Thailand	Chaovisitsaree et al. (2005)
Normal bleeding	11.0	Switzerland	Bitzer et al. (2004)
	8.7	Thailand	Chaovisitsaree et al. (2005)
	8.0	Egypt	Laban et al. (2012)
Menorrhagia	11-39.9	SA	Pillay et al. (2017a); Mrwebi et al. (2018)
	35.4	Brazil, Chile, Zimbabwe, Dominican Republic, Hungary, Thailand	Bahamondes et al. (2015)
	10.3	Australia, Germany, France, UK, Norway and Sweden	Mommers et al. (2012)
	1.2-3.9	Nigeria	Ojule et al.(2012); Roberts et al. (2015)
Irregular bleeding	86.0	Brazil, Chile, Zimbabwe, Dominican Republic, Hungary, Thailand	Bahamondes et al. (2015)
	70	Maylasia	Mastor et al. (2011)
	52.9	Bangkok	Booranabunyat and Taneepanichsku (2004)
	29.3	Turkey	Şahİn et al. (2009)
	27.0	India	Bhatia et al. (2011)
	14.8	Nigeria	Balogun et al. (2014)
	9.1	Brazil	Guazzelli et al. (2010)

SA=South Africa, UK=United Kingdom

[1] Calculated as bleeding pattern/total women.

2.4.1.2 Non-menstrual adverse drug reactions

The proportions of ADR per organ system differed between two international studies (Figure 2-1). Darney et al. (2009) reported female reproductive disorders (excluding menstrual) as the most commonly occurring ADR per organ system. Some of the ADRs that constituted female reproductive disorders included: vaginitis (14.5%), breast pain (12.8%), leukorrhea (9.6%) and dysmenorrhea (7.2%). Simon et al. (2016) also noted reproductive ADRs as the most frequently affected system and included menstrual changes and pain or abnormalities in the breast or pelvis. Lower proportions of all ADRs per organ system, except reproductive disorder and complications at implant site, were reported by Simon et al. (2016) compared to Darney et al. (2009).

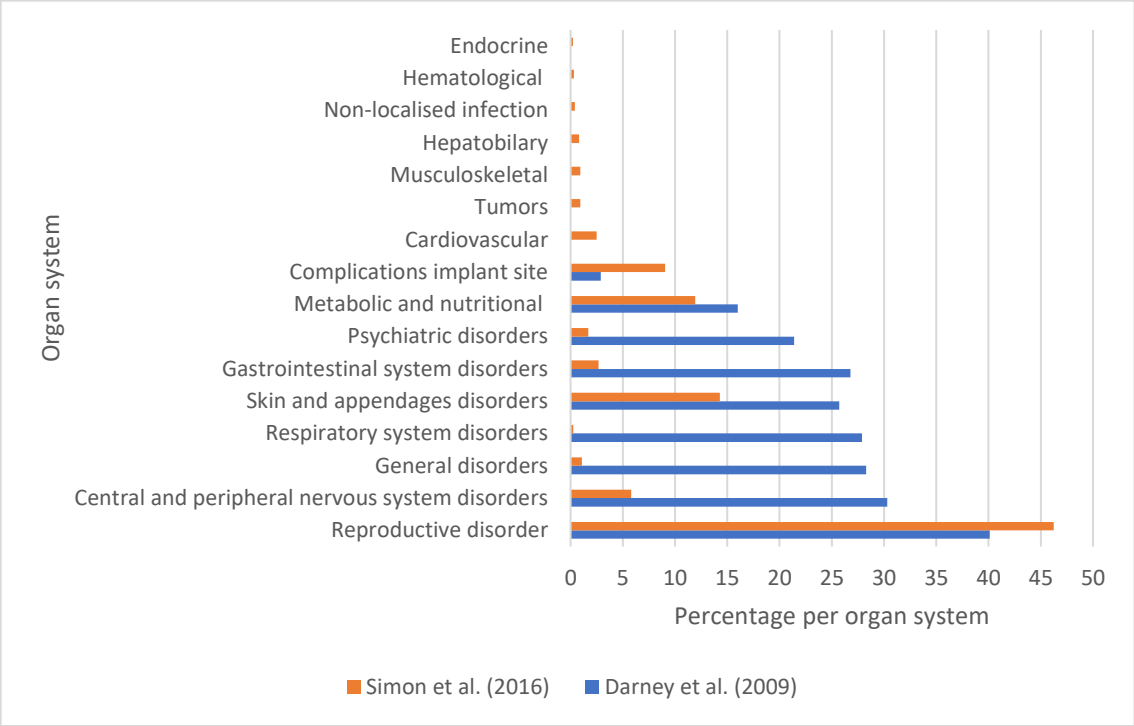

Figure 2-1: Adverse drug reaction reported per organ systems (Simon et al. 2016; Darney et al. 2009)

A summary of etonogestrel implant studies that reported common non-menstrual ADRs are described in Table 2-4. It is necessary to be cognizant that more than one ADR could be reported in some cases.

Headache: Headache is the most common non-menstrual ADR and is suggested to be steroid related (Brache, Faundes, Alvarez, & Cochon, 2002). There is a wide range in the proportion of headache reported across studies (range: 1.1-59.6%), the highest being mainly in upper-middle income countries, a possible reason being an increase in the incidence compared to prior to insertion (ŞahİN et al. 2009). The proportion of headache reported in African studies was on the lower end of the scale, which could be due to changes in the incidence with time (Roberts et al. 2015). An excerpt from Pillay et al. (2017a:819) reports "*I experience a headache on early days when I inserted it, but now I'm ok and I would like to continue using it."*

Weight increase: Weight increase is the second most common non-menstrual ADR, this being reported by over two-thirds of studies across regions, the range being 0.6%-23.6%. Weight increase was more frequently reported in high and upper middle-income countries, and in regions outside Africa. A recent multicenter randomized trial revealed that etonogestrel implant users

experienced a significant mean weight increase of three kilograms after 36 months of use (Bahamondes, Brache, Ali, & Habib, 2018). Brache et al. (2002:67) remarked that:

> "*weight gain has been a consistent finding in all implant clinical trials, but it has also been reported among nonhormonal contraceptive users, suggesting that other factors may also be related, such as the natural increase in weight related to aging*."

It is uncertain whether the weight gain expressed by users is Implanon® related or normal average weight gain for an adult (Bahamondes et al. 2018).

Acne: Acne could be caused by the androgenic effect of progestogen (Brache et al. 2002), the majority reporting it is ranging from 1.2%-45.2% of users. It must be noted that only one study conducted in Africa reported acne implying that it may not be a common ADR in the region. It was argued by Funk et al. (2005) that 84.0% reported no change in acne and may therefore not have been a significant ADR for some users. The highest proportions of acne were reported by users in mainly upper-middle income countries. Yildizbas, Sahin, Kolusari, Zeteroglu, & Kamaci, (2007) reported that 26.8% of women experienced acne who did not have acne at baseline, this being higher than the percentage reported by Funk et al. (2005) of 16%.

Loss/reduced libido: The loss of libido could possibly be related to implant use (Brache et al. 2002), with changes having been reported by over a third of studies, the proportions ranging from 1.0-21.7%. Al-Jefout et al. (2015) reported that 21.7% of changes in libido could be attributed to the high prevalence of menstrual disturbances, but that if this outlier is removed, small proportions of changes were reported. While there appears to be a considerable range of ADR proportions across studies, there is no definite trend based on age and region. In particular, studies from Africa have reported relatively fewer and lower proportions of ADRs. An important note is that some studies have revealed that not all ADRs were related to Implanon® (Darney et al. 2009; Funk et al., 2005) and Nexplanon® (Mommers et al. 2012).

There were several other ADRs reported, some of which include: weight loss (Gezginc et al. 2007), vomiting (Mastor et al. 2011), local arm irritation (Riney, O'Shea, and Forde 2009) and back pain (Mrwebi et al. 2018).

Table 2-4: Summary of etonogestrel implant studies showing common non-menstrual adverse drug reactions

Non-menstrual ADRs	Percentage (%)[1]	Region	Reference
Headache	59.6	Brazil, Chile, Hungary, Thailand, Turkey, Zimbabwe, Dominican Republic	Bahamondes et al. (2015)
	6.5-41.2	Turkey	Duvan et al. (2010); Yildizbas et al. (2007); Şahİn et al. (2009)
	24.9	Mexico	Flores,Balderas, Bonillaa and Vázuez Estrada, (2005)
	21.7	Jordan	Al-Jefout et al. (2015)
	20.1	Ethiopia	Birhane, Hagos, and Fantahun (2015)
	15.5	USA, Chile, Asia, Europe	Darney et al. (2009)
	6.4-14.3	SA	Mrwebi et al. (2018); Pillay et al. (2017a)
	1.1-13.3	Nigeria	Balogun et al. (2014); Roberts et al. (2015)
	12.7	USA	Funk et al. (2005)
	12.3	Australia, Finland, France,Norway, Sweden, UK	Apter et al. (2016)
	9.0	Australia, Germany, France, UK, Norway, Sweden	Mommers et al. (2012)
	8.6	Malaysia	Mastor et al. (2011)
	4.0	Switzerland	Bitzer et al. (2004)
	3.0	Ireland	Riney et al. (2009)
Dizziness	34.5-46.3	Turkey	Şahİn et al. (2009); Yildizbas et al. (2007)
	44.5	Brazil, Chile, Hungary, Thailand, Turkey,Zimbabwe, Dominican Republic	Bahamondes et al. (2015)
	1.0	Switzerland	Bitzer et al. (2004)
	0.5	SA	Mrwebi et al. (2018)
Weight increase	23.6	Malaysia	Mastor et al. (2011)
	23.2	Jordan	Al-Jefout et al. (2015)
	16.0	Turkey	Duvan et al. (2010)
	12.1	USA	Funk et al. (2005)
	12.0	USA,Chile, Asia, Europe	Darney et al. (2009)
	0.6-11.7	Nigeria	Ojule et al. (2012); Balogun et al. (2014); Roberts et al. (2015)
	11.0	Australia,Germany, France,UK,Norway, Sweden	Mommers et al. (2012)
	9.0	Switzerland	Bitzer et al. (2004)
	8.0	Ireland	Riney et al. (2009)
	7.5	India	Bhatia et al. (2011)
	4.8	SA	Mrwebi et al. (2018)
	2.8	Mexico	Flores et al. (2005)

	2.1	Ethiopia	Birhane, Hagos, and Fantahun (2015)
Pain at implant site	15.2	Thailand	Chaovisitsaree et al. (2005)
	9.6	SA	Mrwebi et al. (2018)
	4.0	Australia, Germany, France, UK, Norway, Sweden	Mommers et al. (2012)
	3.2	Turkey	Duvan et al. (2010)
	2.9	USA, Chile, Asia, Europe	Darney et al. (2009)
Abdominal pain	50.4	Brazil, Chile, Hungary, Thailand, Turkey, Zimbabwe, Dominican Republic	Bahamondes et al. (2015)
	23.9	Thailand	Chaovisitsaree et al. (2005)
	15.0	Mexico	Flores et al. (2005)
	5.2	USA, Chile, Asia, Europe	Darney et al. (2009)
	3.0	Switzerland	Bitzer et al. (2004)
	0.5	SA	Mrwebi et al. (2018)
Emotional lability	14.2	USA	Funk et al. (2005)
	5.8	USA, Chile, Asia, Europe	Darney et al. (2009)
Breast pain	8.6-12.2	Turkey	Şahİn et al. (2009); Yildizbas et al. (2007)
	10.2	USA, Chile, Asia, Europe	Darney et al. (2009)
	1.4	Mexico	Flores et al. (2005)
	0.6-1.1	Nigeria	Ojule et al. (2012); Balogun et al. (2014)
Acne	45.2	Brazil, Chile, Hungary, Thailand, Turkey, Zimbabwe, Dominican Republic	Bahamondes et al. (2015)
	1.6-26.8	Turkey	Duvan et al. (2010); Gezginc et al. (2007); Şahİn et al. (2009); Yildizbas et al. (2007)
	16.3	Thailand	Chaovisitsaree et al. (2005)
	15.5	Australia, Finland, France, Norway, Seden, UK	Apter et al. (2016)
	14.5	USA	Funk et al. (2005)
	12.3	Australia, Germany, France, UK, Norway, Sweden	Mommers et al. (2012)
	12.0	Switzerland	Bitzer et al. (2004)
	11.8	USA, Chile, Asia, Europe	Darney et al. (2009)
	10.0	Malaysia	Mastor et al. (2011)
	6.3	Mexico	Flores et al. (2005)
	5.8	Jordan	Al-Jefout et al. (2015)
	1.2	Ethiopia	Birhane et al.(2015)
Breast tender-ness	6.5-18.8	Turkey	Duvan et al. (2010); Gezginc et al. (2007)
	16.3	Thailand	Chaovisitsaree et al. (2005)

	11.0	Switzerland	Bitzer et al. (2004)
	4.3	Mayalsia	Mastor et al. (2011)
Depressive mood	2.5-17.1	Turkey	Gezginc et al. (2007); Şahİn et al. (2009); Yildizbas et al. (2007)
	7.3	USA	Funk et al. (2005)
	2.0	Switzerland	Bitzer et al. (2004)
Loss of libido	4.3	Malaysia	Mastor et al. (2011)
	1.6-2.5	Turkey	Duvan et al. (2010); Gezginc et al. (2007)
	1.1	SA	Mrwebi et al. (2018)
	1.0	Switzerland	Bitzer et al. (2004)
Decreased libido	21.7	Jordan	Al-Jefout et al. (2015)
	7.6	Thailand	Chaovisitsaree et al. (2005)
	5.9	Mexico	Flores et al. (2005)
Nausea	29.3-38.2	Turkey	Yildizbas et al. (2007); Şahİn et al. (2009)
	13.4	Mexico	Flores et al. (2005)
	5.0	Mayalsia	Mastor et al. (2011)
Dysmenorrhea	12.3	Australia, Finland, France, Norway, Sweden, UK	Apter et al. (2016)
	9.7	USA	Funk et al. (2005)
	2.4-5.7	Turkey	Yildizbas et al. (2007); Şahİn et al. (2009)
	4.0	Ireland	Riney et al.(2009)
	3.7	Australia, Germany, France, UK, Norway, Sweden	Mommers et al. (2012)
Mood changes/ swings	21.7	Jordan	Al-Jefout et al. (2015)
	17.4	Thailand	Chaovisitsaree et al. (2005)
	9.5	Mexico	Flores et al. (2005)
	5.0	Maylasia	Mastor et al. (2011)
	3.0	Switzerland	Bitzer et al. (2004)
	1.1	Nigeria	Balogun et al. (2014)
Hirsutism	3.2-5.7	Turkey	Duvan et al. (2010); Şahİn et al. (2009)
	1.5	Jordan	Al-Jefout et al. (2015)
Hair loss	13.6	Malaysia	Mastor et al. (2011)
	1.6	SA	Mrwebi et al. (2018)

ADRs=Adverse drug reactions, SA=South Africa, UK=United Kingdom, USA=United States of America
[1] Calculated as ADR/Total women.

There were 5.9% of participants who experienced 77 serious ADRs in the clinical trials (Darney et al., 2009). The most common serious ADRs were gastrointestinal conditions (1.1%), neoplasms (0.7%), and liver and biliary system disorders (0.6%) (Darney et al. 2009). Other serious ADRs included heart disorders, abdominal pain, and breast neoplasms (2009). Findings from a pharmacovigilance study reported 7% of serious ADRs cases (excluding pregnancy), the incidence of serious ADRs being estimated at 0.32 / 1000 patients for Implanon® and 0.09 / 1000 for Nexplanon® (Simon et al. 2016). Migration/withdrawal problems, implant site reactions, neurological conditions and cardiovascular conditions were considered serious ADRs (2016). A Nexplanon® study reported several serious ADRs e.g. migraine, bipolar disorder and ovarian cysts, however, none were considered to have a definite relationship to the drug (Mommers et al. 2012). Serious ADRs were reported by 2.4% of participants in a multicenter study, but only cerebral infarction was related to the implant (Apter et al. 2016). Funk et al. (2005) mentioned that 10 participants reported serious ADRs, but only a ruptured ovarian follicle and acute exacerbation of depression were deemed possibly related to Implanon®. Overall, under 10% of etonogestrel implant users experienced serious ADRs and only a few were related to Implanon® and Nexplanon®.

2.4.1.3 Complications of etonogestrel implants

Noteworthy ADRs are complications that relate to the implant site and device, with a case study reporting a red, swollen implant site with purulent discharge in a woman using Nexplanon® (Chaudhry, 2013). Skin infection post-Nexplanon® insertion (Partridge & Bush, 2013) and hypersensitivity reaction (Serati, Bogani, Kumar, Cromi, & Ghezzi, 2015; Niederhauser, Magann, & Hoffman, 2011) were also reported, while two cases reported allergic reactions to the barium in Nexplanon® (Pedroso, Martins, Palma, & Machado, 2015; Sullivan, 2012). Several case reports noted migrated (Baek, Kim, Seo, & Kim, 2012; Park, Bae, Lee, Bae, & Park, 2017; Kew, Senanayake, Djearaman, & Bishay, 2017), broken (Tomás-Tello & Hodgson, 2010; Myrick, Howell, & Ramakrishnan, 2012; Torres, Mendes, Machado, & Marques, 2013) and bent implants (Doshi, 2011). Cases testified the migration of Implanon® (O'Brien, O'Reilly, Sugrue, Lawler, & Farrelly, 2015) and Nexplanon® (Akhtar et al. 2018) from the insertion site to a pulmonary artery, which resulted in embolism. Another study established that 30% reported migration of Implanon® devices from their insertion site (Vidin, Garbin, Rodriguez, Favre, & Bettahar-Lebugle, 2007). A case report on distal migration of Implanon NXT® found 10 other cases of distal migration reported (Park et al. 2017), while the results from a pharmacovigilance database revealed 38 cases of migration of etonogestrel implants (Kang, Niak, Gada, Brinker, & Jones, 2017). The etonogestrel implants migrated to various locations e.g. chest wall, lung, pulmonary artery, axilla

and other body sites (2017). Some patients reported pain, discomfort, skin reactions, pulmonary fibrosis and dyspnea (2017). Location failures or migrations (24%), curved or broken etonogestrel implants (11%) and expulsions or absence of etonogestrel implants were noted in a pharmacovigilance study (Simon et al. 2016). A USA study reported 23 broken or cut implant rods, 15 bent and nine expelled rods to an etonogestrel implant monitoring programme (Creinin et al. 2017). Implant device fractures were found in 70% of Nexplanon® and 26% of Implanon® users in a recent study (Crouthamel, Schiff, Oelschlager, Prager, & Debiec, 2018). The implant fractures were due to patient manipulation (23%), unintentional trauma (11%), interpersonal violence (8%), lifting/carrying (6%) and fracture at discontinuation (6%) (2018). The bleeding pattern was not altered in majority of cases (78%), indicating no significant change in effects of Implanon® and Nexplanon® (2018). However, a case report specified that a patient had a change in bleeding pattern after Implanon® had broken (Pickard & Bacon, 2002). In SA, there were 14 cases of discontinuation reported due to broken Implanon NXT® (Pillay et al. 2017b). Evidently, deformities of etonogestrel implants and migration of the implant is not a rare occurrence. Drug interactions with etonogestrel implants has also been described in several studies and is a notable ADR, which is explored in the next section.

2.4.2 Drug interactions

Drug interactions are changes in a drug effect that may result in ADR or therapeutic failure (Lynch, 2016). There are different types of drug interactions e.g. drug-drug interactions, drug-disease interactions and drug-laboratory test interactions. Drug-drug interactions can occur due to recent or concurrent use of another drug/s, which may increase or decrease the effects of one or both drugs (2016). "*A drug–disease interaction occurs when an administered drug exacerbates an underlying disease in a patient."* (Lindblad, 2007). Drugs can interfere with the analytics of laboratory tests due to the *"potential for drugs and endogenous compounds to modify the concentrations of various analytes in body fluids"* (Young, 1997:579). The *in vivo* ADR of the drugs can also result in abnormal test results (1997).

2.4.2.1 Drug-drug interactions

Evidence exists regarding drug interactions between etonogestrel implants and concomitant drugs. Phenytoin, carbamazepine and phenobarbital induce microsomal enzymes in the CYP450 pathway and increase sex hormone binding globulin levels, thereby accelerating the metabolism process of etonogestrel and impacting on its effectiveness (Gaffield, Culwell, & Lee, 2011). In a prospective study, 10 women were analysed to determine the impact of carbamazepine in

Nexplanon® users (Lazorwitz, Davis, Swartz, & Guiahi, 2017). There was a median percent decrease of 61% in etonogestrel levels for most participants between pre-carbamazepine initiation and post-carbamazepine initiation (2017), with 80% of participants having below effective etonogestrel concentrations to prevent pregnancy (<90pg/ml) (2017). Less potent CYP450 inducers, such as Topiramate and Oxcarbazepine, alter the plasma levels of contraceptive steroids to a small degree (Gaffield et al. 2011). A study revealed that progesterone only contraceptives did not affect the serum concentration of Lamotrigine (Reimers, Helde, & Brodtkorb, 2005). Despite evidence of reduced effectiveness with some anticonvulsants, the WHO and Centre for Disease Control (CDC) recommend that they may be used concurrently with implants, as the advantages of using the method generally outweigh the theoretical or proven risks (WHO, 2015b; Curtis et al. 2016). Nonetheless, it is recommended that other contraceptives must be promoted in long-term users of anticonvulsants (WHO, 2015b).

Rifampicin is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, which lowers the plasma concentrations of etonogestrel (Commonwealth of Australia, 2007). Maximum enzyme induction generally takes two to three weeks after initiation (2007). Rifampicin is known to cause a 55% reduction in the area under the concentration time curve in pharmacokinetic drug interaction studies (Gbolade, 2010). According to the WHO and CDC, the advantages of using implants with rifampicin generally outweigh the theoretical or proven risks (WHO, 2015b; Curtis et al. 2016). It must be noted that WHO encourages the use of alternate contraceptives for long-term rifampicin users due to reduced effectiveness (WHO, 2015b).

St John's wort (Hypericum perforatum L.) is a herbal drug that reduces the effectiveness of hormonal contraceptives (UK-MHRA, 2014), with the CDC having found the following evidence:

> *"Although clinical data are limited, studies with pharmacokinetic and pharmacodynamics outcomes raise concern that St. John's wort might decrease effectiveness of hormonal contraceptives, including increased risk for breakthrough bleeding and ovulation and increased metabolism of estrogen and progestin. Any interactions might be dependent on the dose of St John's wort, and the concentration of active ingredients across types of St. John's wort preparations may vary"* (Curtis et al. 2016: 49).

Therefore, the CDC states that implants may be used in women taking St John's Wort as the advantages generally outweigh the theoretical or proven risks (Curtis et al. 2016).

Protease Inhibitors and NNRTIs are metabolized by CYP3A4 and inhibit or induce cytochrome P450, resulting in respective increases or decreases in the concentration of etonogestrel (Nanda et al. 2017). Protease Inhibitors primarily inhibit various CYP enzymes, with most NNRTIs being CYP inducers (Tseng & Hills-Nieminen, 2013). Lopinavir/Ritonavir based treatment, a Protease Inhibitor, was associated with an increase in etonogestrel bioavailability i.e. 52% increase in etonogestrel area under the curve, 60.6% increase in Cmax and 33.8% increase in Cmin (Vieira et al. 2014). Etonogestrel may be significantly reduced in the presence of efavirenz due to CYP3A4 induction (Tseng & Hills-Nieminen, 2013). An article by Shelton (2015) specified that efavirenz accelerates normal degradation of contraceptive progestin when using the implant and lowers the progestin blood levels by approximately half (2015). Progestin blood levels reduce over time, therefore continued concomitant use of efavirenz and the implant will result in some loss of effectiveness and an increased risk of pregnancy (2015). A Pharmacokinetic study demonstrated a reduction in etonogestrel bioavailability in efavirenz users, namely a 63.4% decrease in area under the curve, a 53.7% decrease in maximum concentration and a 70% decrease in minimum concentration (Vieira et al. 2014). While similar effects may occur with nevirapine, which is a moderate CYP3A4 inducers, etonogestrel concentrations were found to be 82% lower among those on efavirenz based therapy compared to those not on ART after 24 weeks of treatment, with nevirapine being found not to significantly affect etonogestrel concentration (Chappell et al. 2017). Updated prescription guidelines, released in December 2014 for SA recommends that patients on long-term drugs, which are strong enzyme inducers, such as efavirenz, should not use implants (Republic of South Africa, National Department of Health, 2014). These guidelines continue that patients who already have the implant inserted and are on long-term strong enzyme-inducing drugs should be counselled on the increased risk of pregnancy and may continue with the device if acceptable by the user (2014). According to the WHO, the advantages of using implants in efavirenz, nevirapine and ritonavir users generally outweigh the theoretical or proven risks (WHO, 2015b).

2.4.2.2 Drug-condition interaction

The WHO recommends that implants should not be used in those with current breast cancer and those with past and no evidence of current disease for five years (WHO, 2015b). WHO states that "*Breast cancer is a hormonally sensitive tumour, and the prognosis of women with current or recent breast cancer may worsen with POC use*." (2015b:174). However, studies on breast cancer risk in progestin contraceptives revealed no association between increased risk of breast cancer and progestin use (Marchbanks et al. 2002; Shapiro et al. 2000; Strom et al. 2004; Backman et al. 2005). One study in particular suggested an association of increased risk of breast cancer in

prolonged progestogen use in users over the age of 40 (Fabre et al. 2007). Another study found the same level of breast cancer risk with combined oral contraceptives (COCs) and progestin-only pill (Kumle et al. 2002).

The WHO recommends that implants should not be used in those with acute deep vein thrombosis and pulmonary embolism as the risk outweigh the advantages (WHO, 2015b). WHO details that:

> *"Although evidence on the risk of venous thrombosis with the use of POCs is inconsistent in otherwise healthy women, any small increased risk is substantially less than that with COCs (134–136)." (WHO, 2015b:161).*

Poulter, Chang, Farley, Marmot, & Meirik, (1998) maintain that there is little or no increased risk of stroke, venous thromboembolism or acute myocardial infarction associated with the use of progestogen-only contraceptives. Implants are not recommended in those with unexplained vaginal bleeding, severe cirrhosis, benign hepatocellular adenoma and hepatoma (WHO, 2015b).

2.4.2.3 Drug-laboratory interaction

A statistically significant increase in cholesterol and triglycerides levels was observed with Implanon® at the end of three years, but values were still within normal range (Inal et al. 2008). Dilbaz, Ozdegirmenci, Caliskan, Dilbaz, & Haberal, (2010) revealed that there was a significant decrease in total cholesterol (TC), high-density lipoprotein cholesterol (HDL) and triglycerides up to six months post insertion. Olumuyiwa, Adeyemi, Adeniran, Michael, & Olatubosun (2018) also established that TC rose, and serum triglycerides reduced, neither being significant throughout their use. Moreover, their study maintained that HDL levels were significantly higher, and that the lower Low-density lipoprotein (LDL) were not statistically significant. In addition, the HDL/TC and HDL/LDL ratios were significantly higher than those at baseline. There is contradicting evidence on the lipid profile effect, but it is recommended that:

> "*Women who are being treated for hyperlipidemia should be followed closely if they elect to use Implanon NXT. Some progestagens may elevate LDL levels and may render the control of hyperlipidemia more difficult"* (Merck Sharp & Dohme, Australia, 2010:5).

A study evaluating the haematological indices in Implanon® users concluded that it has a safe profile in 36 months of use (Aisien & Enosolease, 2017). The study suggested that there were no statistically significant changes in white blood cell concentration and packed cell volume. The platelet concentration rose to a statistically significant value at 36 months, but remained within normal concentrations (Aisien & Enosolease, 2017; Henry, McPherson, & Pincus, 2011). A

significant increase in Haemoglobin was noted after six months, which could be due to amenorrhoea (Dilbaz et al. 2010).

A statistically significant increase in mean Alanin aminotransferase (ALT) level at six months was found with Implanon® utilisation (Dilbaz et al. 2010), the study concluding that the above changes would not lead to clinical issues (2010). A study by Biswas, Biswas, & Viegas, (2004) established a significant increase in mean total and unconjugated bilirubin and the gamma-glutaryl transferase levels after two years of Implanon® use but remained within the normal range. While the ALT levels were fairly unchanged in Implanon® users (2004), the aspartate aminotransferase and Lactate Dehydrogenase levels increased in the first year of utilisation and decreased towards initial reading in the second year (2004). Alkaline phosphate levels decreased, but not significantly, and no significant change was found in the serum albumin levels (2004).

A study on carbohydrate metabolism in etonogestrel users indicated no difference in carbohydrate metabolism due to Implanon after 12 months of use (Biswas, Viegas, Bennink, Korver, & Ratnam, 2001). Meckstroth & Darney (2004) established that there were several studies where a significant effect in carbohydrate metabolism was noted, but that they were small. Additionally, a study on biochemical and metabolic parameters found no statistically significant differences in user levels of fasting blood glucose, blood urea nitrogen, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, serum low-density lipoprotein, high-density lipoprotein, free 3,5,3'-tri-iodothyronine, free thyroxine and thyroid stimulating hormone after three years of Implanon® use (Inal et al. 2008). Another study maintained that Implanon® had no significant effect on thyroid function, and that there were minimal changes in cortisol levels due to increased sex hormone binding globulin levels (Biswas et al. 2000) This study concluded that the changes would not be clinically significant in healthy individuals.
These studies therefore suggest that while Implanon® does not have a significant clinical effect on laboratory parameters those using Implanon® and Implanon NXT® should be cognizant of potential consequence on exiting conditions.

2.4.3 Discontinuation of etonogestrel implants

It is evident from the literature that a proportion of users choose to discontinue etonogestrel implants as highlighted in Table 2-5. Some studies define premature Implanon® discontinuation as ceasing to use it within the first two and a half years of its insertion (Birhane et al. 2015; Asaye, Nigussie, & Ambaw, 2018; Harvey, Seib, & Lucke, 2009) while others consider this to be three years (Burusie, 2015; Tadesse et al. 2017). The discontinuations across regions range from

0-80%, indicating a wide variability in study reports. High income countries reported approximately a quarter of women discontinued etonogestrel implants within 12 months, except in the study by Berlan, Mizraji & Bonny (2016). Nigerian studies reported lower discontinuation rates (4.5%-26.6%) compared to those in Ethiopia (16%-80%). In African studies, approximately 21% discontinued in studies lasting 24 months if the two outliers are discounts. An unusually higher discontinuation incidence was reported in SA in 24 months (Pillay et al. 2017a).

Table 2-5: Summary of studies reporting discontinuation of etonogestrel implants

Percentage of discontinuation (%)	Total number of women	Approximate duration of use (months)	Region	Reference
80.0	100	30	Ethiopia	Burusie (2015)
68.9	1397	48	UK	Cea Soriano, Wallander, Andersson, Filonenko, and García Rodríguez (2015)
65.0	4492	30	Ethiopia	Asaye et al. (2018)
47.0	149	36	Australian	Weisberg, Bateson, McGeechan, and Mohapatra (2014)
46.5	314	36	Ethiopia	Siyoum, Mulaw, Abuhay, & Kebebe (2017)
44.8	69	36	Jordan	Al-Jefout et al. (2015)
40.1	152	24	SA	Pillay et al. (2017a)
37.0	200	36	India	Bhatia et al. (2011)
35.0	942	24-48	USA, Chile, Asia, Europe	Darney et al. (2009)
35.0	116	36	USA	Obijuru, Bumpus, Auinger, and Baldwin (2016)
34.9	356	36	Spain	Arribas-Mir et al. (2009)

27.2	110	12	India	Singh et al. (2015)
26.8	381	12	Australia, Finland, UK, France, Norway, Sweden	Apter et al. (2016)
26.6	121	48	Nigeria	Madugu, Abdul, Bawa, and Kolawole (2015)
24.0	14938	12	USA	Law, Liao, Lin, Yaldo, and Lynen (2018)
23.7	991	12	Switzerland	Bitzer et al. (2004)
23.0	140	36	Malaysia	Mastor et al. (2011)
22.6	190	12	UK	Smith and Reuter (2002)
21.7	304	24	Egypt	Aziz, El-Gazzar, & Elgibaly, (2018)
21.4	295	24	Nigeria	Ezegwui, Ikeako, Ishiekwene, and Oguanua, (2011)
16.0	244	30	Ethiopia	Birhane et al. (2015)
13.0	200	24	China	Zheng et al. (1999)
10.3	750	12	USA	Berlan et al. (2016)
7.0	1366	6	USA	Grunloh, Casner, Secura, Peipert, and Madden (2013)
5.4	168	48	Nigeria	Ojule et al. (2012)
4.5	669	24	Nigeria	Muthir and Nyango (2010)
0	44	12	Brazil	Guazzelli et al. (2010)

SA=South Africa, UK=United Kingdom, USA=United States of America

The number of women discontinuing Implanon® increased over time, as noted in an Australian study, which described the following proportions: 26.3% at one year, 49.7% at two years and 87.3% at three years (Harvey et al. 2009). A SA study reported higher proportions of Implanon

NXT® discontinuations over time, with 27.2% doing so within six months, 67.3% in 12 months and 94.4% after 24 months (Mrwebi et al. 2018).

In an Ethiopian study (Siyoum et al. 2017) and Nigerian study (Muthir & Nyango, 2010), discontinuation of Implanon® commenced as early as two weeks post insertion. The average duration of use ranged from 6.6 months to 27 months across studies as shown in Table 2-6. The median duration of use was reported in the first year of use for half of the studies and in the second year for the rest of etonogestrel implant studies. Two SA studies reported that discontinuers used Implanon NXT® for a median of 8-10 months (Mrwebi et al. 2018; Pillay et al. 2017a). There is, therefore, a trend in the literature of premature discontinuation of etonogestrel implants.

Table 2-6: Summary of studies reporting median and mean duration of etonogestrel implant use

Median duration of use (months)	Mean duration of use (months)	References
23.5		Obijuru et al. (2016)
19.5		Burusie (2015)
12.0		Siyoum et al. (2017)
10.0		Mrwebi et al. (2018)
8.0		Pillay et al. (2017a)
	27.0	Pam et al. (2014)
	Approximately 24.0	Darney et al. (2009)
	24.0	Mastor et al. (2011)
	21.5	Asaye et al. (2018)
	Approximately 20.0	Law et al. (2018)
	13.4	Muthir and Nyango (2010)
	11.2	Mrwebi et al. (2018)
	9.2	Bitzer et al. (2004)
	7.5	Berlan et al. (2016)
	6.6	Birhane et al. (2015)

Some factors that influence discontinuation are inconsistent in the literature such as past pregnancy as one study found that no previous pregnancy was associated with discontinuation (Siyoum et al. 2017) whereas another found that it was (Berlan et al. 2016). In the USA, participants who had a prior pregnancy/delivery were more likely to discontinue their implant compared to those who did not ($p<0.001$) (Law et al. 2018). Contradictory evidence was also found regarding the number of children (Asaye et al. 2018; Tadesse et al. 2017) and level of education (Siyoum et al. 2017; Tadesse et al. 2017) associated with discontinuation. It was clear that those who had no counselling or follow-up was associated with greater odds of discontinuation (Asaye et al. 2018; Siyoum et al. 2017; Birhane et al. 2015). Age appears to influence discontinuation, with young age at insertion being associated with greater odds of discontinuation (Tadesse et al. 2017). In a UK study, younger Implanon® users had a greater risk of discontinuation (Smith & Reuter, 2002). Conversely in a USA study, participants aged 20-24 years old and 25-44 years old were more likely to discontinue the etonogestrel implant within one year of insertion compared to 15-19-years old (Berenson, Tan, & Hirth, 2015). In an Australian study, the clinic where Implanon® was inserted influenced discontinuation as those who attended regional clinics experienced significantly shorter time to discontinue than those who attended metropolitan clinics (Harvey et al. 2009). Additional factors found to be associated with greater odds of discontinuation include: medical care sought for implant concerns (Berlan et al. 2016), history of abortion (Tadesse et al. 2017) and perceived satisfaction (Siyoum et al. 2017; Birhane et al. 2015). Other factors, such as religion, counselling about benefit, counselling effectiveness, age, residence, parity, main decider, telephonic consultations and source of information, were tested for association but were not statistically significant.

Those who experienced ADRs were established to have greater odds of discontinuation than those who did not (Asaye et al. 2018; Siyoum et al. 2017; Birhane et al. 2015). Contrary to the trend, Tadesse et al. (2017) found that ADRs were not significantly associated with discontinuation. Specific ADRs, such as headache, bleeding and weight gain, were not significant factors for discontinuation in one study (Birhane et al. 2015). Obese women were to be found 2.6 times less likely to discontinue etonogestrel implant for bleeding than overweight and normal weight women (Casey et al. 2013). However, Burusie (2015) offered that participants who complained of heavy/prolonged menstrual bleeding were significantly more likely to discontinue prematurely than for other reasons. Additionally, Berenson et al. (2015) reported that etonogestrel implant users were more likely to discontinue their devices within 30 days of visiting their doctor after reporting abnormal bleeding. Harvey et al. (2009) suggested that metropolitan women were significantly more likely to discontinue Implanon® use because of dissatisfaction with altered

bleeding patterns while, regional women cited multiple reasons for discontinuing. It appears that factors affecting discontinuation may be region or patient specific, as studies are not consistent.

2.4.4 Reasons for discontinuation of etonogestrel implants

The major reason for discontinuation of etonogestrel implants were due to ADRs as affirmed in both global and local studies (Lakha & Glasier, 2006; Asaye et al. 2018; Pillay et al. 2017a; Mrwebi et al. 2018). Possible reasons for discontinuation are offered in an international qualitative study, which proposed that some participants endured ADRs for a period of time but resorted to discontinuation due to their intolerability (Lunde et al. 2017). Multiple ADRs could have also played a role in discontinuation (Pillay et al. 2017a), another possible reason being that bleeding irregularities and reduced libido affected the participants sex life (Inoue et al., 2016, Pillay et al., 2017a). The negative experiences of ADRs on women's relationships and finances led to discontinuation in some cases (Flore et al. 2016). The ADRs that led to etonogestrel implant discontinuation are summarized in Table 2-7.

All studies displayed in Table 2-7, irrespective of region, reported bleeding changes, which led to discontinuation. A scoping review confirmed that contraceptive induced menstrual bleeding changes was the main cause, or one of the main causes, for discontinuation (Polis et al. 2018). The irregular bleeding pattern ranged from 0.3%-44.39%, and menorrhagia ranged from 3.7-12.4%. A study conducted in the Netherlands endorsed that irregular bleeding was associated with the shortest duration of use of Implanon® (Teunissen et al. 2014), with amenorrhoea ranging from 0.07-4.5%. There was a wide variability across regions, which was also acknowledged by Darney et al. (2009) who held that regional differences could be due to cultural and social factors. They also speculated that acceptability of ADRs plays a role in discontinuation, as those frequently reported may not be the same as those leading to discontinuation. Bleeding irregularities and weight gain were the main reasons for discontinuation in a French study, but other ADRs, though frequent, were not often a reason (Sergent, Clamageran, Bastard, Verspyck, & Marpeau, 2004).

Weight increase was a commonly reported ADR, as shown in Table 2-4, with a low percentage of women discontinued due to weight increase. Some African studies reported a higher percentage of women who discontinued due to weight increase compared to regions outside Africa. Multiple ADR, as mentioned earlier in this section, in addition to weight gain, could have resulted in increased reports, as indicated by a participant in Pillay et al. (2017a:819). "*At first it was fine, but now I'm experiencing headache, bleeding and I'm also gaining weight, so I want to remove it now".* It can be argued that perception of weight increase is patient specific, with Muthir and

Nyango (2010) reporting that an average weight increase of only 1.9 kg was observed from time of insertion to discontinuation.

Almost all studies in Africa revealed headache as a reason for discontinuation, with a SA study reporting the highest percentage. The following quote from Pillay et al. (2017a:819) highlights that poor tolerability and severity of headaches was influential:

> *"These were described as 'constant headaches' and 'headaches every day'. One woman said: It was fine in the beginning, but then as the months went by it [the implant] started to cause me severe migraines."*

Acne was a commonly reported reason for discontinuation in studies outside Africa, but the percentages were low (range 0.3-5.2). Low reporting of acne as a reason for discontinuation could be due to a small proportion of women reporting worsening of acne as expressed earlier in this chapter (Funk et al. 2005).

Compared to other global studies, African studies reported pain at insertion site more frequently, particularly in Ethiopia. Counselling and management may be lacking in Ethiopia, as Burusie (2015) recommended reassurance and pain management for those experiencing pain. Another possible reason for pain being due to poor insertion techniques. Studies outside Africa reported emotional lability, depression and low sex drive, which were absent in the studies from Africa. Darney et al. (2009) implied that emotional lability, depression and abnormal sexual function were more frequently reported reasons for discontinuation in USA sites compared to non-USA sites, implying there may be a regional difference. A notable reason for discontinuation in SA was due to pregnancy, but the proportions were low, with pregnancy and causes of pregnancy being elaborated later in the chapter. There were several other ADR related reasons for discontinuation reported such as pelvic pain (Sznajder et al. 2017), back pain (Singh et al. 2015), breast tenderness (Ezegwui et al. 2011) and tiredness (Smith & Reuter, 2002).

Desire to conceive was the most common non-ADR reason for discontinuation, being endorsed in all studies in Tables 2.8. A study conducted in the Netherlands reported that desire to conceive was associated with a short duration of Implanon® use (18.9 months) (Teunissen et al. 2014). Blumenthal, Gemzell-Danielsson, and Marintcheva-Petrova (2008) maintained that discontinuation due to desire to conceive was more frequent in the second and third year compared to the first year. There is a small range 0.2-12.4% for desire to conceive observed in studies outside Africa. Ezegwui et al. (2011) attested that desire to conceive was reported as prematurely

as between six months and one-year post insertion, and Aziz et al. (2018) explained that the desire to conceive was common after the first year of usage. The highest percentages for discontinuation due to desire to conceive was evident in Nigerian studies. It was suggested by Muthir and Nyango (2010) that Implanon® was viewed as a temporary method (73.3%), and that the average duration of use in these women was one year.

In African studies, a prominent reason for discontinuation was husband opposition, which was absent in studies outside the continent. Nevertheless, an Implanon® qualitative study conducted in Australia proved that partner disapproval influenced decision to discontinue (Inoue et al. 2016). Another qualitative study conducted in Ethiopia validated that some women did not tell their husbands about using the implant due to pressure from husbands to continue having children (Zerihun et al. 2015). A quarter of women in a study conducted in Spain claimed full-term use of Implanon® (Arribas-Mir et al. 2009), whereas studies from Africa implied small percentages reaching expiry in Implanon® (Pam et al. 2014) and Implanon NXT® users (Mrwebi et al. 2018). Arribas-Mir et al. (2009) suggested that the low premature discontinuation rates in the study could be related to the high quality of pre-insertion counselling, which included information on possible ADRs and their high acceptability by the women.

The health practitioner also plays an essential role in discontinuation, with two African studies indicating that provider advice was a reason for discontinuation, but with low percentages. Aziz et al. (2018) justified that practitioners advised discontinuation unnecessarily and due to complaints unrelated to Implanon®. There appears to be various reasons for discontinuation in Africa compared to outside the continent e.g. request by mother-in-law, religious opposition, rumors and on concomitant treatment. According to a qualitative Ethiopian study, additional reasons for discontinuation were: declined productivity, health problems, peer pressure, myths and interference with work/daily activity (Zerihun et al. 2015). Community members and religious leaders also influenced discontinuation decision, as myths about Implanon® led to hasty withdrawal and negative perceptions (2015).

A study conducted on the influence of age on reasons for implant discontinuation revealed no statistically differences (López del Cerro et al. 2018). From the literature in Tables 2-7, there is no distinct trend in age as reasons for discontinuation due to ADR.

Contraceptive method failure and pregnancy were notable reasons for discontinuation and will be discussed in detail in the next section.

Table 2-7: Summary of studies reporting adverse drug reactions as reasons for etonogestrel implant discontinuation

ADR	Percentage (%)[1]	Region	Reference
Menstrual changes	60.7	SA	Pillay et al. (2017a)
	4.2-33.3	Nigeria	Pam et al. (2014); Ezegwui et al. (2011);Muthir and Nyango (2010)
	4.5-26.7	Ethiopia	Birhane et al. (2015); Siyoum et al. (2017); Asaye et al. (2018)
	21.6	Australia	Harvey et al. (2009)
	14.4	Switzerland	Bitzer et al. (2004)
	6.7-13.4	USA	Berlan et al. (2016); Sznajder, Tomaszewski, Burke, and Trent (2017)
	7.4-13	UK	Smith and Reuter (2002);Lakha and Glasier (2006)
	12.9	Malaysia	Mastor et al. (2011)
	11.5	Australia, Finland, France, Norway, Sweden, UK	Apter et al. (2016)
	11.1	USA, Chile, Asia,Europe	Darney et al. (2009)
	11.0	Europe	Short, Dallay, Omokanye, Stauch, & Inki (2014)
Emotional lability	2.3	USA, Chile, Asia, Euroupe	Darney et al. (2009)
	0.9	USA	Berlan et al. (2016)
Weight increase	1.7-13.3	Nigeria	Pam et al. (2014);Muthir and Nyango (2010)
	13.1	SA	Pillay et al. (2017a)
	2.0-5.8	Ethiopia	Birhane et al. (2015); Siyoum et al. (2017); Asaye et al. (2018)
	0.3-5	US	Grunloh et al. (2013); Berlan et al. (2016); Sznajder et al. (2017)
	2.6-4.3	UK	Smith and Reuter (2002); Lakha and Glasier (2006)
	2.3	Switzerland	Bitzer et al. (2004)
	2.3	USA, Chile, Asia,Europe	Darney et al. (2009)
	1.8	Australia, Finland,France,Norway, Sweden,UK	Apter et al. (2016)
	1.7	Australia	Harvey et al. (2009)
	1.3	Egypt	Aziz et al. (2018)
	0.9	Europe	Short et al. (2014)

Headache	39.9	SA	Pillay et al. (2017a)
	1.9-10.5	Ethiopia	Siyoum et al. (2017);Birhane et al. (2015); Burusie (2015); Asaye et al. (2018)
	0.5-6.7	Nigeria	Pam et al. (2014); Muthir and Nyango (2010)
	3.7	UK	Smith and Reuter (2002)
	1.6	USA, Chile,Asia, Europe	Darney et al. (2009)
	1.0	Egypt	Aziz et al. (2018)
	0.5-0.7	USA	Grunloh et al. (2013); Berlan et al. (2016)
Acne	5.2	Australia, Finland,France,Norway,Sweden,UK	Apter et al. (2016)
	3.8	Switzerland	Bitzer et al. (2004)
	3.3	Nigeria	Muthir and Nyango (2010)
	2.6	Euopre	Short et al. (2014)
	1.6	UK	Smith and Reuter (2002)
	1.3	USA, Chile, Asia, Europe	Darney et al. (2009)
	0.3-0.4	USA	Grunloh et al. (2013); Berlan et al. (2016)
Depression	1.7	Switzerland	Bitzer et al. (2004)
	1.6	UK	Smith and Reuter (2002)
	1.0	USA, Chile, Asia, Europe	Darney et al. (2009)
Changes in mood	9.5	Nigeria	Ezegwui et al. (2011)
	3.4	UK	Lakha and Glasier (2006)
	2.9	Ethiopia	Siyoum et al. (2017)
	2.5	Australia	Harvey et al. (2009)
	0.3-2.5	USA	Grunloh et al. (2013); Sznajder et al. (2017)
	1.6	Australia, Finland,France,Norway,Sweden,UK	Apter et al. (2016)
Irregular bleeding	44.4	Nederlands	Teunissen et al. (2014)
	10.0	India	Bhatia et al. (2011);Singh et al. (2015)
	6.7	Nigeria	Muthir and Nyango (2010)
	3.7	USA	Grunloh et al. (2013)
	0.3	Australia, Finland, France, Norway, Sweden,UK	Apter et al. (2016)
Amenorrhoea	4.5	India	Bhatia et al. (2011)
	1.1	Spain	Arribas-Mir et al. (2009)
	0.1	USA	Grunloh et al. (2013)
Menorrhagia	12.4	Spain	Arribas-Mir et al. (2009)

	10.0	Nigeria	Muthir and Nyango (2010)
	3.7	Australia, Finland, France, Norway, Sweden,UK	Apter et al. (2016)
	3.4	India	Singh et al. (2015)
Heavy/prolonged bleeding	60.7	SA	Pillay et al. (2017a)
	36.0	Ethiopia	Burusie (2015)
Pain in arm	7.3-15.1	Ethiopia	Siyoum et al. (2017); Burusie (2015); Asaye et al. (2018)
	6.3	Nigeria	Ezegwui et al. (2011)
	3.0	Egypt	Aziz et al. (2018)
	1.1	UK	Smith and Reuter (2002)
	0.3	USA	Grunloh et al. (2013)
Abdominal pain	1.1	UK	Smith and Reuter (2002)
	0.4	USA	Berlan et al. (2016)
Low sex drive	1.3	Australia, Finland, France, Norway, Sweden,UK	Apter et al. (2016)
	1.1	UK	Smith and Reuter (2002)
Prolonged bleeding	16.7	Nigeria	Muthir and Nyango (2010)
	9.9	Egypt	Aziz et al. (2018)
	6.36	India	Singh et al. (2015)
Pregnancy	1.6-5.3	SA	Pillay et al. (2017a); Mrwebi et al. (2018)

ADR=Adverse drug reaction, SA=South Africa, UK=United Kingdom, USA=United States of America

[1] Calculated as reason for discontinuation/Total women

Table 2-8: Summary of studies reporting common non-adverse drug reaction reasons for etonogestrel implant discontinuation

Reason for discontinuation	Percentage (%)[1]	Region	Reference
Desire to conceive	16.0-42.9	Nigeria	Pam et al. (2014); Muthir and Nyango (2010); Ezegwui et al. (2011)
	6.2-24	Ethiopia	Tadesse et al. (2017); Birhane et al. (2015) ; Siyoum et al. (2017); Asaye et al. (2018); Burusie (2015)
	12.4	Spain	Arribas-Mir et al. (2009)
	7.1	Malaysia	Mastor et al. (2011)
	7.0	Netherlands	Teunissen et al. (2014).
	4.3-4.9	SA	Mrwebi et al. (2018); Pillay et al. (2017a)
	3.6	Switzerland	Bitzer et al. (2004)
	0.2-3.4	USA	Sznajder et al. (2017) Grunloh et al. (2013)

	3.4	Australia	Harvey et al. (2009)
	3.0	Egypt	Aziz et al. (2018)
	3.0	Europe	Short et al. (2014)
	1.5-2.1	UK	Lakha and Glasier (2006); Smith and Reuter (2002)
	1.0	Australia, Finland, France, Norway, Sweden,UK	Apter et al. (2016)
	0.9-1.0	India	Singh et al. (2015); Bhatia et al. (2011)
Patient or partner sterilized	2.9	Malaysia	Mastor et al. (2011)
	1.1	UK	Smith and Reuter (2002)
Chose to switch to another contraceptive	12.2	Netherlands	Teunissen et al. (2014)
	11.9	Nigeria	Pam et al. (2014)
	4.5	Ethiopia	Birhane et al. (2015)
	3.0	Europe	Short et al. (2014)
	1.4	Malaysia	Mastor et al. (2011)
Continuation with new implant	39.3	Spain	Arribas-Mir et al. (2009)
	25.2	Switzerland	Bitzer et al. (2004)
Contraception no longer required	3.3	Nigeria	Muthir and Nyango (2010)
	2.1	Australia	Harvey et al. (2009)
	2.0	Egypt	Aziz et al. (2018)
	1.1	Spain	Arribas-Mir et al. (2009)
	0.9	Nigeria	Pam et al. (2014)
	0.1	US	Grunloh et al. (2013)
Partner opposition	2.5-9.2	Ethiopia	Birhane et al. (2015);Tadesse et al. (2017); Asaye et al. (2018)
	1.8-6.7	Nigeria	Pam et al. (2014); Muthir and Nyango (2010)
Method failure	3.3	Nigeria	Muthir and Nyango (2010)
	0.8	Ethiopia	Birhane et al. (2015)
Inconvenience	1.2-8.8	Ethiopia	Birhane et al. (2015); Tadesse et al. (2017)
Religious opposition	0.8-3.8	Ethiopia	Birhane et al. (2015); Tadesse et al. (2017)
Divorce/no longer in relationship	3.3	Nigeria	Muthir and Nyango (2010)
	2.0	Ethiopia	Asaye et al. (2018)
	0.3	UK	Lakha and Glasier (2006)
Husband travelling	1.6	Egypt	Aziz et al. (2018)
	1.4	Ethiopia	Asaye et al. (2018)
Discontinued due to implant expiry	25	Spain	Arribas-Mir et al (2009)
	4.2	Nigeria	Pam et al. (2014)
	1.1	SA	Mrwebi et al. (2018)

SA=South Africa, UK=United Kingdom, USA=United States of America

[1] Calculated as reason for discontinuation/total women

2.4.5 Contraceptive method failure

Contraceptive failure is defined as:

> "*a conception that occurred during a month in which a woman (or her partner) was using a contraceptive method, as long as she did not report that she (or he) had stopped use before having become pregnant*" (Fu, Darroch, Haas, & Ranjit, 1999:57).

In the developing world, 30% of the 74 million unwanted pregnancies that occur annually are due to failure of traditional or modern contraceptive methods (Polis et al. 2016), with Implanon® being a highly efficacious modern contraceptive, with a 0.05% failure rate in typical and perfect use (Trussell, 2011).

The Pearl Index is used to report efficacy and is calculated using the "*expected number of pregnancies per100 woman-years of exposure*" (Darney et al. 2009:1648). A woman year is defined as "*a period of 365.25 days and this is the equivalence of roughly 13 cycles*" (Pam et al. 2014:93). A study by Darney et al. (2009) on an Implanon® clinical trial study reported that: six pregnancies occurred during the clinical trials, resulting in a 0.38 cumulative Pearl Index. The pregnancies occurred within two weeks of discontinuation of Implanon® and, according to the FDA, any pregnancy within this time of a hormonal method is considered contraceptive method failure. The manufacturing company recorded 1 688 spontaneous pregnancies over a nine-year period, therefore resulting in a post-marketing Pearl Index of 0.024, which was based on voluntary reports. Additionally, the clinical trial did not include participants who weighed more than 130% of their ideal body weight and who were using enzyme inducing drugs, these variables having been shown to affect Implanon® efficacy. The incidence of reported pregnancies in a study by Bensouda-Grimaldi, Jonville-Bera, Beau-Salinas, Llabres, and Autret-Leca (2005) is estimated to be $0.359/10^3$ implants, and the estimated Pearl Index was 0.06. The approximate failure rate in the post-marketing phase in Australia is 0.1%, or 1 in 1000 insertions (Harrison-Woolrych & Hill, 2005). Similarly, the contraceptive method failure rate in the USA monitoring program was 0.17% (Creinin et al. 2017). The incidence of pregnancy in studies from Africa was low as shown in Table 2-9 (Tadesse et al. 2017; Pam et al. 2014; Muthir & Nyango, 2010) with the exception of Patel et al. (2015) who reported a total of 86 pregnancies in their study. The average time of onset of pregnancy in a French post-marketing study (n= 104) was 13 months (median 10.7 months) (Simon et al. 2016). Three pregnancies occurred in the first year of etonogestrel implant use and three in the second year in a USA monitoring program (Creinin et al. 2017).

Evidence from the literature in Table 2-9 indicates that pregnancies with etonogestrel implants can be due to reasons other than true contraceptive method failure. A notable reason for pregnancy, as established in several studies, was pregnancy prior to insertion. Practitioner-related reasons for pregnancy, such as insertion technique failure, and untimely insertion (Bensouda-Grimaldi et al. 2005; Harrison-Woolrych & Hill, 2005), were also cited. User-dependent reasons for pregnancy were noted in only two cases and included improper use of implant (Creinin et al. 2017) and unprotected sexual intercourse practiced in the first week of insertion (Obijuru et al. 2016). In studies from Africa, pregnancy was due to drug interaction, contraceptive method failure and pregnancy prior to insertion as highlighted in Table 2-9 Tadesse et al. 2017; Pam et al. 2014; Muthir & Nyango, 2010; Patel 2015).

One of the most common reasons for pregnancy was due to drug interaction with antiepileptics, ARVs, antituberculosis and St. John's wort (Simon et al. 2016, Harrison-Woolrych & Hill, 2005). While some studies have reported pregnancy in etonogestrel implant use (Olowu, Karunaratne, & Odejinmi, 2011; Rezai et al. 2018; Bouquier et al. 2012), others have particularly reported on failure of Implanon® in patients using efavirenz based therapy (Matiluko et al. 2007; Leticee, Viard, Yamgnane, Karmochkine, & Benachi, 2012; McCarty, Keane, Quinn, & Quah, 2011; Lakhi & Govind, 2010). Patel et al. (2015) revealed a three times higher risk of implant contraceptive failure in efavirenz than nevirapine users.

Implanon NXT® efficacy may be affected by body mass index (BMI) however, there are contradicting arguments on this issue. The etonogestrel plasma levels is inversely related to body weight hence variations in serum concentration levels is possibly due to differences in body weight (Merck Sharp & Dohme, Australia, 2010). Creinin et al. (2017) suggested that BMI may influence failure and reported failure in one patient who was normal weight, two who were overweight and two who were obese. However, these results are insufficient to make a conclusion about possible effect of BMI on Implanon NXT® effectiveness. Xu et al. (2012) commented that one unwanted pregnancy over 1377 women-years resulted in an overall cumulative implant failure rate of 0.00 per 100-woman years, and 0.23 per 100-woman years in obese patients (2012). Mornar et al. (2012) also established that the estimated etonogestrel exposure for obese women in a three-year period was found to be 40% lower than in those of normal weight. Projected plasma concentrations at one, two and three years after device insertion in the obese women were 133, 102, and 98 pg/mL respectively (2012). The projected etonogestrel concentrations for the third year was still above 90 pg/ml, which is an effective concentration to suppress ovulation. It is therefore evident that increased weight could be a factor in the contraceptive failure due to Implanon NXT®.

Table 2-9: Possible causes of pregnancy in etonogestrel implant use

Possible cause	Frequency (n)	References
Drug interaction	59	Simon et al. (2016)
	57	Patel et al. (2015)
	32	Australian Government (2010)
	32	Commonwealth of Australia (2007)
	8	Harrison-Woolrych and Hill (2005)
	4	UK-MHRA (2014)
	2	Bensouda-Grimaldi et al. (2005)
	2	Lakhi and Govind (2010)
	2	Leticee et al. (2012)
	1	Gbolade (2010)
	1	Lange, Teal, and Tocce (2014)
	1	Matiluko et al. (2007)
	1	McCarty et al. (2011)
	1	Patni, Ebden, Kevelighan, and Bibby (2006)
	1	Schindlbeck, Janni, and Friese (2006)
Method failure	13	Harrison-Woolrych and Hill (2005)
	6	Creinin et al. (2017)
	6	Darney et al. (2009)
	2	Boucoiran, Trastour,Faraj,Delotte and Bongain (2011)
	2	Tadesse et al. (2017)
	1	Bensouda-Grimaldi et al. (2005)
	1	Muthir and Nyango (2010)
	1	Pam et al. (2014)
Insertion technique failure	203	Simon et al. (2016)
	84	Harrison-Woolrych and Hill (2005)
	30	Bensouda--Grimaldi et al. (2005)
Pregnant prior to insertion	71	Simon et al. (2016)
	46	Harrison-Woolrych and Hill (2005)
	6	Pam et al. (2014)
	4	Creinin et al. (2017)
	3	Robinson, Register, Ebner, and Orr (2015)
	2	Bahamondes et al. (2015)
	2	Muthir and Nyango (2010)
	2	Obijuru et al. (2016)
	2	Sznajder et al. (2017)
	1	Cooling and Pauli (2006)
	1	Devonald (2006)

2.5. Challenges reported with the use of Implanon NXT® in South Africa

There are some specific challenges that have emerged regarding the use of Implanon NXT® in SA.

2.5.1 Training of health practitioners

Insufficient training of health practitioners on Implanon NXT® has been emphasized in a SA study, with the following excerpts from Adeagbo et al. (2017:823) concisely capturing the severity of the lack of training:

> *"We were only trained for two days. I feel like the training was not sufficient. I think I need intense trainings in order for me to deliver the service effectively." (Professional nurse H, DKKD)*

"We had some trainings and we were shown how to insert and remove the implant and each clinic was expected to do that. It was like a once-off thing" (Professional nurse E, CoJ) "I was trained by another professional nurse, I would really not call it a proper training honestly"

Health practitioners felt ill-equipped to provide the method to patients, which directly affected the quality of service due to insufficient knowledge, poor skills and lack of understanding of the insertion method (2017). Practitioners were weary to perform the procedure due to concerns about complications, concern about the time it would take, and the impact of these aspects on their daily duties (2017). Special training on insertion and discontinuation is suggested to ensure a steady release of etonogestrel and a smooth discontinuation (Lee, 2010).

Training on drug interactions has also been identified as an added concern (Pleaner et al. 2017), while Lince-Deroche et al. (2016) reported the lack of understanding on drug-drug interactions and concerns about appropriateness of method for women. An ongoing qualitative study from the Western Cape Province revealed that health practitioners are concerned about inserting implants in all HIV positive patients, regardless of their treatment status (Patel et al. 2017). Additionally, a lack of understanding about and difficulty communicating information on drug interactions to patients, and the potential negative medical and legal outcomes from concomitant use, have been raised as practitioner concerns (2017). This has resulted in unnecessary discontinuation or practitioners not offering the method (Pleaner et al. 2017).

2.5.2 Counselling of implanon NXT® users

A challenge for practitioners was counselling patients, which was found to be inadequate (Adeagbo, 2017). This was expressed by Potgieter et al. who provided evidence that:

> *"Poor communication and reluctance from clinic staff to discuss ImplanonNXT® during antenatal visits contributed to poor knowledge about the implantable device and its side effects" (2018:174).*

According to the contraception counselling guidelines, method-specific counselling should include: common ADRs, how to use the method, when and why to return for follow-up, and when the use of dual protection was appropriate (Republic of South Africa, National Department of Health, 2013). Pillay et al. (2017a) noted that less than half of users and discontinuers were counselled on the effectiveness of Implanon NXT®, its safety, palpability and preventing STIs at the initial consult. Approximately half of the women in the same study were counselled on its ADRs and when to return for discontinuation, and approximately two thirds were counselled on duration of use (2017a). Similarly, in Ethiopia, not all women were counselled on ADR, the benefits of Implanon®, and the duration of its action and effectiveness (Siyoum et al. 2017; Birhane et al. 2015; Asaye et al. 2018). A study conducted in a Brazil investigated the effect of counselling styles on discontinuation rates and revealed that routine counselling is adequate to help reduce premature discontinuation rates (Modesto, Bahamondes, & Bahamondes, 2014). A study investigating different counselling styles found a majority in both groups felt they received enough information, and most were happy with their decision (Rubenstein, Rubenstein, Barter, & Pittrof, 2011). The "cautious" group had higher continuation rates at one year (96%) compared to the "just try it" group (80%) (2011). It appears that different counselling styles could be adopted in practice to achieve high continuation rates.

An additional challenge is the health practitioners' negative attitudes towards the method, which is concerning, as it could interfere with counselling patients (Adeagbo et al. 2017). The following excerpt from Adeagbo et al. sheds light on practitioner's perception of Implanon NXT®:

> *"To tell you the truth, lately, I hardly suggest Implanon unless a client wants it" (Professional nurse H, DKKD) "I wouldn't go for it. I would stick to the known method – the pill or the injection. They've been around forever … I don't think it's [Implanon NXT] working, honestly, because of the removals we are doing and they [users] will tell you that they will never go for this method again" (Professional nurse B, DKKD)(2017:825)*

Nurses plays a central role in contraceptive choice, provision and continuation in the public health sector in SA (Lince-Deroche et al. 2016) hence counselling of Implanon NXT® is a crucial gap in the implementation and success of Implanon NXT®.

2.5.3 Management of adverse drug reactions

Managing ADRs has been identified as a challenge for health practitioners in SA (Adeagbo et al. 2017), with those experiencing ADRs having reportedly opted for discontinuation due to inefficient treatment options (2017). While there were no standardized guidelines for ADR management prior to 2018, the SA Standard Treatment Guideline 2018 recommends oral contraceptives for breakthrough bleeding (Republic of South Africa, National Health Department, 2018b). However, Pillay et al. (2017a) identified that oral contraceptives to treat bleeding only provided short-term relief, therefore there may still be a gap in the management of menstrual ADRs. Other options to manage frequent and/or prolonged bleeding may be the use of mifepristone plus ethinyl estradiol and doxycycline alone (Weisberg et al. 2006). An algorithm for treating prolonged, frequent and/or menorrhagia with Implanon® was proposed by Adams and Beal (2009). It includes using bleeding diaries and treatment with COC or low dose oestrogen or doxycycline or non-steroidal anti-inflammatory drugs (2009). Another area of concern is that there is still no recommended management of non-menstrual ADR of Implanon NXT® in SA, except for pain after insertion (Republic of South Africa, National Department of Health, 2018b). The challenges and barriers related to usage of Implanon® are not well known (Prosad, Mashamba-Thompson, & Ojewole, 2018) hence S Prosad is undertaking a scoping review, which is aimed at mapping evidence on patients' challenges and barriers linked to its use.

2.6 Conclusion

This chapter provided a detailed description of etonogestrel implants including Implanon NXT®, contextualized the experiences related to their use, and described the challenges reported in SA in particular. This literature review demonstrated that ADRs, discontinuation and failure with etonogestrel implants including Implanon NXT® are problematic globally. Although experiences are common, SA possesses contextually unique reasons for the use and discontinuation of Implanon NXT® related to disease profile and cultural factors. There is no definite trend about ADR profiles, specifically bleeding patterns. A significant proportion of etonogestrel implant failure is due to technique and prescribing issues. It was also acknowledged that there is a paucity of evidence on women's experiences regarding Implanon NXT® in SA compared to etonogestrel implant studies globally.

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CHAPTER 3: SUBMITTED MANUSCRIPT

3.1 Introduction

Chapter three highlights the following manuscript that was submitted to an international peer reviewed journal:

Prosad S, Ojewole E, Dheda M & Tlou B 2018. Adverse drug reactions and discontinuation of Implanon NXT® among users at public health facilities in South Africa. The European Journal of Contraception and Reproductive Health Care. Submitted manuscript. Reference number: DEJC-2018-0138.R1

This chapter is presented in the format stipulated by the author guidelines of the journal and is the revised version. The copies of the manuscript submission letters are attached as annexure 5.

This is the first manuscript based on the data generated in this study and presents the significant findings.

3.2 Submitted Manuscript

Adverse drug reactions and discontinuation of Implanon NXT® among users at public health facilities in South Africa.

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Adverse drug reactions and discontinuation of Implanon NXT® among users at public health facilities in South Africa.

Abstract

Purpose: Discontinuation of Implanon NXT® in South Africa is concerning, however, national data on its surveillance is lacking. This study quantified adverse drug reactions and evaluated Implanon NXT® discontinuation.

Methods: Secondary data analysis was performed using 3743 cases obtained from South African National Pharmacovigilance Centre for Public Health Programmes. Demographics, patient history, adverse drug reactions and discontinuation details were extracted and analysed using SPSS® version 25. Tests of association were performed and univariable and multivariable models were used to identify factors associated with Implanon NXT® discontinuation.

Results: The frequently reported adverse drug reactions were menorrhagia (52.01%; 712/1369), headache (20.45%; 280/1369) and dizziness (11.18%; 153/1369). Discontinuation of Implanon NXT® was reported by 63.56% (2379/3743) of cases and early discontinuation by 81.1% (1210/1492). Experience of adverse drug reactions was associated with Implanon NXT® discontinuation (AOR= 11.98, CI: 8.10-17.72, $p<0.001$). Discontinuation was mainly due to adverse drug reactions (83.99%; 1784/2124). Pregnancy was reported by 4.97% (68/1369) cases. Almost a third were on efavirenz and was suspected to be associated with pregnancy ($p<0.001$).

Conclusion: Implanon NXT® discontinuation due to adverse drug reactions was identified in this study. efavirenz-based therapy could have resulted in pregnancy among Implanon NXT® users. Rigorous screening and monitoring should be applied to prevent user discontinuation.

Keywords: Implanon NXT®, adverse drug reaction, user discontinuation, reasons for discontinuation, pregnancy

Introduction

Studies conducted at various countries worldwide have reported that approximately a quarter of users remove their Implanon® within 12 months [1, 2, 3]. In Ethiopia, the overall proportion of early discontinuations ranged from 16% to 80% [4, 5, 6, 7]. The overall proportion of discontinuations ranged from 4.48% to 21.36% as reported in studies from Nigeria [8, 9]. Adverse drug reactions (ADRs) especially bleeding pattern changes have been reported globally [10, 11, 12, 13]. ADRs is the primary reason for Implanon® discontinuation among users [2, 14, 15, 16]. Experience of ADRs is a factor associated with early discontinuation of Implanon NXT® in Africa [5, 6, 7]. Recently, there were reports of early Implanon NXT® discontinuation among users in South Africa (SA) [17, 18, 19, 20]. There were 820 Implanon NXT® removed as at December 2014 [21], however this figure has increased to about 5000 Implanon NXT® in April 2015 [19]. The demand for discontinuation of Implanon NXT® resulted in the public questioning the safety and efficacy of the product [21]. The efficacy of the use of Implanon NXT® in women on antiretroviral therapy has been raised as a concern in SA [21, 22]. The negative experiences highlighted in SA studies were ADRs, early Implanon NXT® discontinuation and Implanon NXT® failure. Moreover, one SA study reported that the use of concomitant drugs namely antiretroviral (ARV), antipsychotics and antituberculosis drugs necessitated the discontinuation of Implanon NXT® [20].

Poor monitoring of Implanon NXT® discontinuations has resulted in the true extent of discontinuations being unknown [19, 21]. There is a lack of evidence on ADRs of Implanon NXT®, frequency and reasons for discontinuation in SA [19, 20, 21, 23]. Clearly, a need still exists to quantify the experiences of Implanon NXT® users in terms of ADR, discontinuation and reasons for discontinuation particularly at the national and provincial level.

The aim of this study was therefore to quantify ADRs and evaluate discontinuation of Implanon NXT® among users in SA by analysing secondary data collected from a national pharmacovigilance database. The objectives included: quantifying ADRs of Implanon NXT®, determining the frequency of Implanon NXT® discontinuation,determining

factors associated with Implanon NXT® discontinuation and identifying reasons for Implanon NXT® discontinuation.

Methods

Study design

Secondary data analysis was conducted using data obtained from the National Pharmacovigilance Centre (NPC) in SA. The NPC carried out surveillance where case forms were completed by clinicians prior to insertion and discontinuation of Implanon NXT® and report of ADR. The use of secondary data provided a large sample size and population-level data for the study [24, 25, 26].

Data set

The entire data set was analyzed in this study. A total of 3743 case reports that were submitted to the Subdermal Implant National Surveillance Programme from 1 April 2015 to 11 September 2017 were included in the secondary analysis. All variables related to counselling, laboratory test results and clinicians on the case reports were excluded as it fell out of the scope of this study. Full ethical approval for the study was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE266/17), and permission to use the raw data set was obtained from the NPC.

Data extraction, data processing and data validation

Data was extracted from all the 3743 case reports. Variables describing demographics, patient history, ADR discontinuation and reasons for discontinuation were extracted from the raw data. The main outcomes measured and extracted from the dataset were ADR, discontinuation, premature discontinuation, reasons for discontinuation and pregnancy. Cases extracted per outcome included: ADR (36.57%; 1369/3743), discontinuation (63.56%; 2379/3743), premature discontinuation (81.1%; 1210/1492), reason for discontinuation (56.75%; 2124/3743) and pregnancy (4.97%;68/1369). Multiple ADRs and reasons for discontinuation could be reported per case resulting in total ADRs reported and total reasons for discontinuation calculated as n=2120 and n=2590 respectively. Pregnancy, which is classified as an ADR in the raw data, was used to

evaluate Implanon NXT® failure. Premature discontinuation was defined in this study as discontinuation of Implanon NXT® less than 36 months' post-insertion and was calculated using the difference between date of insertion and date of discontinuation. Not all cases reported insertion and discontinuation dates therefore the sample size used for premature discontinuation is n=1492. Case reports which reported a discontinuation date or a reason for discontinuation were used to calculate the frequency of user discontinuations regardless of early discontinuation. Data processing was conducted for the following additional variables using elements from the raw data and other sources [27, 28, 29, 30, 31]: Health facility type, level of health care, level of urbanisation and body mass index (BMI). Data was then cleaned by identifying and correcting incomplete and inaccurately captured extracted cases. The extracted data was checked for missing case reports and blank cells were identified for missing data. Validation of data extraction was performed by randomly selecting 10% of cases to cross-check with the raw data.

Statistical Analysis

Data was exported from Microsoft Excel 2016 to SPSS® version 25 for analysis. All 3743 case reports were included in analysis. Descriptive analysis was performed, and results presented as frequencies, percentages, measure of central tendency and measure of variability. A 95% Confidence Interval (CI) was used to estimate the population values. CI limits of a proportion was calculated on an online calculator using the Wilson procedure without a correction for continuity [32]. The Pearson's Chi square test and Fischer's Exact Test were performed to test associations between demographics and ADR. A p-value of less than 0.05 was considered statistically significant. Univariable and multivariable binary logistic regression was conducted to identify factors associated with Implanon NXT® discontinuation. The odds ratios, 95% CI and p-values were calculated and a $p<0.05$ was used to identify independent variables that were significantly associated with Implanon NXT® discontinuation. The multivariable model eliminated the confounding variables and identified variables significantly associated with discontinuation of Implanon NXT®.

Results

A total of 3743 case reports were analysed of which 22.26% reported insertion of Implanon NXT® and 63.56% reported discontinuation of Implanon NXT®. Cases which reported only ADRs were 6.06% (227/3743) and only reported demographic information were 8.12% (304/3743). Fifty percent of case reports reported age below 26 years (Interquartile range (IQR)=10 years; 95% CI: 27.09-27.58). Majority of the case reports were received from urban areas in SA (Table 1) [Table 1 near here]. Almost half of the cases were parity ≥1 (48.89%;1830/3743) and 47.58% (1781/3743) reported gravidity ≥1. Previous contraceptive use was reported in 44.30% (1658/3743) of cases and 1.3% (48/3743) reported no previous contraceptive use. The remaining case reports did not report on previous contraceptive use. A third (33.58%;1257/3743) reported previously using the injection. Fifty percent of the cases reported weight above 66kg (IQR=25.15kg; 95% CI: 68.71-70.08) and the median BMI was calculated as 26.01 kg/m^2 (IQR=9.67; 95% CI: 27.05-28.85). The highest reported concomitant condition was HIV/AIDS (10.23%, 383/3743). The most reported concomitant drugs were: ARV (6.01%, 225/3743), antihypertensives (0.0067%, 25/3743), antituberculosis drugs (0.0032%; 12/3743) and antiepileptic drugs (0.0021%; 8/3743). efavirenz (4.62%,173/3743), tenofovir (4.35%, 163/3743) and emtricitabine (4.22%,158/3743) were the most frequently reported ARVs. There were 4.9% (185/3743) of the cases who reported breastfeeding while using Implanon NXT®.

There were 457 cases which experienced two to four ADRs and 20 cases experienced five or more ADRs. The onset of ADR was higher in the first year of Implanon NXT® use than in the second and third year of use. The median and IQR for time between onset of ADR and the report of ADR was 91 days and 290 days respectively (95% CI: 191.30-235.24). The commonly reported ADRs (n=1369) included: menorrhagia (52.01%), headache (20.45%), dizziness (11.18%) and irregular menstruation (8.11%) (Table 2) [Table 2 near here]. The Pearson Chi Square test was performed to associate age and commonly reported ADR. Headaches ($p=0.039$) and menorrhagia ($p<0.001$) were found to be associated with age. Reports of headache and menorrhagia increased with advancing age up to 44 years.

The median time between report of ADR and discontinuation of Implanon NXT® was 0 days (IQR=29 days; 95% CI: 45.25-65.30). The median and IQR for the duration of Implanon NXT® use was reported as 573 days and 595 days respectively (95% CI: 605.07-642.37). Implanon NXT® was discontinued prematurely in 81.1% (1210/1492) of cases. Implanon NXT® was removed more frequently in the 2nd year of use which accounted for 35.79% (534/1492) of cases. Parity, gravidity, age, BMI and cases who reported ADR were found to have a statistically significant association with Implanon NXT® discontinuation (Table 3) [Table 3 near here]. After adjusting for parity, gravidity, age and BMI, cases which reported ADR were 11.98 times more likely to remove Implanon NXT® than those who did not report ADR ($p<0.001$). Parity, gravidity, age and BMI were not associated with discontinuation of Implanon NXT® in the adjusted model. Age was marginally significantly associated with Implanon NXT® discontinuation ($p=0.055$). Those who were overweight (AOR= 0.83) and obese (AOR=1.19) were less likely to remove Implanon NXT® than those who were underweight (AOR=1.71) however this finding was not statistically significant ($p=0.211$).

Reasons for discontinuation due to ADR accounted for 83.99% (1784/2124) and other reasons accounted for 37.95% (806/2124) (Table 4) [Table 4 near here]. Not all ADR reported were reasons for discontinuation (2120 vs. 1784) e.g. 280 cases reported headache (Table 2) but only 218 cases reported headache as a reason for discontinuation (Table 4). There were 16.95% (360/2124) of cases who reported more than one reason for discontinuation. The most commonly reported reasons for discontinuation (n=2124) included: menorrhagia (34.27%), expiry after three years of use (29.57%), headache (10.26%) and desire to conceive (5.93%).

There were 4.97% (68/1369) of pregnancy cases reported with concurrent Implanon NXT® use. Of these, two indicated that users may have been pregnant at the time of insertion and three indicated possible drug interaction with concurrent ARV use. The Fischer Exact Test was performed to associate pregnancy and age and a statistically significant association was found ($p=0.011$). Pregnancies were more frequently reported by 30-34-year olds (28.36%; 19/67) followed by 25-29-year olds (23.88%, 16/67) and 35-39-year olds (20.90%, 14/67). An association between efavirenz users and non-users

against cases reporting pregnancy was tested using the Fischer Exact Test. A statistically significant association between Implanon NXT® users on efavirenz-based therapy and pregnancy was found ($p<0.001$). There were 29.41% (20/68) of pregnancy cases using efavirenz-based therapy. Over a quarter (27.94%, 19/68) of pregnancy cases also reported greater than normal BMI, however, BMI and pregnancy was not statistically significant ($p=0.468$).

Discussion

Findings and Interpretation

All age groups of women of reproductive age were represented in this study but 20-24-year olds were the most frequent. Expected menstrual and non-menstrual ADR were commonly reported. Menorrhagia appears to be a distinctive ADR experienced in SA as menorrhagia was reported by more than half of the cases. Almost a tenth of ADRs (9.06%;124/1369) found in this study were not listed on the Implanon NXT® product leaflets [33, 34] and Implanon® prescribing leaflet [35]. Although unlisted, these ADRs may warrant further investigation to determine if they are associated with Implanon NXT® use. Older aged Implanon NXT® users were more prone to experience menorrhagia and headache suggesting that age of users influences experience of certain ADR. Fifty percent of users who reported ADRs to a clinician removed Implanon NXT® on the same day. This suggests that ADRs were intolerable and discontinuation was therefore requested. On the other hand, it also suggests that treatment and management of ADRs were not accepted by users or not encouraged by clinicians. Early discontinuation of Implanon NXT® has been highlighted in this study (81.1%; 1210/1492). Discontinuation of Implanon NXT® was mainly due to experience of ADR but independent factors such as expiry and desire to conceive were also reasons for discontinuation. The proportion of pregnancies reported while using Implanon NXT® was 4.97% (68/1369). The reason for pregnancy could not be determined in most cases due to limited details provided. Possible reasons for pregnancy could be due to conception before insertion of Implanon NXT® and drug-drug interactions. Efavirenz-based antiretroviral therapy was found to be associated with pregnancy. The concomitant use of these drugs is of concern as efavirenz is a widely used drug to treat HIV in SA.

Strengths and Weaknesses of the Study

A large sample size was included for analysis in this study. A national pharmacovigilance database was used as a source of data which provided 'real-world' evidence on experiences of Implanon NXT® users. A limitation of the study was missing data and incomplete case reports. A secondary data set was used as the source of data for this study therefore the principal investigator did not have control over the primary data collection. Underreporting on variables may have affected the outcome of study results. A small sample was used to associate pregnancy and ARV agents which could limit significance of result. There may have been gaps in the monitoring system as reporting was not rigorously monitored as is done in other study designs such as clinical trials. According to the standard operating procedure, serious adverse events were to be reported directly to the NPC and this may have resulted in exclusion of serious ADR from the study.

Similarities and differences in relation to other studies

The results from this study varied with results from SA and international literature but there were a few similar findings. The common ADR identified in this study were consistent with the ADR found in local [17, 18, 20] and international studies [10, 11, 36, 37] but proportions of ADR differed. A SA study by Mrwebi et al. [20] reported lower proportions of the commonly reported ADR found in this study namely: menorrhagia, headache, back pain, weight gain, weight loss, dizziness and abdominal pain. In this study, menorrhagia was reported at a higher frequency compared to other studies [18, 36]. Irregular bleeding and amenorrhoea were more frequently reported in continental and international literature [10, 38, 39, 40]. Headache was reported at a lower proportion in several studies [10, 40][2] and weight gain was reported at higher proportions in studies [10, 11, 40]. Some of the unlisted ADR have been reported in research articles such as abdominal bloating [39], dyspareunia [41, 42], painful lower limbs [42], weakness [42], weakness in arm [11], swollen vagina [10], abdominal distention [7], anaemia [43], and varicose veins [42]. There is contradicting evidence on the effect of age on ADR experienced with Implanon NXT®. Berenson et al [41] found that older etonogestrel users were more likely to experience menorrhagia however, Casey et al [13] found no association between age and reported bleeding. There is limited research on the effect of age on non-menstrual ADR of Implanon NXT® but one study on contraceptive implants

found side effect incidence not significantly associated with age [44]. A higher percentage of premature discontinuations was reported in this study compared to Ethiopian studies which cited 65% [5] and 46.5% [6] of early discontinuers. Internationally, lower discontinuation rates were reported with 47% of discontinuers within three years [12], 26.8% of discontinuers within 12 months [2] and 35% of discontinuers within 32 months in adolescents [45]. In the clinical trials of Implanon NXT®, 35% discontinued due to an ADR and more frequently due bleeding irregularities [46]. ADR is a factor associated with discontinuation of Implanon NXT® in Africa [5, 6, 7]. In addition, ADR is predominantly the reason for Implanon NXT® discontinuation [5, 6, 18, 20, 47]. Discontinuation due to menorrhagia was reported at comparable proportions in some studies [4, 18] and at a higher proportion in one studies [3]. Discontinuation due to irregular bleeding [48] discontinuation due to painful arm [4, 5, 6] and discontinuation due to headache and weight gain [5, 6, 18, 49] were reported at higher proportions in other studies. Geographic location and demographic profile are factors associated with Implanon NXT® discontinuation and this may be a reason for the difference in the above findings [3, 49]. While one study [50] reported lower number of pregnancies with Implanon® as compared to the present study, other studies have reported higher frequency of pregnancy [11, 51]. Similar to this study, a South African article reported a significant proportion of participants who fell pregnant while using Implanon NXT® (5.3%) [20]. Some reasons for pregnancy provided in studies included: inefficient etonogestrel levels, incorrect timing of insertion, non-insertion, pregnant at time of insertion and use of enzyme inducing medication [11, 50, 51] The study conducted in the United States found that 4 of the 6 cases reporting method failure had a BMI of above normal range [50]. The enzyme inducing drugs resulting in pregnancy included antiepileptics, ARVs, antituberculosis drugs and herbal medication [11, 51]. Efavirenz-based therapy has been associated with a reduction in etonogestrel bioavailability which impairs contraceptive efficacy in HIV patients [52, 53, 54]. A study in Kenya found that efavirenz-based therapy had a three times higher risk of implant failure than nevirapine-based therapy [55]. Similar to this study findings, pregnancy was found in Implanon NXT® users on efavirenz therapy [11, 55, 56, 57, 58]. However, some studies found no failures with concurrent Implanon NXT® and efavirenz use [56, 59]. The abovementioned studies show contradicting evidence on efavirenz use in Implanon NXT® users.

Relevance of the findings: Implications for clinicians and policymakers

Interventions need to be applied in clinical practice to alleviate this problem and ensure higher continuation rates of Implanon NXT®. The initial counselling visit is crucial to assess if Implanon NXT® is a viable option for the patient. Additional counselling on increased risks need to be provided to patients using concomitant enzyme-inducing drugs. Additional non-hormonal contraception must be offered to these patients to prevent pregnancy. Clinicians can target their pre-insertion counselling includes expectations of ADR and inform patients on the procedure to address them. A regular follow-up schedule should be applied as onset of ADR were experienced in the first year of utilization and discontinuation was common in the second year of utilization. These follow-ups should include: report of any ADR, treatment of ADR and assessment of the insertion site for any abnormalities.

Open questions and Future research

True contraceptive method failure could not be established in this study due to insufficient information provided by cases reporting pregnancies. Additional information such as date of conception in relation to insertion date, timing of insertion, etonogestrel concentration levels must be provided to establish the reason for failure. An investigation study on ARV based therapy in Implanon NXT® users particularly in SA may be necessary to confirm an association between the drugs. It may be useful to identify differences between ADRs experienced among provinces and further explore differences in ADRs among age groups to provide interventions in needy demographics. It is unclear whether advice and treatment options for ADR management was not well received by users or whether it was not encouraged by clinicians. Further investigation needs to be conducted to identify the reason for those who removed their implanon NXT® rather undergo treatment for ADRs. Aspects related to counselling and clinicians were not included in this study, therefore interventional studies on counselling and management practices of Implanon NXT® may be conducted. The design of a follow-up protocol and a standardised algorithm for Implanon NXT® ADR management is necessary to ensure patients receive effective and high-quality care.

Conclusion

This study determined a high frequency of early Implanon NXT® discontinuation at a national level. ADR was identified as the main factor associated with Implanon NXT® discontinuation. A possible association between efavirenz- based therapy and pregnancy in Implanon NXT® users was found. Interestingly, a small proportion reported pregnancy while on Implanon NXT®. Thorough screening and rigorous monitoring of users should be performed in practice to prevent user discontinuation.

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Declaration of interest statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1: Demographics of Implanon NXT® cases reported in South Africa (N=3743).

	Number of cases	Percentage (%)	Confidence Interval (95%)
Age (years)			
<15	32	0.85	0.60-1.20
15-19	469	12.53	11.51-13.63
20-24	962	25.70	24.33-27.12
25-29	886	23.67	22.34-25.06
30-34	627	16.75	15.59-17.98
35-39	354	9.46	8.56-10.44
40-44	184	4.92	4.27-5.66
45-49	63	1.68	1.32-2.14
>49	12	0.32	0.18-0.56
No data	154	4.11	-----
Province			
Eastern Cape	1011	27.01	25.61-28.46
Free State	792	21.66	19.88-22.50
Gauteng	717	19.16	17.93-20.45
Limpopo	547	14.61	13.51-15.78
Northern Cape	264	7.05	6.27-7.91
North West Province	219	5.85	5.14-6.65
KwaZulu-Natal	84	2.24	1.81-2.77
Western Cape	78	2.08	1.67-2.59
Mpumalanga	31	0.83	0.59-1.18
Level of Urbanisation			
Urban	3168	84.64	83.45-85.76
Tribal/Traditional	352	9.40	8.51-10.38
Farm	3	0.08	0.03-0.24
No data	220	5.88	-----
Health Care Facility Type			
PHC Clinic	1794	47.93	46.33-49.53
CHC	600	16.03	14.89-17.24
District Hospital	783	20.92	19.65-22.25
Regional Hospital	241	6.44	5.70-7.27
Provincial Tertiary Hospital	49	1.31	0.99-1.73
National Central Hospital	55	1.47	1.13-1.91
No data	221	5.90	-----
Level of Health Care			
Level 1	3177	84.88	83.70-85.99
Level 2	241	6.44	5.70-7.27
Level 3	49	1.31	0.99-1.73
Level 4	55	1.47	1.13-1.91
No data	221	5.90	-----
Body Mass Index Category (kg/m^2)			
Underweight(below 18.5)	73	1.95	1.55-2.44
Normal weight(18.5-24.9)	546	14.59	13.50-15.76
Overweight(25.0-29.9)	341	9.11	8.23-10.07
Obese(30.0 and above)	435	11.62	10.63-12.69
No data	2348	62.73	-----

Note: PHC, Primary Health Care; CHC, Community Health Centre

Table 2: Adverse Drug Reactions with Implanon NXT® reported in South Africa (n=1369).

Adverse Drug Reaction	Number of Cases	Percentage (%)
Menstrual -related ADR		
Menorrhagia	712	52,01
Irregular menstrual period	111	8,11
Amenorrhea	90	6,57
Spotting	15	1,10
Breakthrough bleeding	5	0,37
Prolonged bleeding	3	0,22
Menstrual bleeding[a]	2	0,15
Total menstrual related ADR	938	68.52
Non-menstrual related ADR[b]		
Central and peripheral system disorders	433	31,63
Metabolism and nutrition disorders	169	12,34
Application site related disorders	104	7.60
Gastrointestinal system disorders	85	6,21
Pregnancy	68	4,97
General disorders	44	3.21
Musculoskeletal and connective tissue disorders	42	3,07
Skin and subcutaneous tissue disorders	30	2,19
Psychiatric disorders	28	2,05
Drug interaction	13	0,95
Nervous system disorders	12	0,88
Contraindication	9	0,66
Reproductive system and breast disorders	9	0,66
Complications related to product	6	0,44
Immune system disorders	2	0,15
Vascular disorders	2	0,15
Infection	2	0.15
Total non-menstrual related ADR	1056	77.14
Unlisted ADR[c]		
Numbness in arm	53	3.87
Epistaxis	10	0,73
Eye related disorders[d]	4	0,29
Numbness of lower limbs[e]	4	0.29
Swelling of lower limbs[f]	4	0,29
Chest pain	3	0,22
Implanon NXT® interferes with daily activity	3	0,22
Loss of appetite	3	0,22
Painful lower limbs[g]	3	0.22
Varicose veins	3	0,22
Weakness	2	0,15
Neck pain	2	0,15
Cramps on arm/s	2	0,15
Other unlisted ADR[h]	28	2,05
Total unlisted ADR	124	9.06

Note: ADR, Adverse Drug Reaction

[a] The type of bleeding pattern was not indicated in the case report. Menses/menstrual bleeding was indicated as an ADR. [b] The non-menstrual ADRs include*: Central and peripheral system disorders:* dizziness (11.18%), headache (20.45%)*; Metabolism and nutrition disorders:* weight gain (6.65%), weight loss (5.70%)*; Application site disorders:* septic Implanon NXT® area (0.07%), painful insertion site (0.07%), itchy insertion site (0.07%), painful arm (7.01%), swollen arm (0.22%), Itchy arm (0.07%), bruising of arm (0.07%);*Gastrointestinal system disorders:* abdominal pain (3.87%), nausea (1.39%), vomiting (0.95%);*Pregnancy:* pregnancy; *General disorders:* fatigue (1.90%), general pain (1.10%), tiredness (0.07%), oedema (0.07%), influenza(0.07%); *Musculoskeletal and connective tissue disorders*: back pain (2.99%), painful joints (0.07%);*Skin and subcutaneous tissue disorders:* acne (0.15%), hair loss (0.80%), rash (1.10%), itchiness (0.15%);*Psychiatric disorders:* mood swings (0.29%), loss if libido (0.37%), mood changes (0.88%), depression (0.15%), low libido (0.29%), insomnia (0.07%);*Drug interaction:* adverse drug reaction; *Nervous system disorders:* drowsiness (0.80%), seizures (0.07%)*; Contraindication:* contraindication; *Reproductive system and breast disorders:* dysmenorrhea (0.15%), enlarged breasts (0.07%), painful breasts (0.29%), itchy vulva (0.15%); *Complications related to product:* bent Implanon NXT® (0.07%), displaced Implanon NXT® (0.15%), broken Implanon NXT® (0.22%); *Infections*: Vaginal infection (0.15%); *Immune system disorders:* allergic reaction (0.15%); *Vascular disorders:* hot flushes (0.07%), hypertension (0.07%); *Infections*: Flu (0.07%). [c] Includes ADRs that were not listed in the Implanon NXT® product information and characteristics and Implanon NXT® prescribing information leaflet. [33,34,35] [d] Includes the following categories: painful eyes (0.07%), blurred vision (0.15%), vision changes (0.07%).[e] Included the following categories: numbness of lower limbs (0.15%) and numbness in leg (0.15%). [f] Included the following categories: swollen legs (0.07%) and swollen feet (0.22%). [g] Includes the following categories: painful feet (0.07%) and painful legs (0.15%). [h] Other unlisted ADRs includes the following categories with only reported 1 case: swollen face, anaemia, tender arm, abdominal distention, hypocalcaemia, skin disease, tremors, pale, swelling, bipolar-mood disorder, palpitation, painful hand, abscess, abdominal bloating, dyspareunia, loss of concentration,, swollen tongue, swollen vagina, tender nipples, burning sensation, weakness in arm, loss of balance, waist ache, painful face, swollen hand, malaise, memory loss, heartburn.

Table 3: Univariable and multivariable analysis of odds ratio (95% CI) for factors associated with discontinuation of Implanon NXT®

	Univariable model			Multivariable model		
Variable	Odds Ratio	Confidence Interval	*p*-value	Adjusted odds ratio	Confidence interval	*p*-value
Level of Urbanisation[a,b]						
Tribal/Traditional	0.933	0.74-1.17	0.544	----- [g]		
Urban	1	-----	-----			
Para[c]						
≥1	1.49	1.16-1.92	0.002	1.07	0.52-2.17	0.860
None	1	-----	-----	1	-----	-----
Gravida[d]						
≥1	1.33	1.01-1.75	0.042	0.98	0.49-1.99	0.962
None	1	-----	-----	1	-----	-----
Age Group (years)[e]						
<15	0.022	0.02 -0.17	0.001	0.00	0.000	0.999
15-19	0.408	0.12- 1.35	0.141	0.33	0.02-5.63	0.442
20-24	0.84	0.25- 2.82	0.782	0.50	0.03-8.26	0.631
25-29	0.94	0.28- 3.14	0.918	0.65	0.04-10.67	0.764
30-34	1.20	0.36- 4.02	0.774	0.91	0.06-14.89	0.945
35-39	1.22	0.36 -4.14	0.751	0.87	0.05-14.47	0.923
40-44	1.17	0.34- 4.06	0.801	1.31	0.08-22.83	0.853
45-49	0.76	0.21- 2.79	0.680	0.52	0.03-10.36	0.674
>49	1	-----	-----	1	-----	-----
Body Mass Index Category (kg/m^2)[f]						
Underweight(below 18.5)	1.722	1.04-2.84	0.036	1.71	0.77-3.78	0.185
Overweight(25.0-29.9)	1.54	1.17-2.02	0.0021	0.83	0.55-1.26	0.381
Obese(30.0 and above)	1.67	1.29-2.15	0.000	1.19	0.81-1.74	0.379
Normal weight(18.5-24.9)	1	-----	-----	1	------	-----
Cases reporting ADR/s						
Yes	4.62	3.93-5.45	<0.001	11.98	8.10-17.72	<0.001
No	1	-----	-----	1	-----	-----

ADR, Adverse drug reaction

[a] Data on level of urbanisation is missing for 220 case reports therefore n= 3523 case reports. [b] Farm was excluded from analysis for association due to low frequency. [c] Data on para is missing for 1630 case reports therefore n= 2113 case reports. [d] Data on gravida is missing for 1729 case reports therefore n= 2014 case reports. [e] Data on age is missing for 154 case reports therefore n= 3589 case reports. [f] Data on body mass index is missing for 2348 case reports therefore n= 1395 case reports. [g] Variable is not included in multivariable analysis as p< 0.05.

Table 4: Reasons for Implanon NXT® discontinuation reported in South Africa (n=2124).

Reason for discontinuation	Number of Cases	Percentage (%)
Frequently reported >25 cases		
Menorrhagia	728	34,27
Expiry[a]	628	29,57
Headache	218	10,26
Desire to conceive	126	5,93
Dizziness	106	4,99
Irregular menstruation	76	3,58
Painful arm	72	3,39
Weight gain	67	3,15
Pregnancy	65	3,06
Weight loss	63	2,97
Risk of ADR[b]	46	2,17
Abdominal pain	37	1,74
Numbness in arm	37	1,74
Amenorrhea	33	1,55
Contraindication	31	1,46
Patient request	30	1,41
Less frequently reported ≥10 to ≤25 cases		
Back pain	24	1,13
General pain	17	0,80
Nausea	12	0,56
Drug interaction	11	0,52
Fatigue	11	0,52
Rash	11	0,52
Vomiting	11	0,52
Few cases <10 cases		
Spotting	9	0,42
Mood changes	8	0,38
Broken Implanon NXT®	6	0,28
Epistaxis	6	0,28
Influenced by family/friends	6	0,28
Change in contraception method	5	0,24
Other reasons[c]	90	4.24

ADR, Adverse Drug Reaction

[a] Cases were due for discontinuation of Implanon NXT® after three years of use. [b] Risk of ADR category includes cases reporting the following reasons for discontinuation: patient commencing ART, patient on ART but no drug interaction indicated and patients on antituberculosis medication, but no drug interaction indicated. [c] Includes the following categories and number of cases:

4 cases: drowsiness, low/loss of libido, swollen lower limbs,syncope

3 cases: dysmenorrhea, hair loss, inserted incorrectly,palpitation, varicose veins

2 cases: seizures,allergic reaction, anaemia, chest pain,discolouration of Implanon NXT® site, displaced Implanon NXT®, feeling unwell with Implanon NXT®, painful breast, painful eyes,religious beliefs, swollen face

1 case: acne, swollen arm, tender arm, skin condition, skin disease, insomnia, low Hb, itchy implant site, pale, swelling, poor vision, numbness in leg, vaginal infection, swollen hand, painful hand, hot flushes, abscesses, hormonal imbalance, blurred vision, abdominal bloating, dyspareunia, painful joints, numbness of the limbs, painful legs, neck pain, itchiness of vulva, recurrent VDS, itchiness, memory loss, menstrual bleeding, Polymenorrhea, hysterectomy, travelling, patient feels unsafe, cultural beliefs, desire to menstruate normally and interferes with daily activities.

CHAPTER 4: MANUSCRIPT FOR SUBMISSION

4.1 Introduction

This chapter presents the second manuscript based on the results from the comparisons of experiences of Implanon NXT® users in the provinces of SA.

The manuscript: Prosad S, Ojewole E, Dheda M & Tlou B Comparisons of experiences of Implanon NXT® users between provinces in South Africa, was prepared and is to be submitted to the South African Medical Journal for publication. The guidelines for authors was followed and it is available from http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines.

4.2 Manuscript

Comparisons of experiences of Implanon NXT® users between provinces in South Africa

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Abstract

Background: While premature discontinuation of Implanon NXT® has been reported in South Africa, there is a lack of evidence about the frequency of this occurence. The concomitant use of Implanon NXT® and antiretroviral drugs has been suggested to result in reduced efficacy of the contraceptive, this being problematic in an Human Immunodeficiency Virus (HIV) rampant environment, such as KwaZulu-Natal Province. The study of Implanon NXT® in varying demographics (e.g. age and location) and different population groups (e.g. HIV positive women) is important to isolate areas that require individual intervention. KwaZulu-Natal and Gauteng Provinces are examples of under researched provinces with regard to Implanon NXT® user experiences. These provinces were also chosen for this study to represent different contexts in SA in terms of demographic and disease profile, implant usage and discontinuation.

Objectives: To compare the experiences of Implanon NXT® users between the provinces of South Africa.

Methods: A retrospective study was conducted utilizing secondary data obtained from the South African National Department of Health Pharmacovigilance Centre for Public Health Programmes. A total of 3743 national case reports were analysed, with patients' demographics, history and discontinuation details being extracted and imported into SPSS® version 25 for analysis. The following outcomes were extracted: discontinuation, premature discontinuation, adverse drug reactions and reasons for discontinuation. Results were presented descriptively for demographic and discontinuation variables. A comparative analysis between Gauteng and KwaZulu-Natal province was performed using Chi square test and Mann-Whitney U-Test.

Results: Discontinuation of Implanon NXT® was more frequent in under 30-year old, their most frequent reasons being desire to conceive, expiry, dizziness, headache and menorrhagia. The proportion of premature discontinuation was higher in Gauteng (82.6%, 252/305) than KwaZulu-Natal (76.7%, 23/30); (p=0.01208). Significantly higher proportions of adverse drug reactions, apart from drug interaction, was reported in Gauteng compared to KwaZulu-Natal. Reasons for discontinuation, such as desire to conceive, bleeding patterns, headache, pain in arm, pregnancy and abdominal pain, were

significantly higher in Gauteng than KwaZulu-Natal. Notable reasons for discontinuation in KwaZulu-Natal were pregnancy and drug interactions.

Conclusion: The users of Implanon NXT® from Gauteng were more prone to discontinue than those from KwaZulu-Natal. A common reason for user discontinuation in KwaZulu-Natal was due to possible drug interaction with the Implanon NXT®. Interestingly, users experiences, particularly reasons for discontinuation are different between the provinces, hence tailored interventions may be required.

Keywords: *Adverse drug reaction; Discontinuation; Implanon NXT®; South African provinces, drug interactions.*

Background

Implanon NXT® is a single-rod etonogestrel contraceptive implant that lasts for three years.[1] The product was introduced in South Africa (SA) to provide a complete range of family planning methods at public health facilities,[2, 3] being made available in public health facilities in February 2014.[4]

Contraceptive implants usage prevalence ranges from 0.1% to 18.1% among 113 countries worldwide with growing acceptance globally, including sub-Saharan Africa.[5, 6] However, user discontinuation of etonogestrel implants is also occurring simultaneously, ranging from 34.9% to 47% from 32 to 36 months post-insertion.[7-9] Studies indicate an increase in early discontinuation rate in the Netherlands,[10] Australia,[11] United Kingdom (UK),[12] India,[13] Ethiopia [14] and Nigeria.[15] These studies reported discontinuation from 3%-10.5% at six months, 8.1% to 28% at one year, and from 19.3% to 49.7% at 2 years. The prominent reason for discontinuation of etonogestrel implants globally are adverse drug reactions (ADRs).[10, 14, 16-18]

Reports of early implant discontinuations emerged shortly after its introduction in SA,[19, 20] with the South African Health Review reporting 820 discontinuations between February and December 2014, and estimated rate of 0.1%.[19] According to estimates, 5 000 implant discontinuations have been recorded up till April 2015, this figure being expected to increase.[20] KwaZulu-Natal (KZN) Province reported 3884 discontinuations in 2014/15, this equating to a discontinuation frequency of 1.67%.[21] Empirical data on

Implanon NXT® discontinuation from departmental documents in Gauteng was inaccessible, but an online newspaper article published in 2015 alluded to discontinuation figures of 250, equating to 0.5%.[22] A study from the Eastern Cape Province indicated that 27.2% of participants discontinued Implanon NXT® within six months of use, 67.3% within the first year and 94.4% after the second year.[23] A study conducted in Gauteng and North West Provinces reported that 60% of discontinuations occurred less than a year post insertion.[24]

Studies in SA have highlighted ADRs associated with Implanon NXT® discontinuation.[23-25] A study conducted in the Eastern Cape revealed that over 70% of participants discontinued Implanon NXT® due to the experience of ADRs,[23] while Gauteng and North West Provinces reported 90% discontinuation due to intolerable ADRs across both provinces, specifically bleeding pattern changes.[24]

A particular area of concern in SA is the knowledge gap on discontinuation of Implanon NXT®,[20] with a lack of data on its frequency of and associated reasons.[4] In SA, where the incidence of Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) is very high, the concomitant use of Implanon NXT® and antiretroviral therapy (ART) is particularly concerning.[19, 26, 27] This is a concern in provinces where the HIV/AIDS prevalence is high, such as in KZN.[28] In 2014, the national prescription guidelines changed, the policy recommending discontinuation of Implanon NXT® in those using enzyme inducing drugs, such as efavirenz, rifampicin, carbamazepine, phenytoin and phenobarbital.[26] This could have had a direct effect on the increased early discontinuations in SA given the disease profile of the country. A SA study identified a need for implant surveillance data in young and adolescent women and in patients using enzyme inducing drugs.[29] The above knowledge gaps in SA are of concern, given that the product has been in use for four years.

Recent publications provided some evidence on user discontinuation of Implanon NXT® and the associated reasons, but samples were limited to a few health facilities and focused only on those in the Eastern Cape, Gauteng and North West Provinces.[23-25] Geographic and clinic location is reported to be associated with Implanon® discontinuation.[11, 30] Hence, these findings may not necessarily be applicable to users in other provinces in the country. SA is a diverse country with varying demographics in terms of women's

proportion of ages, level of urbanisation and health conditions. The study of Implanon NXT® in different demographics (e.g. age and location) and among various population groups (e.g. HIV positive women) is essential to identify areas that require tailored interventions, especially in undocumented province, such as KZN. This is essential to developing effective strategies and guidelines to address user discontinuation. This study compared the experiences of Implanon NXT® users among the provinces of SA and focussed on a comparative analysis between Gauteng and KZN Implanon NXT® users.

Methods

A total of 3743 case reports regarding the insertion, discontinuation and report of ADRs of Implanon NXT® from 01 April 2015 to 11 September 2017 were attained from the Pharmacovigilance Centre for Public Health Programmes, National Department of Health, SA.

Design

A retrospective study design was used, and secondary data analysed using comparative analysis techniques. Permission to use the raw data was obtained from the Pharmacovigilance Centre for Public Health Programmes, National Department of Health, South Africa and the study was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BE266/17). The analysis of secondary pharmacovigilance data provided a substantial volume of cases for analysis on a wide scale.[31]

Setting

Implants are available at all service levels in the public health care system, which includes primary, secondary and tertiary level facilities.[19] All nine provinces in SA, and 36 out of the 52 districts reported Implanon NXT® case reports to the national surveillance program. The main focus of this study was a comparative analysis between two provinces in SA, which were selected as examples to represent different contexts. This choice was based on the following criteria: demographic and disease profile, implant usage and discontinuation. The majority of Gauteng's population resides in urban areas (97%),[32]

while KZN province has a 47% urban population.[33] In terms of disease profile, the HIV prevalence was higher (16.9%) in KZN than in Gauteng (12.4%) in 2012.[28] KZN was also one of the higher reporters of implant users among currently married and sexually active unmarried women (4.1%) and Gauteng was one of the lower reporters (3.1%).[34] As mentioned in the background, KZN also reported higher discontinuation figures than Gauteng, hence these factors provide a reflection of the spectrum of users across the country.

Outcomes measured

The outcome selection was informed by the available variables, which were discontinuation, premature discontinuation, ADRs and reasons for discontinuation. Discontinuation was defined as termination of using Implanon NXT® and was identified by report of a discontinuation date and/or a reason for discontinuation. Premature discontinuation was defined as the discontinuation of Implanon NXT® before 36 months post-insertion, and was created for analysis by calculating the difference between the insertion and discontinuation dates. The following variables were analysed from the raw data: province, age, para, gravida, concomitant conditions, concomitant drugs, insertion date, discontinuation date, ADRs and reasons for discontinuation. Level of urbanisation and health facility type were new variables processed for analysis. The health facility name, sub-district and district data was used to determine level of urbanisation from the Statistics SA website.[35] The health facility name was used together with the referal system guide,[36] health sites webpage [37] and EML Clinical Guide APP [38] to determine health facility type. The dataset for the comparative analysis was restricted to cases only from Gauteng(n=717) and KZN (n=84). A comparative analytical approach was used to measure the following outcomes: ADRs, premature discontinuation and reasons for discontinuation.

Data analysis

The extracted data was analysed using SPSS® (version 25), and descriptive analysis performed for all variables. Data was analysed using the median and interquartile range (IQR) for skewed continuous variables, and frequencies and percentages were generated

for categorical variables. A 95% confidence interval (CI) was used, and confidence limits generated. The Chi square test was used to determine significant differences for categorical data in the comparative analysis. This was done using SPSS to determine the p-value for all provinces an online calculator to determine the p-value for Gauteng and KZN.[39] A p value of <0.05 was considered statistically significant, and the proportions of significant variables were compared between Gauteng and KZN provinces. The Mann-Whitney U-Test was used to compare continuous variables between Gauteng and KZN.

Results

Provincial demographics of discontinuers

A total of 63.6% (2 379/3 743) of Implanon NXT® cases reported discontinuation, with the associated provincial demographics being presented in Table 1. The overall median age was 27 years (IQR=10, CI:27.84-28.43), and discontinuation was more frequent in under 30-year-olds. All health care facility types were accessed for discontinuation and most cases were reported from urban areas, with the exception of Limpopo, where 41.4% of cases were reported from tribal/traditional areas. Of those who reported, most discontinuation cases were para ≥1 (range: 26.4%-70.9%) and gravida ≥1 (range: 26.6%-63.6%). Discontinuers who reported HIV&AIDS ranged from 1.8%-27.6% (n=283) (p<0.001) across all provinces. Those who reported using antiretrovirals (ARVs) ranged from 2.2%-32.6% (n=181) (p<0.001) across the provinces. Very few cases (≤10 cases) reported other concomitant conditions, such as Tuberculosis, Epilepsy and Psychiatric conditions.

Table 1: Demographics of discontinuation cases in relation to provinces (n=2379)

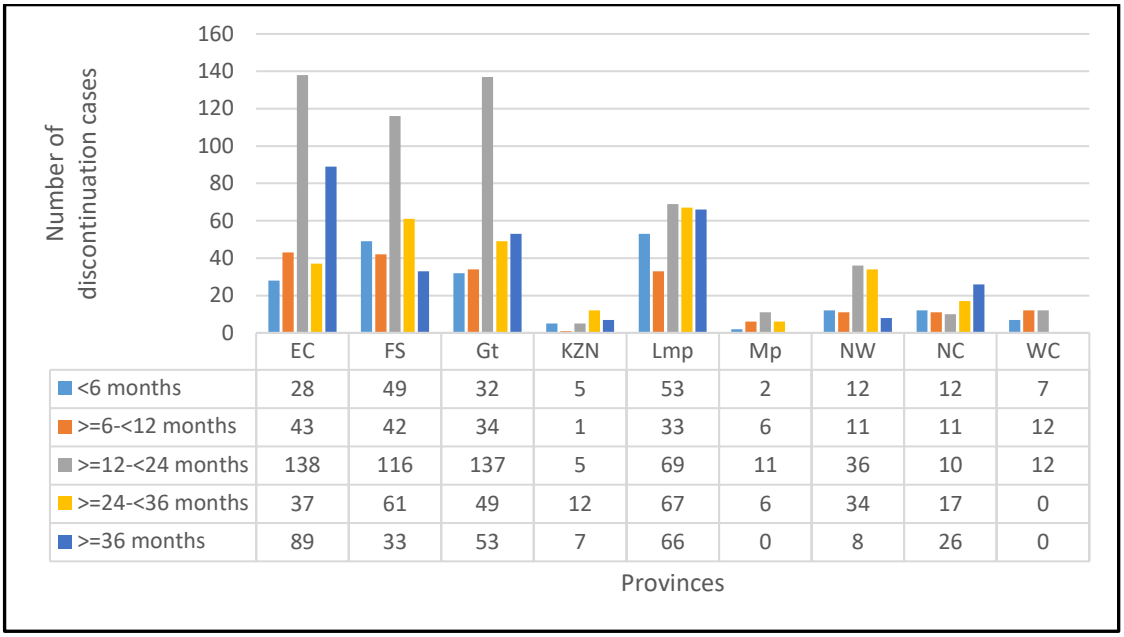
Variable	**EC n=459**	**FS n=524**	**Gt n=479**	**KZN n=72**	**Lmp n=481**	**Mp n=29**	**NW n=160**	**NC n=120**	**WC n=55**
	%	%	%	%	%	%	%	%	%
Age									
<15	0.2	0	0	0	0	0	0	0	0.0
15-19	9.2	7.6	5.6	5.6	15.4	10.3	6.3	5	5.5
20-24	20.5	28.2	25.1	26.4	25.8	24.1	28.8	26.7	25.5
25-29	27.9	21.9	22.3	29.2	21.2	34.5	26.9	23.3	43.6
30-34	19.0	16.2	20.5	25	18.1	17.2	16.3	21.7	18.2
35-39	13.3	10.1	14.2	5.6	6.7	10.3	13.1	5	5.5
40-44	6.3	4.6	4.8	1.4	6.7	0	4.4	10	1.8
45-49	1.5	1.9	1.0	0	3.3	0	0	0	0.0
>49	0.7	0.2	0	1.4	0.4	0	0	0.8	0.0

Missing data	1.5	9.2	6.5	5.6	2.5	3.4	4.4	7.5	0
Level of urbanisation									
Urban	98.0	87.2	98.1	95.8	46.6	89.7	97.5	96.7	100
Farm	0	0	0	0	0	10.3	0	0	0
Tribal/traditional	0.4	2.7	0	4.2	41.4	0	0	0.8	0
Missing data	1.5	10.1	1.9	0	12.1	0	2.5	2.5	0
Health care facility type visited									
PHC	9.2	74.0	57.2	31.9	30.6	0.0	3.8	75	61.8
CHC	29	10.1	29.4	47.2	5.4	10.3	0.6	21.7	38.2
District hospital	60.3	5.7	0.0	0.0	41.4	0.0	13.8	0.0	0.0
Regional Hospital	0.0	0.0	0.0	20.8	1.5	89.7	79.4	0.0	0.0
Provincial tertiary	0.0	0.0	0.0	0.0	9.1	0.0	0.0	0.0	0.0
National Central	0.0	0.0	11.5	0.0	0.0	0.0	0.0	0.0	0.0
Unlisted[f]	1.5	9.9	0.6	0.0	11.0	0.0	2.5	2.5	0.0
Missing data	0	0.2	1.3	0	1.0	0	0	0.8	0
Para									
0	2.4	10.9	4.4	2.8	6.4	3.4	10.6	3.3	0
≥1	47.1	50	56.8	41.7	26.4	55.2	51.3	55.8	70.9
Missing data	50.5	39.1	38.8	55.6	67.2	41.4	38.1	40.8	29.1
Gravida									
0	2.2	9.5	3.3	0	5.8	3.4	8.8	4.2	0
≥1	45.8	51.1	49.9	33.3	26.6	55.2	53.8	55	63.6
Missing data	52.1	39.3	46.8	66.7	67.6	41.4	37.5	40.8	36.4

PHC = Primary Health Care facility; CHC = Community Health Centre; EC=Eastern Cape; FS=Free State; Gt=Gauteng; KZN=KwaZulu-Natal; Lmp=Limpopo; Mp=Mpumalanga; NW=North West; NC=Northern Cape; WC=Western Cape

Provincial representation of Implanon NXT® discontinuation

The median duration of Implanon NXT® use was 573 days (approximately 19 months) (IQR: 595, CI: 605.07-642.37). Figure 1 depicts cases discontinued Implanon NXT® per province, with the data to calculate duration of use being available for 39.9% of cases (1 492/3 743).



	EC	FS	Gt	KZN	Lmp	Mp	NW	NC	WC
<6 months	28	49	32	5	53	2	12	12	7
>=6-<12 months	43	42	34	1	33	6	11	11	12
>=12-<24 months	138	116	137	5	69	11	36	10	12
>=24-<36 months	37	61	49	12	67	6	34	17	0
>=36 months	89	33	53	7	66	0	8	26	0

Figure 1. Number of discontinuation cases from initiation until 36 months or longer in relation to provinces (n=1492) *

*Cases based on the difference in number of months between insertion and discontinuation date. (EC=Eastern Cape; FS=Free State; Gt=Gauteng; KZN=KwaZulu-Natal; Lmp=Limpopo; Mp=Mpumalanga; NW=North West; NC=Northern Cape; WC=Western Cape)

Discontinuation was frequently reported ≥12 - <24 months post-insertion apart from KZN and Northern Cape. Table 2 shows the frequently reported ADRs in relation to age and provinces of the users, with most being under 30 years. The three frequently reported ADRs were dizziness (4.09%; 153/3 743), headache (7.48%; 280/3 743) and menorrhagia (19.02%; 712/3 743), and were also reported as reasons for discontinuation (Table 3). A small proportion (0-25.8%) reported discontinuation due to expiry (discontinuation after three years of use) across provinces. The highest proportion of full-term users were reported in Limpopo, Gauteng and Free State Provinces. Major reasons for discontinuation in the 20-34 year-olds were desire to conceive and expiry.

Table 2: Frequently reported adverse drug reactions among Implanon NXT® users distributed by age and province

	Dizziness	Irregular menstruation	Pain in arm	Menorrhagia	Headache
	n (%)	n (%)	n (%)	n (%)	n (%)
Age (years) *					
<15	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (0.4)
15-19	19 (12.7)	18 (17.0)	12 (12.6)	80 (11.6)	35 (12.8)
20-24	36 (24.0)	29 (27.4)	28 (29.5)	214 (31.0)	65 (23.7)

25-29	57 (38.0)	29 (27.4)	25 (26.3)	172 (24.9)	89 (32.5)
30-34	24 (16.0)	17 (16.0)	15 (15.8)	131 (19.0)	54 (19.7)
35-39	8 (5.3)	11 (10.4)	9 (9.5)	54 (7.8)	21 (7.7)
40-44	3 (2.0)	1 (0.9)	4 (4.2)	33 (4.8)	9 (3.3)
45-49	3 (2.0)	1 (0.9)	2 (2.1)	5 (0.7)	0 (0)
>49	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total (n)	**150**	**106**	**95**	**690**	**274**
Province					
EC	35 (22.9)	20 (18.0)	31 (32.3)	196 (27.5)	77 (27.5)
FS	38 (24.8)	31 (27.9)	17 (17.7)	148 (20.8)	44 (15.7)
Gt	40 (26.1)	19 (17.1)	22 (22.9)	184 (25.8)	77 (27.5)
KZN	4 (2.6)	0 (0)	2 (2.1)	22 (3.1)	4 (1.4)
Lmp	16 (10.5)	17 (15.3)	4 (4.2)	56 (7.9)	24 (8.6)
Mp	5 (3.3)	0 (0)	4 (4.2)	13 (1.8)	7 (2.5)
NW	10 (6.5)	18 (16.2)	7 (7.3)	42 (5.9)	27 (9.6)
NC	4 (2.6)	6 (5.4)	1 (1.0)	38 (5.3)	10 (3.6)
WC	1 (0.7)	0 (0)	8 (8.3)	13 (1.8)	10 (3.6)
Total (n)	**153**	**111**	**96**	**712**	**280**

ADR=Adverse drug reaction; EC=Eastern Cape; FS=Free State; Gt=Gauteng; KZN=KwaZulu-Natal; Lmp=Limpopo; Mp=Mpumalanga; NW=North West; NC=Northern Cape; WC=Western Cape
*Data on dizziness missing for 3 cases therefore percentage based on n=150; data on irregular menstruation missing for 5 cases therefore percentage bases on n=106; data on pain in arm missing for 1 case therefore percentage based on n=95; data on menorrhagia missing for 22 cases therefore percentage based on n=690 and on headache missing for 6 cases therefore percentage based on n=274.

Table 3: Frequently reported reasons for Implanon NXT® discontinuation among users distributed by age and province

Variables	**Expiry**	**Dizziness**	**Desire to conceive**	**Menorrhagia**	**Headache**
	n (%)	n (%)	n (%)	n (%)	n (%)
Age (years)*					
<15	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)
15-19	24 (4.2)	12 (11.4)	4 (3.3)	89 (12.7)	20 (9.5)
20-24	106 (18.4)	33 (31.4)	32 (26.2)	228 (32.4)	61 (28.9)
25-29	135 (23.4)	39 (37.1)	41 (33.6)	170 (24.2)	69 (32.7)
30-34	127 (22.0)	14 (13.3)	32 (26.2)	127 (18.1)	37 (17.5)
35-39	104 (18.1)	5 (4.8)	10 (8.2)	47 (6.7)	19 (9.0)
40-44	53 (9.2)	1 (1.0)	3 (2.5)	34 (4.8)	5 (2.4)
45-49	22 (3.8)	1 (1.0)	0 (0)	7 (1.0)	0 (0)
>49	5 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)
Total (n)	**576**	**105**	**122**	**703**	**211**
Province					
EC	110 (17.5)	19 (17.9)	16 (12.7)	143 (19.6)	47 (21.6)
FS	123 (19.6)	27 (25.5)	31 (24.6)	162 (22.3)	33 (15.1)
Gt	133 (21.2)	25 (23.6)	25 (19.8)	164 (22.5)	58 (26.6)
KZN	23 (3.7)	2 (1.9)	1 (0.8)	22 (3.0)	7 (3.2)
Lmp	162 (25.8)	23 (21.7)	22 (17.5)	135 (18.5)	23 (10.6)
Mp	0 (0)	2 (1.9)	1 (0.8)	12 (1.6)	7 (3.2)
NW	27 (4.3)	3 (2.8)	18 (14.3)	45 (6.2)	24 (11.0)
NC	49 (7.8)	4 (3.8)	7 (5.6)	32 (4.4)	7 (3.2)

WC	1 (0.2)	1 (0.9)	5 (4.0)	13 (1.8)	12 (5.5)
Total (n)	**628**	**106**	**126**	**728**	**218**

EC=Eastern Cape; FS=Free State; Gt=Gauteng; KZN=KwaZulu-Natal; Lmp=Limpopo; Mp=Mpumalanga; NW=North West; NC=Northern Cape; WC=Western Cape

*Data on expiry missing for 52 cases therefore percentage based on n=576; data on dizziness missing for 1 case therefore percentage bases on n=105; data on desire to conceive missing for 4 cases therefore percentage based on n=122; data on menorrhagia missing for 25 cases therefore percentage based on n=703 and on headache missing for 7 cases therefore percentage based on n=211.

Comparisons of Implanon NXT® users' experiences in KZN and Gauteng

The median duration of use in Gauteng was 573 days (approximately 19 months) (IQR: 572, CI: 604.07-692.10) and 918 days (approximately 30 months) (IQR: 524, CI: 635.50-919.74) in KZN, but the difference was not statistically significant (p=0.051). The proportion of premature discontinuation was higher in Gauteng (82.6%, 252/305) than KZN (76.7%, 23/30) (p=0.01208) (Figure 1). Table 4 presents the comparison of commonly reported ADRs in Gauteng and KZN. The most frequently reported ADRs in KZN were menorrhagia, drug interaction and pregnancy, whereas menorrhagia, headache and dizziness were more common in Gauteng. Comparatively significantly higher proportions of ADRs were reported in Gauteng, except for drug interaction (Table 4). It is important to note that if numbers are interpreted as a proportion of the total cases in each province, then pregnancy (7.1%; 6/84) was higher in KZN than Gauteng (2.5%, 18/717). The drug interactions reported with Implanon NXT® could be due to the concomitant ARV use. The proportion of discontinuers with reported HIV&AIDS was higher in KZN (26.4%, 19/72) as compared to Gauteng (11.3%, 54/479) (p=0.00044). Proportionately, KZN reported higher ARV use (20.9%, 14/67) than Gauteng (6.6%, 30/456) (p=0.01242).

Table 4: Comparisons of commonly reported adverse drug reactions of Implanon NXT® users in Gauteng and KwaZulu-Natal Provinces

ADR	**Gt**	**KZN**	**Overall p-value**	**P-value from calculating 2 population proportions**
	n (%)	n (%)		
Menorrhagia (n=712)	184 (25.8)	22 (3.1)	<0.001*	<0.0001 *
Headache (n=280)	77 (27.5)	4(1.4)	<0.001*	<0.0001 *
Dizziness (n=153)	40 (26.1)	4 (2.6)	0.001*	<0.0001 *

Irregular menstruation (n=111)	19 (17.1)	0 (0)	0.001*	<0.0001 *
Pain in arm (n=96)	22 (22.9)	2 (2.1)	<0.001*	<0.0001 *
Weight gain (n=91)	24 (26.4)	0 (0)	0.031*	<0.0001 *
Amenorrhoea (n=90)	26 (28.9)	0 (0)	0.018*	<0.0001 *
Weight loss (n=78)	10 (12.8)	1 (1.3)	0.205**	
Pregnancy (n=68)	18 (26.5)	6 (8.8)	0.001*	0.00038*
Abdominal pain (n=53)	17 (32.1)	1 (1.9)	<0.001*	<0.0001 *
Numbness in arm (n=53)	18 (34.0)	1 (1.9)	0.007*	<0.0001 *
Back pain (n=41)	5 (12.2)	0 (0)	0.020*	0.0007*
Spotting (n=15)	6 (40.0)	0 (0)	0.601**	
Drug interaction (n=13)	0 (0)	8 (61.5)	<0.001*	<0.0001 *

ADR=Adverse drug reaction; Gt=Gauteng; KZN= KwaZulu-Natal
*p<0.05 is significant. **No significant difference between distribution of ADR across all provinces therefore not included included for comparative testing.

Table 5 illustrates the comparison of commonly reported reasons for discontinuation, the main three reasons being menorrhagia, expiry and headache in both provinces. Comparatively, the reasons for discontinuation, such as desire to conceive, bleeding pattern, headache, pain in arm and abdominal pain, were significantly higher in Gauteng than KZN. The experiences of dizziness, weight gain, amenorrhoea and numbness in arm as ADRs (as shown in table 4) were significantly different between the provinces, however as reasons for discontinuation were not significantly different (as in table 5).

Table 5: Comparison of commonly reported reasons for Implanon NXT® discontinuation in Gauteng and KwaZulu-Natal Provinces

Reason for discontinuation	Gt	KZN	p-value	P-value from calculating 2 population proportions
	n (%)	n (%)		
Menorrhagia (n=728)	164 (22.5)	22 (3.0)	<0.001*	<0.0001 *
Expiry (n=628)***	133 (21.2)	23 (3.7)	<0.001*	0.00012*
Headache (n=218)	58 (26.6)	7 (3.2)	<0.001*	<0.0001 *
Desire to conceive (n=126)	25 (19.8)	1 (0.8)	<0.001*	<0.0001 *
Dizziness (n=106)	25 (23.6)	2 (1.9)	0.058**	
Irregular menstruation (n=76)	12 (15.8)	0 (0)	<0.001*	8E-05*
Pain in arm (n=72)	14 (19.4)	2 (2.8)	0.002*	0.00016*

Weight gain (n=67)	19 (28.4)	0 (0)	0.107**	
Pregnancy (n=65)	18 (27.7)	6 (9.2)	0.001*	0.00038*
Weight loss (n=63)	7 (11.1)	1 (1.6)	0.057**	
Risk of ADR (n=46)****	3 (6.5)	5 (10.9)	<0.001*	0.13362**
Abdominal pain (n=37)	10 (27.0)	2 (5.4)	0.009*	<0.0001 *
Numbness in arm (n=37)	13 (35.1)	1 (2.7)	0.232**	
Amenorrhoea (n=33)	5 (15.2)	0 (0)	0.423**	
Drug interaction (n=11)	1 (9.1)	6 (54.5)	<0.001*	<0.0001 *

ADR, Adverse drug reaction; Gt=Gauteng; KZN=KwaZulu-Natal
*p<0.05 is significant. **No significant difference between distribution of reason for discontinuation across all provinces therefore not included included for comparative testing. ***Discontinuation after three years of use. ****Risk of ADR category includes cases reporting patient on ARV but no drug interaction indicated.

Discussion

More case reports were obtained from Gauteng (717 cases) than KZN (84 cases). The probable reasons could be due to the fact that discontinuation, associated reasons and ADRs were shown to be under-reported.[22] Another possible reason suggested by Mullick et al.[4] was that women of higher socioeconomic status were using implants, with Gauteng being the wealthier province.

It appears that younger women (<30 years) were more frequent discontinuers of Implanon NXT® in all provinces in the present study. These findings corroborated with other studies on Implanon NXT® [23] and Implanon®. [18, 40] However, a study conducted in Gauteng and North West Provinces reported mean ages of discontinuers as 30 and 31 years respectively, and only 15% ranged from 18-25 years.[24] Young women i.e. under 30-year-old, mostly reported ADRs in the present study, which were common reasons for discontinuation in the same age group. Although the present study implies poor tolerability of ADR in young women, global studies investigating implants in the youth reported a higher tolerability.[41-43] A reason for discontinuation in the present study in 20-34 year olds was the desire to conceive, with women in this age group being of marriageable and childbearing age. This reason is comparable to López del Cerro et al. in contraceptive implant users.[42] Overall, it appears that young women are frequent discontinuers of Implanon NXT®, which may be a significant finding, as the SA target population for implants are the youth.[44]

A clear majority of discontinuation case reports were obtained from urban health facilities in the present study, a possible reason being women's perception of a higher quality of care provided in these facilities. Rural health care users indicated that their experiences in general are affected by staff shortages, poor staff attitudes, long travelling times, lack of medication, and a lack of monitoring and evaluation.[45] A study from Texas suggested that practitioners, especially those practicing in rural areas, are inadequately trained in long acting reversible contraceptives.[46] Another possible reason for increased reports is migration from rural areas to urban areas in SA,[47] this being relevant as Mlambo[47] reported that over 70% of SA population is estimated to be residing in urban areas by 2030. Over 40% of discontinuation case reports were obtained from tribal/traditional health facilities in Limpopo Province, which has the highest rural population in the country (88-90%).[48]

Primary and secondary level facilities i.e. primary health care facilities, community health centers and district hospitals were mainly accessed for discontinuation services in the present study. Higher level facilities were also used in Gauteng, KZN, Limpopo, Mpumalanga and North West Province, as all service levels are required to provide implant services.[19] A possible reason for reports from higher level facilities could be due to referrals from practitioners for discontinuation services as expressed in a study conducted in Gauteng, North West and Western Cape Provinces.[24, 49]

The proportion of discontinuation of case reports across the provinces varied, ranging from 1.2% to 22.0% in the present study, this trend also being evident in Implanon® studies from Ethiopia (16% to 80%)[14, 18, 50, 51] and Nigeria (4.48%-21.36%).[15, 52-54] The proportion of premature discontinuation was only slightly higher in Gauteng (82.6%, 252/305) than KZN (76.7%, 23/30), while the median duration of use was approximately 19 months and 30 months in Gauteng and KZN respectively. These findings deviate from recent studies in Eastern Cape, [23] Gauteng and North West[24] which found that the median duration of etonogestrel implant use were ten and eight months respectively. One thought advanced is that health practitioners advised women to persevere through the symptoms and wait for the body to adjust to the hormones in the implant.[55, 56]

The frequently reported ADRs in the present study i.e. menorrhagia, headache, dizziness, pain in arm and irregular menstruation, were also reported internationally[16, 57-59] and in

studies from Eastern Cape, Gauteng and North West Provinces.[23, 24] In a study from Gauteng and North West Provinces, 10.99% of users reported menorrhagia and 14.29% headaches, as ADRs of Implanon NXT®, however the present study reported higher proportion in Gauteng (25.8%).[24] Generally, it appears that while the same ADRs are reported throughout the country, the proportions differ across the provinces. In the present study, there were a significantly higher proportions of most ADRs in Gauteng as compared to KZN. It appears that the women from Gauteng are less tolerable of ADRs associated with Implanon NXT®.

In the present study, ADRs were common reasons for Implanon NXT® discontinuation, which is in keeping with etonorgestrel implants reports.[10, 18, 23] The reasons for discontinuation in Gauteng i.e. menorrhagia, expiry, desire to conceive, dizziness and headache, were the same as for the entire country. Gauteng reported significantly higher proportions of discontinuation due to ADRs than KZN in the present study. In a study from Gauteng and North West Provinces, a majority of discontinuers (90%) stated that intolerable ADRs were the reason for user discontinuation,[24] with prolonged bleeding, menorrhagia, headache, weight gain, weight loss and pregnancy being the main reasons.[24] In that study, the ADRs, specifically bleeding, negatively affected patients' sex life and led to implant discontinuation in some cases.[24] Global implant qualitative studies have found that unpredictable bleeding patterns, fear of embarrassment from unpredictable bleeding, difficulty managing irregular menstruation and increased financial cost could influence discontinuation.[56, 60-62] The health practitioner may also play a role in encouraging discontinuation as inadequate counselling and management of ADRs were notable challenges.[25] The quality of service may be poor due to insufficient knowledge, poor skills and lack of understanding of the method, as advanced by Adeagbo et al.[25] Treatment for bleeding associated with Implanon NXT® only provided short-term relief, and some women who experienced ADRs opted for discontinuation due to inefficient ADR treatment.[24, 25]

In the present study, two main reasons for discontinuation in KZN were pregnancy and drug interaction, of which drug interaction was significantly higher in KZN than Gauteng possibly due to higher number of HIV positive patients. Discontinuation due to enzyme inducing drugs is shown in a study from the Eastern Cape, where 12.8% discontinued

Implanon NXT® due to concomitant medication.[23] A study from Gauteng and North West Provinces also reported that women were concerned about potential drug interaction with ARVs, which led to discontinuation.[24] Pregnancy in etonogestrel implant users could be due to concomitant ARV use,[59, 63, 64] as efavirenz causes increased metabolism of the hormone, leading to its lower levels and reduced efficacy.[1, 65]

It appears that not all ADRs i.e. dizziness, numbness in arm, weight gain and amenorrhoea, warranted discontinuation in the present study. Possible reason for this were advanced in a study from Gauteng and North West Provinces,[24] which found that some ADRs disappeared over time, and that they changed over time and did not affect the women's health negatively.[24]

The second highest reason for discontinuation was expiry in the present study, although this only accounted for a quarter of total reasons. A smaller percentage (1.1%) reported discontinuation due to expiry in a study from the Eastern Cape.[23] In contrast, an Ethiopian study reported 35% of late Implanon® discontinuers,[18] while another noted that 53.5% of participants retained theirs for >35 months.[14] This may imply that SA has a lower frequency of full-term Implanon NXT® users', which further provides evidence that early discontinuation is a problem in SA. Overall, findings from this study are in keeping with global patterns, which reiterates the point that the experiences with Implanon NXT® in SA are not unusual and mirror those globally.[29]

This study provides empirical data on the discontinuation of Implanon NXT®, a gap having been identified in previous SA publications.[20, 29] To the best of our knowledge, a comparative analysis on Implanon NXT® discontinuation has not been conducted previously in the country. While the scale of the national data is a strength of the study, it has methodological limitations. Secondary data was used, with the primary data being collected by external personnel, which could have resulted in variable quality and completeness of the data, and the data available for KZN was less than for Gauteng. Despite this, cases from a variety of clinics from several districts in KZN were reported.

The evidence from the present study can be used by policymakers in the provinces to support their Implanon NXT® prescription guidelines, counselling protocols and training

materials in public health facilities. The findings of this study may also be informative for health practitioners, as they are the first point of contact for patients.

Conclusion

Young women most frequently chose to discontinue Implanon NXT®, as ADRs and the desire to conceive were considered responsible across the provinces. The women from Gauteng discontinued more frequently than the women from KZN province. The common reasons for discontinuation were pregnancy and drug interaction in KZN. Interestingly, users' experiences, particularly reasons for discontinuation are different between the provinces, hence tailored interventions may be required. It is important to discuss the risk of drug interaction during counseling with users of Implanon NXT®. Research on discontinuation using qualitative methods would be beneficial to gain an in-depth understanding of the reasons, particularly in young women.

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Conflict of Interest

None

Author Contributions

S Prosad designed the research project, performed statistical analysis and interpreted results with the assistance of B Tlou and E Ojewole. M Dheda and his team granted gatekeeper permission and data used in this study. S Prosad, E Ojewole, B Tlou and M Dheda contributed to the manuscript, reviewed, finalised and approved it for submission to the journal.

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CHAPTER 5: SYNTHESIS

5.1 Introduction

While there are international studies on the use and discontinuation of etonogestrel implants, it must be acknowledged that in the SA context, there is a paucity of empirical data and literature on Implanon NXT® user discontinuation (Mullick, Chersich, Pillay, & Rees, 2017). In order to address this existent gap, this study presented and evaluated South African national pharmacovigilance data of Implanon NXT®. This chapter addresses the extent to which the aim was achieved by reviewing the main findings of each objective, and logically demonstrates the associated conclusions reached for each. This is followed by the recommendations for policymakers and practitioners, the study limitations, and an indication of the significance of the findings.

5.2 Aim and objectives and conclusions reached

The aim of the study was to evaluate the users' experiences of Implanon NXT® in the public health sector in SA. The study had five objectives and two manuscripts have been written to address the objectives. The first manuscript addressed objectives one to four and reported a general overview of experiences using the national data for SA. The second manuscript provided an overview of ADRs and discontinuation in all other provinces, which was done to comprehensively understand the experiences of Implanon NXT® use in SA. The second manuscript also addressed objective five and focused on comparing the experiences between two provinces in SA to highlight regional differences.The study objectives, and the conclusions reached for each objective, based on the main study findings are outlined respectively:

1. To identify the demographic profile of Implanon NXT® users

Women of reproductive age and above used Implanon NXT®, and 20-24-year olds were the most frequent (25.70%; 962/3743). Almost half the women had a parity ≥1 (48.89%; 1830/3743) and gravida ≥ 1 (47.58%; 1781/3743). Most case reports were from urban area facilities (84.64%; 3168/3743), and from all levels of health facilities. PHC (47.93%; 1794/3743), CHC (16.03%; 600/3743) and district hospitals (20.92%; 783/3743) being mainly accessed.

2. To identify ADRs of Implanon NXT® reported among users

The ADRs of Implanon NXT® users in SA were identified, with 36.57% (1369/3743) cases reported, being similar to international and local trends. The main ADRs reported in SA were menorrhagia (52.01%; 712/1369), headache (20.45%; 280/1369), dizziness (11.18%; 153/1369) and irregular menstruation (8.11%; 111/1369). Menorrhagia was the main reported ADR and may be a distinctive menstrual pattern experienced by SA users. 9.06% (124/1369) of reported ADRs were not on the product and prescribing leaflets e.g. numbness in arm (3.87%; 53/1369), epistaxis (0.73%; 10/1369), eye related disorders (0.29; 4/1369), numbness of lower limbs (0.29; 4/1369).

3. To determine frequency of discontinuation of Implanon NXT® and reasons for discontinuation

Younger women (<30 years) were more frequent discontinuers of Implanon NXT® (58.51%, 1392/2379), most case reports being from urban health facilities (85.04%; 2023/2379) except in Limpopo Province (46.57%; 224/481). A high frequency of discontinuation (63.56%; 2379/3743), particularly prematurely (81.1%; 1210/1492) was revealed. This indicated that the users in SA were not continuing Implanon NXT® to full term. There were various reasons for discontinuation, with ADRs being the main one (83.99%; 1784/2124) and other to a lesser degree (37.95%; 806/2124). Menorrhagia was the main reason for discontinuation among public health facility users (34.27%; 728/2124), with expiry being second (29.57%; 628/2124). Other common reasons for discontinuation included: desire to conceive (5.93%; 126/2124), headache (10.26%; 218/2124), dizziness (4.99%; 106/2124) and irregular menstruation (3.58%; 76/2124).

4. To determine frequency of failure of Implanon NXT®

The frequency of pregnancy, interpreted as failure, was reported (4.97%; 68/1369). The finding was significant considering the reason behind unwanted pregnancies, with efavirenz-based therapy suspected to be associated with pregnancy in Implanon NXT® use ($p<0.001$).

5. To compare experiences of Implanon NXT® between users in KZN and Gauteng Province

More case reports were available from Gauteng (n=717) than KZN (n=84) and their differing profiles possibly being attributed to KZN's high HIV prevalence. The top reported ADRs in KZN were menorrhagia (3.1%, 22/712), drug interaction (61.5%, 8/13) (possibly with ARVs) and

pregnancy (8.8%, 6/68), while Gauteng reported menorrhagia (25.8%, 184/712), headache (27.5%, 77/280) and dizziness (26.1%, 40/153). Premature discontinuation was higher in Gauteng (82.6%, 252/305) than KZN (76.7%, 23/30) (p=0.01208), the reasons for discontinuation in Gauteng being similar to the overall SA data, such as desire to conceive (19.8%, 25/126) and dizziness (23.6%, 25/106), whereas, in KZN it was due to pregnancy (9.2%, 6/65) and drug interaction (54.5%, 6/11) (possibly with ARVs). Implanon NXT® users' experiences differed between provinces, therefore generalizations cannot be made for all users in SA.

This research expands the reports on discontinuation of Implanon NXT® and capitalized on the use of secondary data to evaluate experiences of Implanon NXT® in the SA population. The findings of this study have contributed to knowledge of Implanon NXT® in SA which includes identification of ADRs, extent and magnitude of discontinuation, reasons for discontinuation and contributed evidence towards associating pregnancy and efavirenz based therapy. This study therefore highlighted the experiences of Implanon NXT users in SA hence the aim and objectives were achieved.

5.3 Significance of the findings

The evidence from the present study can be of significance in the following areas:

- This study identified prevalent ADRs of Implanon NXT® and population groups prone to experiencing specific ADRs. The findings may be used to impact, and supplement policies such as ADR management, counselling guidelines, prescription of Implanon NXT® in those on enzyme-inducing drugs and Implanon NXT® monitoring systems. Enhanced guidelines and application of these guidelines may ultimately benefit users such as improved communication between health practitioners and patients and the provision of evidence-based knowledge during consultations. This could lead to better health outcomes and improved adherence to Implanon NXT®.
- The findings from the study can assist in interventions such as educating users on ADRs of Implanon NXT® and providing awareness on failure of the product.
- The evidence has highlighted that tailored interventions and guidelines may be necessary as problems pertaining to specific provinces in SA were identified. Individual needs should be addressed to assist women of different demographics such as in younger women where discontinuation is frequent and in KZN where drug interaction and pregnancy are common reasons for discontinuation.

- This research has sparked interest on conducting further monitoring and evaluation studies and interventional studies that will address and may reduce ADRs, discontinuation and failure with Implanon NXT®.

5.4 Study Limitations

The following limitations are acknowledged:

- The study was limited by its study design. The use of a secondary data set meant that the principal investigator did not have control over the primary data collection.
- The quality and completeness of the data varied, and missing data and incomplete case reports could have compromised the analysis of key variables. These inconsistencies may affect the reliability of the data.
- Only public health facilities were included, as data for private health facilities have not been identified.
- Small samples were used in some analyses, which provided some measure of association but with limited scope.

5.5 Recommendations

The following recommendations for South African Implanon NXT® users are detailed below. The recommendations are made collectively for all the objectives, with some addressing specific objectives. Although counselling and health practitioners were excluded from the study, the findings that emanated are influenced by these aspects. Hence, counselling and health practitioners are included as part of the recommendations.

5.5.1 Counselling

Routine counselling is recommended to assist in reducing premature discontinuation. The following suggestions are proposed to be included in counselling of Implanon NXT® users:

- It is important for practitioners to thoroughly screen women at the pre-insertion counselling session to ensure that Implanon NXT® is an appropriate option for that particular woman. A comprehensive patient history and discussion of pregnancy planning is also recommended. Additional counselling on the increased risk of pregnancy needs to be provided to women using concomitant enzyme-inducing drugs. During the pre-insertion session, it is also essential to rule out pregnancy, as only 19.1% (714/3743) of case reports stated that a pregnancy test was performed.

- The practitioner is expected to discuss common ADRs during the method-specific counselling session. This discussion should also encourage women to report ADRs to avoid long-term effects and include the procedure for women to follow if they experience an ADR. Women on enzyme-inducing drugs who choose to use Implanon NXT® must be provided with counselling on using additional non-hormonal contraception to prevent pregnancy. It is also important to emphasize that Implanon NXT® is ideally used for three years and is not to be considered a short-term method.

- A regular follow-up schedule should be enforced, as the data demonstrated that the onset of ADRs was experienced in the first year of utilization, with discontinuation being common in the second year. These essential follow-up sessions should include: discussion on satisfaction, any change in needs, report of any ADRs and their treatment, and assessing the insertion site for any abnormalities. The development of individualized counselling tools that address provinces' individual uniqueness, and that utilizes available resources is recommended.

Group counselling is a suitable option in the SA environment where communities and peers play a role in decision-making. Education and counselling should start at the ground level such as schools, community centers, and local clinics. Additionally, it is a time-saving way to create awareness, considering the heavy burden of patients on the public health care system. Moreover, group counselling as a modality of intervention, specifically in SA, maximizes on the number of women that can receive some form of supportive intervention at one time. Being cognizant of the realities of the South African public health environment, another option is the development of concise pre-insertion and method-specific counselling protocols. Alternatively, novel counselling tools e.g. using mobile phone apps or Digital Versatile Discs (DVDs), may be designed to ensure that women receive appropriate information. The use of alternative counselling styles such as cautious, comprehensive counselling and 'just try it' methods is also suggested.

5.5.2 Health care practitioners

Nurses in particular are usually the primary provider of contraceptives in the public health sector and counselling is a large component of Implanon NXT® provision and discontinuation, making comprehensive training essential. It is necessary to keep abreast with new developments, such as updated prescription guidelines and research regarding enzyme inducing drugs and implants.

Moreover, contextually within the public health care sector, the use of a multi-disciplinary approach to support Implanon NXT® users is recommended. Specifically, communication between practitioners within the same facility should be encouraged to effectively manage women. Pharmacy and Therapeutics Committee meetings may be an ideal point of contact of multiple disciplines to conduct evaluations of ADRs and Implanon NXT® discontinuations. A one-stop service delivery approach is also recommended to promote comprehensive care in other settings, such as HIV and TB clinics. In addition, training on the treatment of ADRs, and recording and reporting their occurrence should be on-going, which will be explained in the following sections.

5.5.3 Adverse drug reaction management

ADR treatment algorithms may be useful to reduce discontinuation due to ADRs. There is a SA guideline for short-term treatment for breakthrough bleeding associated with implants but not for long-term treatment. However, there is a need for a long-term treatment option that is safe and effective. Another area that necessitates intervention is treating non-menstrual ADRs, the percentage of total non- menstrual ADRs being greater than the total menstrual ones, as evident in the result of manuscript 1. An algorithm for treating options or referral protocols of common non-menstrual ADR, such as headache, pain in arm and dizziness is therefore recommended.

5.5.4 Recording and reporting protocols

Underreporting and missing data can result in skewed results, which may then not be truly representative of the realities that exist in public health facilities. These have an impact in under estimating the consequences, as the real extent and magnitude of the problem is unknown. An example of this is the recording of laboratory results, which was only completed for ≤2.6% of cases. This makes interpretation of the data difficult and limits its generalizability. Laboratory results were excluded from the analysis in the present study. Another example is that true contraceptive method failure could not be established in this study due to insufficient information provided by cases reporting pregnancies. Additional information, such as date of conception in relation to insertion date, timing of insertion and etonogestrel concentration levels, must be included to establish the reason for failure. The transfer of information has several steps, with multiple personnel being involved. It is recommended that health practitioners complete details fully on the surveillance form, and complete one for every Implanon NXT® user. In addition, it is recommended that data capturers correctly and completely transfer information from the source document to the database. The reason for incomplete data is unknown and may be worth

investigating, a possible explanation being the length of the form or the number of variables to be recorded. An evaluation may need to be conducted with health practitioners, and, should there be potential challenges, the form could be re-designed, or a revised collection tool considered.

5.5.5 Monitoring and evaluations

The NPC is conducting surveillance of sub-dermal implants, with robust monitoring systems being recommended to support areas where discontinuation is high. A multipronged approach to pharmacovigilance and ADR reporting is recommended. Various techniques for robust monitoring systems such as cohort studies and registries are encouraged. Ongoing monitoring and evaluation of Implanon NXT® is recommended, as this will comprehensively and continuously inform and strengthen clinical practice, which ultimately benefits Implanon NXT® users.

5.5.6 Recommendations for future research

A clinical trial investigating appropriate treatment to manage long-term bleeding with Implanon NXT® is also recommended, having long-term ramifications, as the treatment could be applied to other progestogen contraceptives where bleeding is problematic. An investigational study on ARV based therapy in Implanon NXT® users particularly in SA may be necessary to confirm an association between the drugs. The present study used a small sample to associate efavirenz and pregnancy, which limits the significance of the result. It will be beneficial to investigate the severity of ADRs and their relationship to discontinuation in future. The users' role in discontinuation of Implanon NXT® must not be undermined therefore a qualitive study investigating accountability for discontinuation and decision-making needs to be conducted. The findings from qualitative research, in conjunction with empirical data, could guide future interventional research. The experiences were compared between KZN and Gauteng Province, and as the results cannot be generalized to other provinces in SA, a comparative analysis among other provinces, or groups of provinces (e.g. inland vs costal), may be valuable to highlight individual challenges and specific areas requiring intervention.

5.6 Final Statement

The study is a catalyst for future studies and motivates for expanding research within the public and private sector to deepen understanding of discontinuation of Implanon NXT®. Greater vigilance in the collection, monitoring and evaluation of data is suggested to continuously guide and strengthen Implanon NXT® service delivery and ultimately impact user adherence.

ANNEXURE 1: ETHICAL APPROVAL LETTER AND SUBSEQUENT AMENDMENT LETTER

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

31 August 2017

Ms S Prosad (211503540)
Discipline of Pharmaceutical Sciences
School of Health Sciences
prosadshimona@gmail.com

Dear Ms Prosad

Title: Experiences of implanon NXT users at Public Health facilities in KwaZulu-Natal and Gauteng Province, South Africa. Degree: MPharm BREC Ref No: BE266/17

EXPEDITED APPROVAL

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 20 April 2017.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 13 August 2017 to BREC letter dated 31 July 2017 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 31 August 2017.

This approval is valid for one year from **31 August 2017**. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **10 October 2017**.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor V Rambiritch
Deputy Chair: Biomedical Research Ethics Committee

cc supervisor: ojewolee@ukzn.ac.za
cc postgraduate administrator: nenep1@ukzn.ac.za

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Amended letter
08 November 2018

Ms S Prosad (211503540)
Discipline of Pharmaceutical Sciences
School of Health Sciences
prosadshimona@gmail.com

Dear Ms Prosad

Title: Experiences of implanon NXT users at Public Health facilities in KwaZulu-Natal and Gauteng Province, South Africa. Degree: MPharm BREC Ref No: BE266/17

NEW TITLE OF STUDY: Title: Experiences of implanon NXT users at Public Health facilities in South Africa.

We wish to advise you that your response received on 31 October 2018 to BREC letter dated 31 October 2018 has been noted by a sub-committee of the Biomedical Research Ethics.

Your letter requesting approval of Amendments (change of title and other amendments) dated 17 October 2018 for the above approved study has now been **approved** by the sub-committee of the Biomedical Research Ethics Committee.

The committee will be notified of the above at its next meeting to be held on 11 December 2018.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc supervisor: ojewolee@ukzn.ac.za cc postgraduate administrator: nenep1@ukzn.ac.za

ANNEXURE 2: GATEKEEPER PERMISSION LETTER

Franci
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NATIONAL DEPARTMENT OF HEALTH

DATA USER'S AGREEMENT

The National Department of Health, South Africa encourages all interested users to request for Data Sets/ Data on projects conducted by or for the Department. Users are however required to read and sign the User's Agreement for Information, which stipulates the conditions for use of the Data /Data Sets before the requested Data /Data Sets is made available.

Please read the following agreement. All users of all the Data Sets agree to the following conditions listed below. If you accept these conditions, fill in the required information and sign at the appropriate place.

1. The User agrees that the South African Government is the owner of the Data Set(s).
2. The use of these Data Sets in research communication, scholarly papers, journals and the like is encouraged, but the authors of these communications and documents are required to acknowledge/cite the National Department of Health as the source of the Data.
3. **The User will be required to provide sufficient detail for which the data will be used for e.g. research proposal, protocol, evaluation methodology etc.**
4. The User agrees that he/she will not provide/publish any reports/statements without prior discussion with and permission of the Chief Director for Health Information Management, Monitoring and Evaluation.
5. A copy of any document produced from the Data Set for publication or other forms of circulation should be submitted to the Chief Director for Health Information Management, Monitoring and Evaluation.

1/3

6. The User agrees that any use of the Data or reliance by the User or any of the Data is at the User's own risk and that the National Department of Health shall not be liable for any loss or damage howsoever arising as a result of such use.

7. The User agrees that he/she will not attempt to link nor permit others to attempt to link the records of persons in these Data Sets with personally identifiable records from any other source.

8. The User agrees that he/she will not attempt to use nor permit others to use the Data Sets to establish the identity of any person included in any set.

9. The User agrees that he/she will make no statement nor permit others to make statements indicating or suggesting that interpretations drawn are those of the National Department of Health

10. **PENALTY CLAUSE:** The user agrees that non-adherence to the above statements may result in the National Department of Health not making available any datasets to the user in future.

The User agrees that his/her signature indicates his/her agreement to comply with the above-stated requirements (Points 1-9)

Please complete this form

Data/Set/s for which Agreement is signed (Provide detail list):	National Surveillance for Implanon
Name (Print or Type):	Shimona Prosad
Organisation/Department:	University of KwaZulu-Natal
Position:	Master Student
Purpose for which the data will be used (List attachment)	Academic purposes - Master's Dissertation
Anticipated timeframe for completing the analysis/study/project for which data are requested	February 2018
Anticipated timeframe for sharing the results of the analysis/study/project with the National Department of Health	March 2018
Title (Mr/Mrs/Ms/Dr/Prof) :	Ms
Address:	Unit 1, 78 Campbell Drive, Zinga, Umhlanga
City:	Durban
Province:	KwaZulu-Natal
Country:	South Africa
Telephone:	073 136 9751 (Shimona Prosad) or 031 260 7931 (Dr E Ojewole - supervisor)
Fax:	031 260 7792 (Dr E Ojewole - supervisor)
E-mail:	prosadshimona@gmail.com or ojewolee@ukzn.ac.za
Signature:	Sprosad
Date:	21/7/17
Witness: Name	Dr E Ojewole (supervisor)
Witness: Contact No	031 260 7937
Date:	21/7/17

For Department of Health use only:

Approval by DOH Representative*:	
Date:	11/08/2017

- **The Data User's Agreement must be signed by the Chief Director for Health Information Management, Monitoring and Evaluation.**

3/3

ANNEXURE 3: PROSPERO REGISTRATION OF SCOPING REVIEW

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Evidence of Patients' Challenges and Barriers on Usage of Implanon

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.
Not applicable

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
25/07/2017

4 Anticipated completion date
Give the date by which the review is expected to be completed.
23/01/2018

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started √

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Shimona Prosad

7 Named contact email
Enter the electronic mail address of the named contact.
prosadshimona@gmail.com

8 Named contact address
Enter the full postal address for the named contact.
PO Box 2679 Umhlanga Rocks 4320

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
+27 731369751

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of KwaZulu-Natal

Website address:
www.ukzn.ac.za

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Miss	Shimona	Prosad	University of KwaZulu-Natal
Dr	Tivani	Mashamba-Thompson	University of KwaZulu-Natal
Dr	Elizabeth	Ojewole	University of KwaZulu-Natal

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
Funded by the College of Health Sciences Masters Scholarship 2017 University of KwaZulu-Natal

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
What research has been done on patients' barriers and challenges on usage of Implanon?

What research has been done on Implanon user experiences?

What research has been done on Implanon adverse effects?

What research has been done on Implanon discontinuation rate and reasons for discontinuation ?

What research has been done on Implanon failure rate?

16 Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
We will search the following electronic bibliographic databases: Pubmed, MEDLINE, EBSCOhost, Google Scholar and Cochrane library. The search terms will include the following keywords: Females, Use of Implanon, Barriers, Challenges, Experiences, Adverse effects, Discontinuation rate, reasons for discontinuation and Failure rate. Boolean terms will be used to search the articles. Websites such as governmental websites, World Health Organisation and online newspaper sources will be searched for reports and articles related to the research questions. Grey literature will also be included. We will also conduct a hand search of reference list of the included studies. Primary and secondary research studies that address the research question will be included. Studies will not be limited by method design or country. Information from 1998 to present will be included.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.
N/A

I give permission for this file to be made publicly available
Yes

18 Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Usage of Implanon in females.

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Inclusion: Females who used or are using Implanon as a contraceptive option Exclusion: Females using other contraceptives

20 Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Implanon is a subdermal contraceptive implant that is classified as a long-acting reversible contraceptive. It was initially released in 1998.

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Females using contraceptives other than Implanon

22 Types of study to be included
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Inclusion criteria • Studies reporting evidence of barriers and challenges with Implanon usage • Studies reporting evidence of Implanon use • Studies reporting on evidence of patients' experiences of Implanon use • Studies reporting on evidence of Implanon adverse effects • Studies reporting on evidence of discontinuation of Implanon use • Studies reporting on evidence of reasons for discontinuation of Implanon • Studies reporting failure Implanon usage • Information published from 1998 to present • All method designs for appropriate studies included Exclusion criteria • Studies that do not report evidence of experiences of Implanon users • Studies published before 1998. • Studies that report on contraceptives other than Implanon. • Health practitioners' experiences with Implanon

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
No restriction on setting.

24 Primary outcome(s)
Give the most important outcomes.
Barriers and Challenges with Implanon usage from 1998 to present.

Give information on timing and effect measures, as appropriate.
N/A

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
1. Patients' experiences of Implanon use from 1998 to present 2. Adverse effects of Implanon users from 1998 to present 3. Discontinuation rate of Implanon use and reasons for discontinuation from 1998 to present 4. Failure rate of Implanon from 1998 to present

Give information on timing and effect measures, as appropriate.
N/A

26 Data extraction (selection and coding)

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Articles will be searched using the selected databases. The initial title screening will be done by the principle investigator. Included studies at title screening stage will be exported to a library on Endnote reference manager for abstract and full article screening. Abstract and full article screening will be guided by the eligibility criteria. The endnote library will be shared with a second reviewer who will conduct screening and study analysis.Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer. A PRISMA chart will be used to guide the study selection process. Authors of studies will be contacted to access missing studies. The University of KwaZulu-Natal library service will also be used to access articles that are not available as full articles online. A standardised data charting form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: Title, Reference, Research question, Aims and Objectives,Demographics of participants, Recruitment method ,Sampling method,Study design, Data collection method,Data analysis,Intervention,Outcome,Relevant Findings,Conclusion

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Mixed Methods Appraisal Tool (MMAT) version 2011 will be used to appraise identified studies. This tool allows one to assess the quality and appropriateness of the studies.

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

The data extracted from articles will be analysed using thematic analysis. The outcomes of the study will guide the themes. These include: the use of Implanon, patients' experiences of Implanon users, adverse effects of Implanon users, discontinuation of Implanon and failure of Implanon. Emerging themes will also be reported. NVIVO software version 10 will be used to code the data according to themes The identified themes will be analysed and their relationship to the research questions will be assessed. The analysis of findings will be discussed in relation to our study aim and objectives.

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

None planned.

Review general information

30 Type and method of review

Select the type of review and the review method from the drop down list.

Systematic review

Obstetrics and gynaecology

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

South Africa

33 Other registration details

Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the

Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

ANNEXURE 4: PUBLISHED SCOPING PROTOCOL PAPER

Prosad *et al. Systematic Reviews* (2018) 7:157
https://doi.org/10.1186/s13643-018-0827-1

Systematic Reviews

PROTOCOL Open Access

Evidence of patients' challenges and barriers related to usage of Implanon®: scoping review protocol

Shimona Prosad[1], Tivani P Mashamba-Thompson[2] and Elizabeth Ojewole[1*]

Abstract

Background: According to the United Nations Trends in Contraceptive Use 2015 report, at least one in ten married or in-union women in most regions of the world has an unmet need for family planning. Family Planning 2020 reports an estimate of almost 134 million married or in-union women of reproductive age who have an unmet need for modern methods of contraception in 2016 in participating countries. Family planning has therefore been highlighted as a global unmet need. Initiatives such as Family Planning 2020 aim to promote contraceptive use through Implanon® contraceptive implant. Implanon® has been reported to be a highly effective form of contraception. However, poor outcomes from users of the Implanon® have been reported in recent studies. The main objective of this review is to map the literature for the evidence on usage of Implanon® in order to reveal challenges and barriers.

Methods and analysis: A scoping review searching evidence on Implanon® use will be conducted. Relevant studies will be identified from 1998 to present. The following databases: PubMed, MEDLINE, EBSCOhost, Google Scholar and Cochrane library will be searched for peer-reviewed literature. We will also search for grey literature in this study area. The eligibility criteria will guide the study selection. A data charting table will be designed to extract information from the literature. The results of this study will be reported by use of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Data will be analysed using thematic analysis and the NVIVO software version 10. The mixed method appraisal tool (MMAT) will be used to assess the quality of included studies.

Discussion: We anticipate finding relevant studies on the use of Implanon®. Evidence gathered from included studies will help us identify gaps in research and help guide future research on Implanon® usage. This information can also help guide implementers and users on challenges and barriers related to use of Implanon®.

Systematic review registration: PROSPERO CRD42017072926.

Keywords: Etonogestrel implant, Implanon®, Usage, Contraceptive, Barriers, Challenges

Background

Implanon® is a subdermal contraceptive implant that is classified as a long-acting reversible contraceptive. It was initially released in 1998 in Indonesia. Since 1998, more than 3.3 million implants have been dispensed globally [1]. The 2015 United Nations Trends in Contraceptive Use Worldwide report states that more than one in three married or in-union women globally use long-acting or permanent methods namely sterilisation, intrauterine device, and implants [2]. According to the FP2020 Momentum at the Midpoint 2015–2016 report, injectables and implants are the fastest growing methods globally [3]. Implanon® has been reported as a highly efficacious contraceptive [4–8]. However, problems such as adverse effects, early discontinuation of the product, and contraceptive failure have been reported in a variety of studies published globally [1, 8–12].

Despite the reported failures related to Implanon® use, the use of Implanon® is still being promoted globally. Initiatives such as Family Planning 2020 aim to address an unmet need for family planning services through distribution of modern contraceptives like Implanon® [3].

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Full list of author information is available at the end of the article

Their goal is to enable 120 million more females to use contraceptives by 2020 [3]. According to the FP2020 2015–2016 progress report, there were 30.2 million additional users of modern contraception compared to 2012 [3]. This movement will help to achieve the sustainable development goals (SDG), which is aimed at preventing unintended pregnancy and reduce adolescent childbearing through universal access to sexual and reproductive healthcare services [13]. This will also address the SDG, which focuses on gender equality and female empowerment and also aims to ensure universal access to sexual and reproductive health and reproductive rights [13].

Family planning has been highlighted as a global unmet need [2, 3, 13]. Implanon® has potentiation to address this unmet need by improving birth control and preventing unwanted pregnancies. The Pearl Index scores reported for Implanon® are similar to other long-acting reversible contraception as well as similar to sterilisation [4]. Implanon® is convenient, cost-effective, and highly efficacious compared to other contraceptives [14, 15]. Return to fertility is quick with Implanon®, and it can be safely used while breastfeeding [4, 7, 14]. It can also be used by women who cannot tolerate estrogen [4]. However, the challenges and barriers related to usage of Implanon® are not well known. The scoping review is aimed at mapping evidence on challenges and barriers linked to usage of this product since its introduction to the market.

It is anticipated that the results of this study will provide information on challenges and barriers related to Implanon® usage. The study findings will also guide future research as well as inform the policymakers and users of Implanon®.

The objectives of the scoping review are as follows:

- To review research reports on barriers and challenges of usage of Implanon®
- To review research reports on Implanon® users' experiences
- To review research reports on Implanon®'s adverse effects
- To review research reports on discontinuation rate of Implanon® and reasons for discontinuation
- To review research reports on Implanon®'s failure rate

Methodology

Scoping review

We will conduct a scoping review with guidance from Arksey and O' Malley's scoping review framework [16, 17]. The adapted framework that will be used comprises of the following five stages:

Step 1: Identifying the research question
Step 2: Identifying relevant studies
Step 3: Study selection
Step 4: Charting the data
Step 5: Collating, summarising and reporting the results

Identifying the research question

The main research question is what evidence is available on the barriers and challenges of etonogestrel implant (Implanon®) usage? The secondary research questions are as follows:

1. What are patients' experiences of Implanon® usage?
2. What are the adverse effects of Implanon®?
3. What is the discontinuation rate of Implanon® and the reasons for discontinuation?
4. What is the failure rate of Implanon® usage?

Eligibility of research question

The Population Intervention Comparison Outcomes (PICO) framework will be used to determine the eligibility of the research question. PICO is used to break down clinical questions into searchable keywords [18]. Table 1 shows the PICO framework for the research question.

Identifying relevant studies

An electronic search will be conducted using the following databases: PubMed, EBSCOhost (Academic Search Complete, MEDLINE and CINAHL), Google Scholar and Cochrane library. Websites such as governmental websites, World Health Organisation and online newspaper sources will be searched for reports and articles related to the research question. We will also conduct a hand search of reference list of the included studies. Primary and secondary research studies that address the research question will be included. Studies will not be limited by method design or country. Grey literature will also be included. The Boolean search terms will include the following: females and use of Implanon® or barriers or challenges or experiences or adverse effects or discontinuation rate or reasons for discontinuation or failure rate.

Table 1 PICO table to determine eligibility of research question

Criteria	Determinants
Population	Females who used or are using Implanon® as a contraceptive option
Intervention	Usage of Implanon®
Comparison	Absence of usage of Implanon®
Outcome	Main outcome: barriers and challenges related to Implanon® usage Secondary outcomes: patients' experiences of Implanon® usage, adverse effects related to Implanon® usage, discontinuation rate of Implanon® use and reasons for discontinuation, failure rate of Implanon®

used to report the screening results (see Fig. 1). Authors of studies will be contacted to access missing studies. The University of KwaZulu-Natal library service will also be used to access articles that are not available online as full articles. Full articles will be requested from the author if articles are unavailable from the databases. We conducted a pilot search using our keywords, and database results are attached in Table 3 in the Appendix.

Data charting

A data charting table will be designed and used to extract data from included studies. A draft of the data charting form is depicted in Table 2.

Collating, summarising and reporting of results

The data extracted from articles will be analysed using thematic analysis. The themes are derived from our study outcomes. These include the following: barriers and challenges related to Implanon® usage, patients' experiences of Implanon® usage, adverse effects of Implanon® usage, discontinuation rate of Implanon®, reasons for discontinuation of Implanon®, and failure rates of Implanon®. Emerging themes will also be reported. NVIVO software version 10 will be used to code the data according to themes [19].

Synthesis

The identified themes will be analysed, and their relationship to the research questions will be assessed. The analysis of findings will be discussed in relation to the study aim and objectives.

Table 2 Data charting form

Author and date
Title
Reference
Research question
Aims and objectives
Summary of the study results
Sample size
Age
Marital status
Setting
Recruitment method
Sampling method
Study design
Data collection method
Data analysis
Intervention
Outcomes
Relevant findings
Conclusion
Comments

Quality appraisal

Mixed Methods Appraisal Tool (MMAT) version 2011 will be used to appraise identified studies [20]. This tool allows one to assess the quality and appropriateness of the studies. A quality score will be generated using MMAT. We will score qualitative and quantitative studies by dividing the number of criteria met by four and presenting the score using *, **, ***, and **** descriptors. Scores will vary from 25% (*)—one criterion met—to 100% (****)—all criteria met. With regard to mixed methods research studies, the overall quality of a combination cannot exceed the quality of its weakest component therefore the overall quality score is the lowest score of the study components. The score is 25% (*) when QUAL = 1 or QUAN = 1 or MM = 0; it is 50% (**) when QUAL = 2 or QUAN = 2 or MM = 1; it is 75% (***) when QUAL = 3 or QUAN = 3 or MM = 2; and it is 100% (****) when QUAL = 4 and QUAN = 4 and MM = 3 (QUAL being the score of the qualitative component, QUAN the score of the quantitative component, and MM the score of the mixed methods component) [20]. Systematic reviews will be analysed under observational studies.

Discussion

The scoping review will be conducted to map the existing peer-reviewed literature for evidence on challenges and barriers related to usage of Implanon®. Studies on problems with the use of Implanon® have been reported in most countries [1, 5, 9, 10, 21]. However, there is a paucity of literature on the evidence regarding patients' challenges and barriers related to Implanon®. It is important to investigate the trends and extent of these problems, globally. There is a need to consolidate and evaluate this information to guide future practice and policy regarding Implanon®.

This study only focuses on the contraceptive implant Implanon® and not on other contraceptive options. Evidence from 1998 onwards will be screened. Implanon® was put on the market in 1998. Therefore, this study will map literature evidence on the usage of the product since its introduction on the market. Aspects such as experiences of health practitioners with Implanon® are not of interest to this study. The focus of the study is based on user experience with reference to pharmacovigilance of Implanon®. The perspective of the user is essential in pharmacovigilance reporting [22].

The findings from this review may be of interest to healthcare practitioners in terms of improving the provision of Implanon®. The review will also inform policy makers and may influence policy and guidelines related to the use of Implanon®. Researchers may also be interested in filling the gaps exposed through the review.

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Appendix

Table 3 Results of pilot search

Keyword search	Date of search	Search engine used	Number of publications retrieved (results)
(((((((("female"[MeSH Terms] OR "female"[All Fields]) OR "females"[All Fields]) AND ("etonogestrel"[Supplementary Concept] OR "etonogestrel"[All Fields] OR "Implanon*" "[All Fields]))" OR Barriers[All Fields]) OR ("Plan Parent Chall"[Journal] OR "challenges"[All Fields])) OR Experiences[All Fields]) OR ("adverse effects"[Subheading] OR ("adverse"[All Fields] AND "effects"[All Fields]) OR "adverse effects"[All Fields])) OR (Discontinuation[All Fields] AND ("J Rehabil Assist Technol Eng"[Journal] OR "rate"[All Fields]))) OR (Reasons[All Fields] AND discontinuation[All Fields])) OR (Failure[All Fields] AND ("J Rehabil Assist Technol Eng"[Journal] OR "rate"[All Fields]))	25 July 2017	PubMed	2,583,613

Abbreviations

MMAT: Mixed Methods Appraisal Tool; PICO: Population Intervention Comparison Outcomes; PRISMA/-P: Preferred Reporting Systematic Review and Meta-Analysis Protocols; SDG: Sustainable development goals

Acknowledgements

The authors are grateful to the College of Health Sciences Scholarship Committee and the staff of the College of Health Sciences Research Office, University of KwaZulu-Natal for funding.

Funding

Funding was provided by the College of Health Sciences Scholarship Award (CHS Scholarship Application # 533710).

Availability of data and materials

All data generated or analysed during this study will be included in the published scoping review.

Authors' contributions

SP conceptualised this study and prepared the draft manuscript under the supervision of EO. Both EO and TPM-T reviewed draft manuscript. SP, EO, and TPM-T contributed to the reviewed draft manuscript, finalised the manuscript and approved it for submission to the journal.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

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Published online: 12 October 2018

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ANNEXURE 5: MANUSCRIPT SUBMISSION AND REVISED MANUSCRIPT SUBMISSION LETTERS

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Authors
Prosad, Shimona
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29-Jun-2018

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ANNEXURE 6: CONFERENCE PROCEEDINGS

DISCONTINUATION OF IMPLANON NXT® AMONG USERS AT PUBLIC HEALTH FACILITIES IN SOUTH AFRICA

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1. Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal
2. National Pharmacovigilance Center for Public Health Programmes
3. University of KwaZulu-Natal

Background and Objectives: There are concerns with early Implanon NXT® sub-dermal contraceptive implant user discontinuation in South Africa. The true extent of this discontinuation is unknown. Consequently, determination of this extent as well as the reasons for it, particularly at the national and provincial level, is imperative. This study evaluated reasons and factors associated with Implanon NXT® discontinuation.

Methods or Description: A total of 3743 case reports that were submitted to the South African National Department of Health Pharmacovigilance Centre for Public Health Programmes from 1 April 2015 to 11 September 2017 were used in this study. Demographics, patient history, and discontinuation details were extracted from the Microsoft Excel 2016 data set provided and imported into SPSS® version 25 for analysis. Descriptive analysis was performed and results presented as frequencies, percentages, measure of central tendency and measure of variability. Univariable and multivariable binary logistic regression were performed to identify factors associated with Implanon NXT® discontinuation.

Results or Lessons Learned: The Median age was 26 years (IQR = 10 years, 95 % CI: 27.09 – 27 .58). A total of 2379 (63.56%) of the 3743 cases reported discontinuation of Implanon NXT®. Early discontinuation was reported by 81.1% (1210/1492) cases. Adverse drug reactions were associated with Implanon NXT® discontinuation (AOR= 11.98, CI: 8.10-17.72, p<0.001). The median time between the report of ADR and discontinuation was 0 days. The discontinuation of Implanon NXT® was mainly due to adverse drug reactions (83.99%; 1784/2124). The most commonly reported reason for discontinuation was mennorhagia (37.37%; 728/2124).

Conclusions or Way Forward: The extent of discontinuation of Implanon NXT® appeared to be high in this study. The discontinuation of Implanon NXT® was associated to adverse drug reactions. Rigorous screening and monitoring should be applied to prevent user discontinuation.

ANNEXURE 7: POSTER PRESENTATION

Awareness, Attitude and Knowledge of Modified Release Contraceptives among Women Attending Public Family Planning Clinics in eThekwini Kwa-Zulu Natal

Elizabeth Ojewole*, Shimona Prosad*, Hajrah Beemath, Aadila Haniff, Nkosinathi Mpanza, Kirosha Naidoo, Bilkish Shaik
Discipline of Pharmaceutical Sciences,School of Health Sciences
University of KwaZulu-Natal, P B X54001, Durban, South Africa.

Introduction and Aim

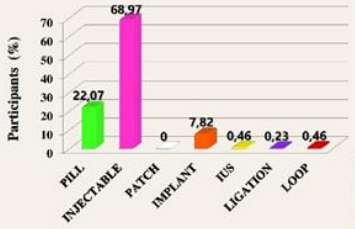
- Modified-release contraceptives (MRCs) include the injectables, transdermal patches, subdermal implants and Intrauterine systems (IUS). They can improve contraceptive adherence among women who use them, hence prevent unintended pregnancies. These MRCs are widely available in many countries, such as USA and Europe[1,2]
- Modified-release contraceptives are shown to improve patient compliance, decrease side effects and improve the effectiveness of drug therapy. However, conventional dosage forms have been shown to exhibit an increase in poor patient compliance, increased patient's chance of missing doses as well as an increased side effects of drugs[3].
- While there is a relatively high awareness and knowledge of various available contraceptive methods among women in South Africa, the reportedly high rates of unintended pregnancy is still of great concern[4,5]. Women's attitude towards the various methods of contraceptives available in SA need to be investigated.
- It was therefore important to investigate the awareness, attitude and knowledge of modified release contraceptives among women who attended public family planning clinics in eThekwini, KwaZulu-Natal

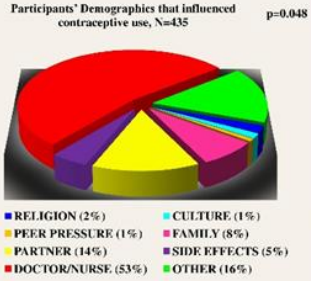
Method

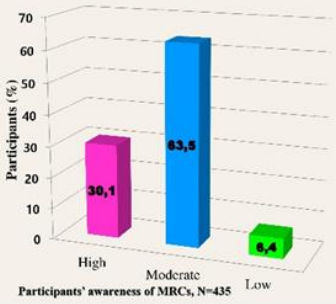
- Study design : A cross-sectional survey was conducted using a structured questionnaire.
- Study setting : Three public family planning clinics
- Population : Women ≥ 18 years who attended family planning clinics throughout the study period.
- Sample size : 435 participants.
- Questionnaire : 21 questions in English language which was then translated into isiZulu was used. A Likert scale format was used to design some of the questions.
- Ethics approval (SHSEC 010/14) and gatekeeper permission were obtained prior to commencement of participants' recruitment for the survey. Participation was voluntary and informed consent obtained.
- Data collection were carried out between June and August 2014 and Data were captured using Microsoft Excel ®.
- Data analysis was conducted using SPSS® version 21. Chi-square test was used to identify any associations between variables.

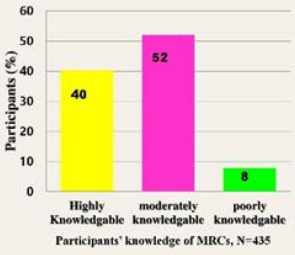
Results and Discussion

- The majority of the participants were aged between 20 - 29 years.
- The injectable was the most identified MRC (54%) followed by the implant (29 %).
- About 26 % of the participants reported missing a dose of their contraceptive.
- Most participants (n=58; 13.3%) reported they became pregnant while taking contraceptives.
- Falling pregnant while on contraceptives were strongly associated with missing a dose (p=0.007)









Conclusions and Recommendations

- Overall, the participants had a moderate awareness and knowledge regarding MRCs.
- The proportion of women falling pregnant as a result of missed doses was high
- Doctors and nurses could impact women's attitude regarding contraceptive use
- Education regarding use of MRCs and importance of adherence should be emphasized

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- The School of Health Sciences for funding, and the KwaZulu-Natal Department of Health for Gatekeeper permission
- All the women who participated in the study.
- All the sisters at the family planning clinics who assisted with access to the patients recruited as participants.

ANNEXURE 8: EXCERPT FROM RESEARCH SYMPOSIUM BOOK OF ABSTRACTS

DISCONTINUATION OF IMPLANON NXT® AMONG USERS AT PUBLIC HEALTH FACILITIES IN SOUTH AFRICA

Prosad, S.*, Ojewole, E.*, Dheda, M.** ,Tlou , B.***

** Discipline of Pharmaceutical Sciences; ** Pharmacovigilance Centre for Public Health Programmes, National Department of Health; *** Department of Public Health.*

Introduction
There are concerns with early Implanon NXT® user discontinuation in South Africa but the true extent of this discontinuation is unknown. Consequently, determination of the extent and the reasons for it is imperative.

Aim
To evaluate discontinuation of Implanon NXT® among users at public health facilities in South Africa

Methods
Secondary data analysis was conducted. A total of 3743 case reports from 1 April 2015 to 11 September 2017 was obtained from South African National Department of Health Pharmacovigilance Centre for Public Health Programmes. Demographics, patient history, and discontinuation details were extracted and imported into SPSS® version 25 for analysis. Results were presented descriptively. Univariable and multivariable binary logistic regression were performed to identify factors associated with Implanon NXT® discontinuation. Results: The median age was 27 years (IQR=10, CI:27.84-28.43). A total of 63.56% (2379/3743) reported discontinuation of Implanon NXT®. Early discontinuation was reported by 81.1% (1210/1492). Adverse drug reactions were associated with discontinuation (AOR= 11.98, CI: 8.10-17.72, $p<0.001$). The median time between the report of ADR and discontinuation was 0 days. The discontinuation of Implanon NXT® was mainly due to adverse drug reactions (83.99%; 1784/2124).

Conclusions
The extent of discontinuation of Implanon NXT® appeared high. The discontinuation of Implanon NXT® was associated to adverse drug reactions. Rigorous screening and monitoring should be applied to prevent user discontinuation.

ANNEXURE 9: STANDARD OPERATING PROCEDURE FOR SUBDERMAL CONTRACEPTIVE IMPLANTS DATA COLLECTION (REPUBLIC OF SOUTH AFRICA, NATIONAL HEALTH DEPARTMENT, N.D)[1]

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

NATIONAL PHARMACOVIGILANCE CENTRE

SOP NUMBER: ADMIN 1.0	
STANDARD OPERATING PROCEDURE	**TITLE: SUBDERMAL CONTRACEPTIVE IMPLANTS DATA COLLECTION**
AUTHOR OF SOP SIMPHIWE DYASI	APPROVAL DATE:
REVIEWED BY:	EFFECTIVE DATE:
APPROVED BY:	PAGES:

1. ABBREVIATIONS:

NPC: National Pharmacovigilance Centre
MNH: Maternal and Neonatal Health
MCWH: Maternal, Child and Women's Health
SOP: Standard Operating Procedure

2. PURPOSE:

The purpose of this SOP is to define the processes and procedures to be followed when collecting data relating to the use of the sub-dermal contraceptive implants.

3. SCOPE/RESPONSIBILITIES:

This SOP applies to all NPC staff, MNH staff and any other personal supporting the efforts of the NPC and MNH with regards to surveillance of the sub-dermal contraceptive implants programme. Staff guided by this SOP include but is not limited to:

- All NPC and MNH Staff members
- All Healthcare workers involved with the surveillance of the sub-dermal contraceptive implant programme
- Technical Advisors/Consultants

[1] Republic of South Africa, National Health Department. n.d. Subdermal contraceptive implants data collection. Standard operating procedure. Pretoria: National Pharmacovigilance Centre.

- Supporting Partners

4. TEMPLATES/RELATED DOCUMENTS

- Active Surveillance Reporting Form for Sub-Dermal Implants

5. DEFINITIONS

Facility:	Any health care facility under the administration of the South African Health Department.
Sub-district:	A local municipality or category B municipality that serves as the third and last local tier of local government.
District:	A district municipality or category C municipality which executes some of the functions of local government for a district.

NB: A pregnancy test should always be done prior to the insertion of the sub-dermal implant and the results clearly documented on the sub-dermal contraceptive implants data collection form. Should the pregnancy test be positive, the health care professional should not continue with the implant insertion procedure.

6. ROLES AND RESPONSIBILITIES

6.1. Filling out the sub-dermal contraceptive implants data collection form, also known as the active surveillance reporting form for sub-dermal implants.

The sub-dermal contraceptive implants data collection form should be completed by any health care professional that either inserts or removes the sub-dermal contraceptive implant.

Insertion: Before the insertion of the implant, the health care professional should complete the sub-dermal contraceptive implants data collection form, documenting all concomitant medicines the patient is currently taking. The health care professional may also use the form as a check list to alert them to potential risk. Should there be no foreseeable suspected risk, the health care professional may

proceed with the insertion procedure after which he or she will document any adverse drug reactions that occurs.

Removal: Before the removal of the implant, the health care professional should complete the sub-dermal contraceptive implants data collection form, documenting all concomitant medicines the patient is currently taking and any adverse drug reactions experienced by the patient. The reason for the removal must be clearly documented.

6.2. Data collection and submission of completed form

Provincial co-ordinators under the MCWH directorate will facilitate the collection of completed forms and will assist with verifying data quality assurance on the forms. Successfully completed forms should be send to District Office (MCWH- Co-ordinator who will fax to Province.

Should the above mentioned methods of direct communication not be possible, MCWH provincial co-ordinators will assist in facilitating a solution they deem fit and proper for their particular province/district/sub-district/facility.

6.3. Adverse Drug Event (ADE)

A serious adverse drug event is a urgent and undesired event occurring as a direct result of an adverse drug reaction (ADR) – such an event should be flagged immediately and reported without delay to both the below mentioned parties:

The National Pharmacovigilance Centre
Maternal and Neonatal Health

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

ACTIVE SURVEILLANCE REPORTING FORM FOR SUBDERMAL IMPLANTS

NATIONAL PHARMACOVIGILANCE CENTRE (NPC)
TEL: 012 395 9506/ 8099
Fax2email: 086 241 2473
Email: npc@health.gov.za

FACILITY NAME			
SUB-DISTRICT			
DISTRICT		TEL	
PROVINCE		FAX	

Please send duplicate to NDoH using the above mentioned details and complete additional information on a separate sheet if necessary

PATIENT DETAILS:

Patient Initials		**Age**		**Date of Birth (dd/mm/yyyy)**	
File No/Reference No		**Weight**		**Height**	

MEDICINES (AND CONCOMITANT MEDICINES, INCLUDING HERBAL PRODUCTS, IF KNOWN)

Concomitant Condition	Medicine taken for concomitant condition
TB ☐ Yes ☐ No	☐ Cycloserine ☐ Ethambutol ☐ Ethionamide ☐ Isoniazid ☐ Lanezolid ☐ Rifampicin ☐ Para-aminosalicylic acid ☐ Protionamide ☐ Pyrazinamide ☐ Teridazone **Other TB Meds (Please Specify)**
HIV/AIDS ☐ Yes ☐ No	☐ Abacavir ☐ Efavirenz ☐ Emtricitabine ☐ Lamivudine ☐ Lopinavir/Ritonavir ☐ Nevirapine ☐ Stavudine ☐ Tenofovir ☐ Zidovudine **Other ARVs (Please Specify)**
Epilepsy ☐ Yes ☐ No	☐ Eslicarbamazepine ☐ Carbamazepine ☐ Clobazam ☐ Lamotrigine ☐ Oxcarbazepine ☐ Phenobarbital ☐ Phenytoin ☐ Primidone ☐ Topiramate ☐ Felbamate **Other Epileptic Meds (Please Specify)**
Any other Meds , INCLUDING HERBAL PRODUCTS (Please Specify)	☐ Garlic ☐ St John's wort

LABORATORY RESULTS: SELECT ABNORMAL ONE(S) AND WRITE THE VALUES (BL=BASELINE; CUR=CURRENT)

	Hb	*CD4*	*Viral Load*	*Other:*
BL				
CUR				

Pregnancy Test Yes ☐ No ☐

Brand Name	*Batch No*	*Expiry Date*

RELEVANT CLINICAL HISTORY (ATTACH ADDITIONAL INFORMATION)

☐ DVT ☐ CA Breast ☐ CVA ☐ **Other (Please Specify)**

Previous Pregnancies	☐ PARA ☐ GRAVIDA
LMP	DATE:
Previous Contraception	☐ Condom ☐ IUD ☐ Injectable contraception ☐ Oral contraception
Breast Feeding (currently)	☐ Yes ☐ No

ADVERSE DRUG REACTION (PLEASE DESCRIBE)

Date of Onset of Reaction (dd/mm/yyyy) _____ Date Reported (dd/mm/yyyy) _____

COUNSELING

Date of counseling (dd/mm/yyyy)	**Suggested Visits**	**Suggested Date**
Topics covered ☐ Traditional Beliefs ☐ Religious Beliefs ☐ Bleeding Profile Changes ☐ Drug Interactions ☐ Efficacy of Sub-Dermal implant ☐ Insertion and Removal Technique ☐ Clinic Visit ☐ Other Insertion date (dd/mm/yyyy): _____ Arm used ☐ Left ☐ Right	Visit 1 – Counseling and insertion- palpable ☐ Yes ☐ No Visit 2 – 1 week after insertion- palpable ☐ Yes ☐ No Visit 3 – 3 months after insertion- palpable ☐ Yes ☐ No Other visits – free to return to the clinic Was X-Ray taken when not palpable ☐ Yes ☐ No Removal Date (if applicable) Reason for removal (if applicable)	_____ _____ _____ _____ _____ _____

REPORTED BY:

Name				Highest Qualification	
Designation	☐ Doctor ☐ Nurse ☐ Pharmacist ☐ Other			Email	
Tel		Signature		Date	

Version 3.5