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A pharmacoeconomic analysis of monotherapy versus combination therapy in the treatment of Pelvic Inflammatory disease

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1.0 INTRODUCTION

1.1 Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is the result of infection ascending from the endocervix causing inflammation and infection of the upper genital tract in women, typically involving the endometrium, fallopian tubes, ovaries, and surrounding structures. In most African countries between 17 and 40% of gynaecological admissions are for PID (1, 2). There is concern over the acute morbidity associated with PID, as well as the sequelae of PID that occur in reproductive-age women. These sequelae include an increased risk of infertility, ectopic pregnancy, recurrent episodes of PID, and chronic abdominal pain leading to surgical intervention. Delay in diagnosis and effective treatment probably contributes to inflammatory sequelae in the upper reproductive tract. It was estimated that the total direct and indirect costs of PID and its sequelae were over 7 billion dollars in the United States (2, 3).

1.2 Treatment

For the treatment of PID, empiric antibiotic therapy (e.g. doxycycline, erythromycin, nitrofurantoin, trimethoprim, trimethoprim-sulfomethoxazole, amoxicillin, and fluoroquinolones) is the norm in community-based patients, with the initial choice of therapy being influenced by clinical efficacy, cost, adverse events, patient allergy history and knowledge of local bacterial resistance patterns. The increasing incidence of resistance to trimethoprim-sulfomethoxazole among *E. coli*, however, has raised concern about the empiric use of this drug to treat patients with PID. A 1999 surveillance study of the predominant urinary tract isolates from 200 different sites in the US showed that 82.6% of 5883 isolates of *E. coli* were susceptible to trimethoprim-sulfomethoxazole, while 96.8% of these same isolates were susceptible to a fluoroquinolone (4).

PID is a polymicrobial condition, and, although *E. coli* and *C. trachomatis* are major pathogens, therapy should also be active against *Neisseria gonorrhoea, M. hominis* and the non-sporing anaerobes.

For this pharmacoeconomic analysis, we have focused on the role of fluoroquinolones as a treatment option.

Fluoroquinolones are a class of antimicrobial drugs which, as a group, have a broad spectrum of activity against organisms involved in a wide variety of infections. An additional advantage is their availability as an oral dosage form, which offers the option of outpatient therapy. Their broad spectrum of activity has also led to the use of fluoroquinolones to treat infections for which they have not received formal regulatory approval, thus raising concerns of extensive and/ or non-selective use (4).The acquisition costs of fluoroquinolones typically exceed those of most alternative oral antibiotics used for pelvic inflammatory disease. Thus, there is debate regarding the appropriate and cost-effective use of these medications in treating some relatively common infections.

1.3 Objective

Containing the cost of antibiotics is every health professional's responsibility. The main objective is to select antimicrobial agents that provide effective therapy at a reasonable cost. The expenditures for antimicrobial therapy are variable and depend on several factors (4, 5):

- acquisition costs of the drug
- the route and frequency of administration
- combination therapy
- the need for monitoring and adjunctive therapy
- potential side effects and resistance
- therapy failure

The successful application of pharmacoeconomic principles to antimicrobial therapy requires maximizing therapeutic effectiveness while minimizing costs. The objective of our study was to carry out a comparative economic evaluation of moxifloxacin monotherapy versus ofloxacin/metronidazole combination therapy in the treatment of pelvic inflammatory disease. Alternate, cheaper non-fluoroquinolone therapies are available in South Africa; however,

overuse of these can result in resistance. Currently, oral doxycycline is recommended in the EDL for the treatment of pelvic inflammatory disease. In more severe cases ampicillin IV is given, followed by oral amoxicillin plus metronidazole. In very severe cases, gentamicin IV is added to the regimen. Other treatment options include the penicillins and macrolides.

Combination therapy is generally considered first-line in the treatment of PID. Fluoroquinolone therapy is generally used in the private sector for the treatment of PID. Fluoroquinolones are an alternate therapy in patients resistant to conventional therapy. However, the potential effectiveness of ofloxacin/metronidazole combination therapy is reduced if patients do not comply with the recommended twice-daily regimen. Moxifloxacin, a fluoroquinolone, is an effective treatment for PID when administered as a once-daily dosage. Moxifloxacin represents a major advance in therapy for PID because it allows directly administered monotherapy. Internationally, especially in Europe, monotherapy with moxifloxacin is considerably more expensive than a course of ofloxacin/metronidazole, a factor that inhibits the widespread adoption of moxifloxacin for the treatment of PID. Since the introduction of the SEP in South Africa, Avelon (moxifloxacin) cost has been reduced by Bayer (Pty) Ltd. Monotherapy is therefore less costly by R32.76 for a 14 day treatment duration compared to combination therapy with ofloxacin/metronidazole.

1.4 Aim

We compared the health outcomes and costs of conventional ofloxacin/metronidazole therapy with moxifloxacin for women who have PID.

1.5 Perspective

The data for this study is obtained from a clinical trial and the economic analysis is from a funder perspective.

2.0 MATERIALS AND METHODS

2.1 Research Design

Refer to **Appendix C** for the Protocol Approval, Ethics Approval and Informed Consent.

This is a retrospective cost analysis conducted from a funder perspective. The cost analysis is based on the clinical results of the MAIDEN study which is a prospective, randomized, double-blind, multicentre, multinational Phase III study comparing the efficacy and safety of moxifloxacin 400 mg once daily orally for 14 days with ofloxacin 400mg twice daily orally plus metronidazole 400mg twice daily orally for 14 days in patients with uncomplicated pelvic inflammatory disease. The clinical trial was carried out at 7 centres across South Africa. After ethical approval for the trial had been obtained, 222 patients with a diagnosis of PID were enrolled between 2003 and 2004. Data for economic evaluation were obtained for 222 patients (moxifloxacin group 111 patients, ofloxacin/metronidazole group 111 patients) with the following reasons for withdrawal:

Table 2.1 Reasons for patient withdrawals

	Moxifloxacin group (n = 111)	**Ofloxacin/metronidazole group (n = 111)**
Consent withdrawn	4	3
Lost to follow up	2	2
Adverse Drug Reaction	2	2
Patient non-compliance	2	2
Protocol violation	2	1
Other	0	1

The study was analyzed on the basis of intention-to-treat. Treatment was for a period of 14 days with follow up at 42 days. This length of therapy was set to ensure that an adequate course of treatment was available for patients with PID and recurrence. Assessment of clinical signs and symptoms was made by the treating physician at baseline, during therapy, at test-of-cure and at follow up. Treating physicians used the following definitions in their assessments:

Clinical Resolution: Disappearance of acute signs and symptoms of infection such that alternate antimicrobial therapy was not required or administered.
Clinical Improvement: Improvement of acute signs and symptoms of infection such that alternate antimicrobial therapy was not required or administered.
Clinical Failure: No apparent response to therapy, persistence of signs and symptoms of infection, or reappearance of signs and symptoms at or before the test-of-cure visit, or use of additional antimicrobial therapy for the current infection.
Indeterminate: Patients in whom clinical assessment was not possible to determine.

The economic analysis of this study assessed:

1. drug acquisition cost
2. medication to treat adverse events
3. medication to treat clinical failure/recurrence of PID
4. additional physician consultations to treat adverse events and clinical failures

The principle of cost minimization was used to analyze the economic impact of the study as both treatment options were found to be equivalent with regard to overall efficacy (i.e. clinical success). Within each group, differences were apparent with regard to the treatment of adverse events and clinical failures. In particular, when clinical successes were broken down into clinical resolution and clinical improvement, differences were apparent in the individual treatment of adverse events and clinical failures. For this reason, decision analysis was used to characterise the clinical and economic outcomes. Healthcare costs and benefits that were common to both treatments were not included as they cancelled out when comparisons were made (e.g. travelling allowance granted to each patient in the clinical trial). Direct medical costs and benefits were evaluated from the perspective of the funder, hence, indirect costs such as those incurred through lost wages or productivity were not evaluated. Not all of the direct medical costs and benefits were captured (e.g. nursing and pharmacy time), because of the

artificial constraints of the clinical trial design. Discounting was not necessary, as the treatment did not extend beyond one year. As this was a controlled clinical trial, assessment of patient compliance could not be used to determine a real-life situation; therefore patient compliance was not of value to the pharmacoeconomic analysis.

2.1.1 Inclusion Criteria

Patients fulfilled the following criteria for inclusion in the study (1):

1. Female patients aged 18 years or older
2. Diagnosis of PID based on:
   2.1 All of the following symptoms:
   - Direct lower abdominal tenderness with or without rebound tenderness
   - Adnexal tenderness on bimanual vaginal examination
   - Cervical motion tenderness on bimanual vaginal examination

   2.2 one or more of the following signs:
   - i) Rectal/ tympanic/ oral temperature value > 38.0˚C or axillary/ cutaneous temperature value > 37.5˚C
   - ii) Erythrocyte sedimentation rate > 15 mm/hr
   - iii) Elevated C-reactive protein value (above the upper limit of normal value for the respective laboratory)
   - iv) White blood cell count $\geq$ 10,500/mm^3
   - v) Laparoscopic evidence of PID
   - vi) Signs suggestive of cervical infection including mucopurulent cervical discharge (defined as the presence of a grossly yellow or greenish exudates) or positive Gram stain for Gram-negative intracellular diplococci from the endocervix.
   - vii) Untreated recent (less than 14 days) documented gonococcal or chlamydial cervicitis
3. Endocervical cultures performed within 48 hours prior to entry into study
4. Patients who are willing to use condoms as barrier contraception during the course of study
5. Patients must have signed an informed consent form prior to study entry

2.1.2 Exclusion Criteria

Patients with any of the following criteria were to be excluded from participation in the study (1):

1. Patients who are pregnant or lactating
2. Known hypersensitivity to either of the study drugs, related compounds or any of the excipients
3. Previous history of tendinopathy associated with quinolones
4. Clinically relevant bradycardia
5. Clinically relevant heart failure with reduced left-ventricular ejection fraction
6. Previous history of symptomatic arrhythmias
7. Known to have congenital or documented acquired QT prolongation or receiving concomitant medication reported to increase the QT interval (eg anti-arrhythmics class IA, anti-arrhythmics class III, neuroleptics, tricyclic antidepressive agents, certain antimicrobials, certain antihistamines and cisapride)
8. Patients with known electrolyte disturbances, particularly uncorrected hypokalaemia
9. Patients with CNS disorders which may predispose to seizures or lower the seizure threshold
10. Patients with a family history of, or actual defects in glucose-6-phosphate dehydrogenase
11. Patients with a history of continuous symptomatology longer than 30 days
12. Patients likely to require concomitant systemic antibacterial therapy during the course of the study (Note: one single administration of any systemic antibiotic is permitted)
13. Surgical intervention within the next 24 hours is anticipated
14. Patients receiving systemic antibacterial agents for more than 24 hours within 7 days prior to enrolment
15. Patients with an IUD who refuse to have it removed
16. Patients with a history of uterine or pelvic or abdominal surgery within 30 days prior to treatment
17. Patients who have undergone surgery for tubal ligation or hysterectomy
18. Vomiting patients or patients unable to follow or tolerate and oral antibiotic regimen

19. Patients receiving immunosuppressive therapy, defined as chronic treatment (≥ 2 weeks) with a known immunosuppressive medication, including treatment with > 10mg/day of systemic prednisone or equivalent
20. Patients with known impaired liver function (Child Pugh C, and/ or transaminases increase > 5 fold the upper limit of normal)
21. Patients with known renal impairment (serum creatinine > 1.5 mg/dl or > 135 umol/l)
22. Patients with known neutropenia (<1000/mm^3), or having HIV infection with a CD4 count of < 200/mm^3, or presenting with an AIDS-defining event, or under an highly active antiretroviral therapy.
23. Diagnosis of rapidly fatal illness with a life expectancy of less than 6 months
24. Patients who have been previously enrolled in this clinical study
25. Patients who have taken investigational drugs within the last 30 days

2.2 Treatment

2.2.1 Active Treatment Group: Moxifloxacin

Moxifloxacin is an 8-methoxy-fluoroquinolone antibacterial agent. Characterised by a broad spectrum of activity and bactericidal action, moxifloxacin has *in vitro* activity against a wide range of Gram-positive and Gram-negative organisms, anaerobes, acid-fast bacteria, and atypicals. Against anaerobes, moxifloxacin has activity comparable to that of metronidazole, and overall is at least sixteen-fold more active than ciprofloxacin, ofloxacin, and cefoxitin. The spectrum of activity of moxifloxacin also covers enteric Gram-bacilli with a MIC_{90} of 0.06 mg/L against *Escherichia coli*. (6).

Side Effects:

The most common adverse drug reactions observed in the study included: abdominal pain, nausea, vomiting, abnormal liver function tests, increased and decreased haematocrit, taste perversion, hypertension, gastro-intestinal disorders, anaphylaxis and arthralgia. Treatment of these side effects contributed to the final cost of therapy.

2.2.2 Comparator: Ofloxacin/ Metronidazole combination therapy

For oral treatment of PID, guidelines include the use of ofloxacin in combination with metronidazole as standard combination therapy.

2.2.2.1 Ofloxacin

Ofloxacin is a quinolone carboxylic acid derivative which has a broad spectrum of antibacterial activity against both Gram-positive and Gram-negative bacteria. Ofloxacin has a bactericidal effect. Ofloxacin is indicated for the treatment of the following bacterial infections if these are due to ofloxacin-sensitive pathogens:

Infections of the urinary tract.

Sexually transmitted diseases: Acute uncomplicated urethral and cervical gonorrhoea, urethritis and cervicitis due to *Chlamydia trachomatis*. Mixed infections of the urethra and cervix due to *Chlamydia trachomatis* and *Neisseria gonorrhoea*. (7)

Side Effects

Adverse drug reactions included gastric symptoms, nausea, vomiting, diarrhoea, vaginitis, anaphylaxis, increases in liver enzymes and changes in the blood picture and musculoskeletal disorders. Treatment of these side effects increased the cost of treatment for this group of patients in the clinical study.

2.2.2.2 Metronidazole:

Metronidazole is directly trichomonacidal. It is also directly amoebicidal in very low concentrations. It is active against a variety of anaerobic bacteria, particularly *Bacteriodes fragilis*. Metronidazole is indicated in the oral treatment of:

Urogenital *trichomoniasis* and infections caused by anaerobic bacteria. (8).

Side Effects

The adverse effects of metronidazole are generally dose-related. The most common are gastro-intestinal disturbances, especially nausea and an unpleasant metallic taste; abdominal cramps, epigastric discomfort, nausea, headache, anorexia and vomiting. Diarrhoea, dry mouth, a furred tongue, glossitis, and stomatitis also occurred.

2.3 Statistical Methods and Determination of Sample Size

Refer to **Appendix B**: CALCULATIONS

B.1 Sample size calculation for moxifloxacin group

B.2 95% Confidence interval for success rates

B.3 Gc statistic

B.4 Test for differences between two independent proportions (z-test)

B.5 Test for differences between two independent proportions (χ^2- test)

χ^2- tests were used for between-treatment comparisons.(9). The tests showed that both treatments were comparable for the purpose of this pharmacoeconomic analysis.
We used the Gc statistic to test for two independent proportions with respect to the success rates. (9). The results displayed equivalence with respect to efficacy for both treatment options. When broken down further, the results displayed equivalence with respect to Clinical Resolution and Clinical Improvement and the incidences of Drug Related Adverse Events. This was confirmed by using the z-test and χ^2- tests.

Table 2.2 Clinical response at test-of-cure (patients valid for economic analysis i.e. intention-to-treat) as determined by success rates within a 95% confidence interval

	Moxifloxacin 400mg od		**Ofloxacin 400mg bid + Metronidazole 400 mg bid**	
	/111	**%**	**/111**	**%**
Clinical Improvement	72	65	80	72
Clinical Resolution	32	29	23	21
Clinical Failure	3	3	4	4
Indeterminate	4	4	4	4
Success rate	104	94	103	93
95% Confidence interval	(89.6%; 98.4%)		(88.3%; 97.7%)	

For the moxifloxacin group, the study on 111 patients revealed that the treatment provided clinical success (clinical improvement + clinical resolution) in 104 (94%) of patients to within 4% with a probability of 95%. The sample size of 111 patients was therefore sufficient for purposes of the analysis.

2.4 Type of Analysis

2.4.1 Decision Analysis

The study uses cost minimisation analyses to determine the relative role of moxifloxacin monotherapy versus ofloxacin/ metronidazole combination therapy in the treatment of pelvic inflammatory disease. This analytical technique is applied in situations where the outcomes associated with two alternative means of intervention are equivalent and the objective is thus to compare the total resource costs associated with using the different treatments. (10). The underlying hypothesis was that the net direct cost associated with all medical resources used could be considered to adequately reflect the costs of the treatment itself on the one hand and the clinical outcome on the other. Clinical success was further broken down into clinical resolution and clinical improvement and within these groups, differences in the treatment of adverse events were evaluated. Decision analysis is used to characterise the economic outcomes between the groups and provides a structure upon which to base the sensitivity analyses. The outcomes were depicted on a decision tree which proportionately determined the cost of treatment per patient in the two treatment groups.

Currently published prices were used in this study as listed on the Orderwise Retail Pharmacy Ordering System in September 2004 (11). Cost values for moxifloxacin are based on the retail price of Avelon tablets in South Africa. Cost values for the comparator, ofloxacin and metronidazole, are based on the cheapest available generic on the South African market i.e. Zanocin 400 and Metazol 400 mg respectively.

Break-even analysis, which varied drug acquisition cost, were applied to test the effect of increasing or decreasing the acquisition costs of the two treatment options. We varied drug acquisition costs for moxifloxacin over the range of 2 – 20 %.

2.5 Identification of Resources

2.5.1 Acquisition Costs

The acquisition cost refers to the unit price of the antibiotic. Prior to the promulgation of the new pricing regulations as outlined in Act 101 of 1965 as amended in August 2004, costs

varied according to wholesaler costs, the quantity purchased, buying group arrangements, and rebate programs based on volumes. In general, older drugs, particularly when their patents have elapsed, are less costly to acquire on a per-unit basis than drugs that are still protected by a patent. Based on the current fee structure, a patient presents a prescription at a pharmacy, which is found to be appropriate and can be easily dispensed from products on the shelf without further intervention as is the case with our recommended treatments for PID. The dispensing fee is calculated as 26% of the SEP (Single Exit Price), with a maximum of R26. As this is a fixed percentage, the dispensing fee was not included in this economic evaluation. All drug costs were based on published September 2004 prices.

The study antibacterial costs applied to the primary analysis are as follows:

Rands per 400mg moxifloxacin dose

Rands per 400mg ofloxacin dose

Rands per 400mg metronidazole dose

2.5.2 Route of Administration and Frequency

Moxifloxacin and ofloxacin/metronidazole are administered by the oral route. As these are simple drug formulations, there is no need for manipulation as would be required with an intravenous formulation. Ofloxacin/metronidazole however, is administered twice daily whereas moxifloxacin is administered once-daily.

2.5.3 Other Cost Factors

2.5.3.1 Monitoring Costs

Various factors have been considered in relation to the acquisition and administration costs for patients receiving antimicrobial therapy, such as the cost of monitoring. Antibiotics that warrant monitoring of platelets or periodic liver function tests also illustrate cost factors that need to be calculated to determine the true cost of antimicrobial therapy with different agents. In this study, monitoring costs were included in the treatment of adverse events.

2.5.3.2 Obligatory Costs of Additional Therapy

Obligatory combination therapy is another hidden cost factor to be considered in determining costs of antimicrobial usage. Metronidazole should not be used alone and must always be

combined with an agent with antiaerobic bacterial activity. For this reason, the cost of the obligatory additional drug must be factored in to arrive at the actual cost of using the comparator therapy.

2.5.3.3 Side Effects

Antibiotics that are associated with laboratory abnormalities increase the actual cost of using the drug. Antibiotics that cause clinical side effects (e.g. *Clostridium difficile* diarrhoea, seizures, vomiting, arthralgias, abnormalities in blood tests) are considered in this pharmacoeconomic analysis. The costing is broken down into the following:

Antibacterial-related direct costs:

Additional medication to manage adverse events

Other direct costs:

Cost of additional physician visit to manage adverse events

2.5.3.4 Resistance

Using antibiotics with a known resistance potential may necessitate the use of other more expensive drugs if serious resistance problems are encountered. Opting for drugs with a low resistance potential minimizes the economic and medical implications of antibiotics that have been associated with problems of resistance. Moxifloxacin has not as yet displayed resistance in South Africa as it is a newer fluoroquinolone and its use has been limited.

2.5.3.5 Therapy Failure

The cost of failed therapy is not inconsequential and is often underappreciated. Patients' needs are best served by initiating appropriate antimicrobial therapy as soon as possible after a working diagnosis is made. A stepwise approach to antimicrobial therapy should be avoided because it is costly and forfeits precious time. If an antimicrobial that is less potent than another one is prescribed, the potential for a delayed or ineffective therapeutic response is present. Time is wasted when waiting for a therapeutic response that could have been achieved more quickly with a more effective agent. The chances of curing an infection are best in the early stages. If there is a delay in therapeutic response or if therapy is unsuccessful, the patient must still be given a more potent antibiotic to eradicate the infection. A more potent

and effective antibiotic might, in fact, appear to be more costly on a per unit basis than a less effective antibiotic, but it is more cost-effective in terms of outcome because it does not result in drug-related failure. Sometimes the most effective agent is not the least expensive one to acquire but is, in the clinical setting, the one that is cost effective. The costing for therapy failures included:

Antibacterial-related direct costs:

Additional medication to manage therapeutic failures

Other direct costs:

Cost of additional physician visit to manage treatment failures

2.6 Total Costs and Outcomes

Total costs and total outcomes were reported for each alternative therapy. These totals enable us to better appreciate the magnitudes involved and also allow clearer comparisons. For each clinical outcome, the drug acquisition cost for the study drug, cost of treating adverse events, cost of additional physician visits and cost of treating clinical failures were evaluated. The Clinical Outcomes assessed were:

1. Clinical Resolution:
    - Drug related adverse events
    - Non drug related adverse events
    - No adverse events
2. Clinical Improvement:
    - Drug related adverse events
    - Non drug related adverse events
    - No adverse events
3. Clinical Failure
4. Indeterminate

2.6.1 Decision Model

A model was developed to determine the cost of monotherapy vs combination therapy as a 14-day regimen for pelvic inflammatory disease in women. The basic scheme for each arm of the

tree was as follows: a female patient presents with signs, symptoms and preliminary medical evaluation which indicates a pelvic inflammatory disease, no urine culture is sent at this point (consistent with general clinical practice), but she is treated on an empiric basis with a 14-day course of antibiotic (i.e. choice node); the patient may return in 14 days if symptoms persist, necessitating a change in drug therapy; or the patient may develop side effects (e.g. rash, nausea, vaginitis), also obliging a change in treatment; and finally, the patient may have a recurrence up to 6 weeks after initial therapy, necessitating additional drug therapy to cure the infection.

Structure of the Decision Model: The Basic Tree

Figures 2.1 and 2.2 show the decision model used in our analysis. We calculated health outcomes and costs for two groups of women with PID. One group was treated with the ofloxacin/metronidazole combination therapy strategy and the other group with the moxifloxacin monotherapy strategy. The combination therapy strategy consisted of oral ofloxacin 400 mg twice daily plus metronidazole 400 mg twice daily for 14 days; the monotherapy strategy consisted of moxifloxacin 400 mg once daily for 14 days. Both management strategies were identical in all other respects. Values at the terminal nodes are costs per patient for each branch and values at the choice nodes represent the expected cost for choosing that therapy i.e. the cost of treatment for all patients in that particular group displaying a defined clinical outcome.

Figure 2.1 Basic Decision Tree: Moxifloxacin Group

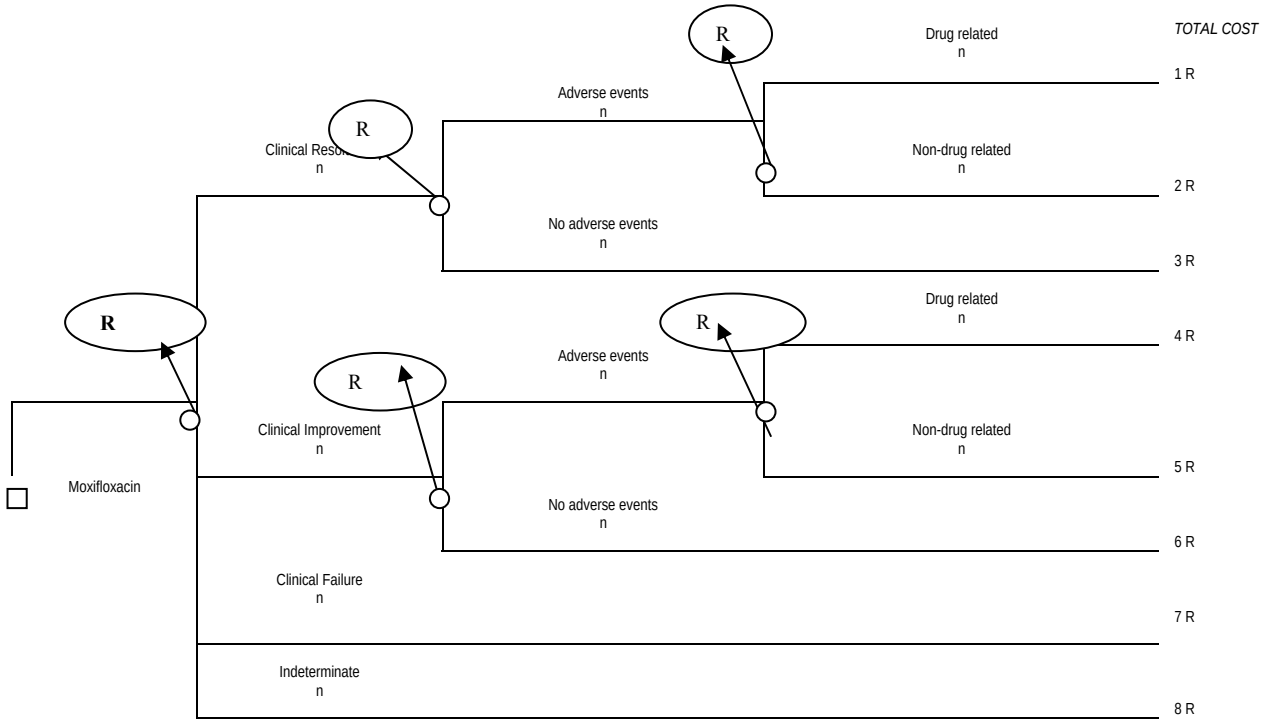
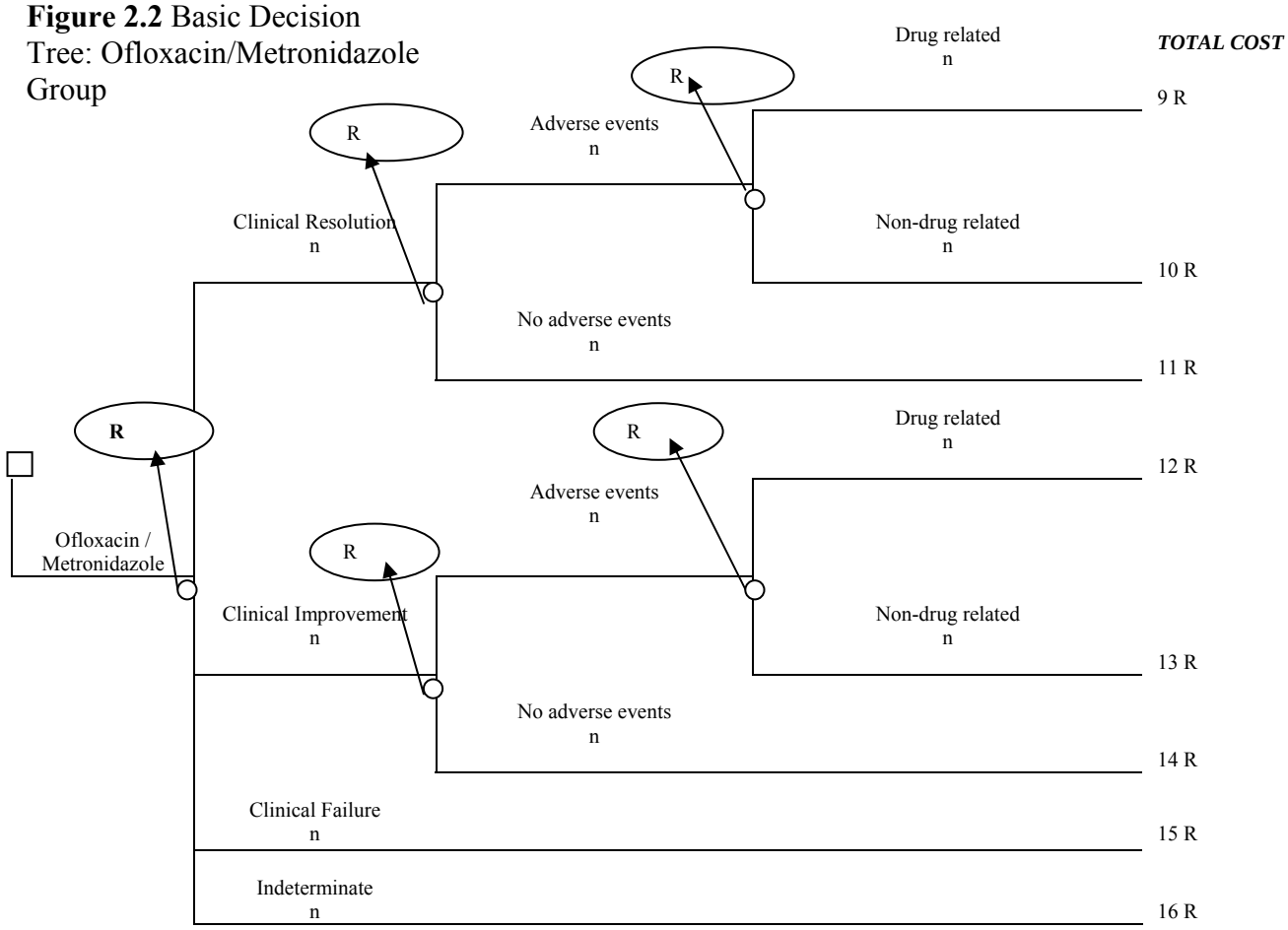


Figure 2.2 Basic Decision Tree: Ofloxacin/Metronidazole Group



2.7 Time Horizon

Cost and outcomes were evaluated out to 6 weeks to capture differences in the risk of recurrent infections between therapies. Due to the short time frame of this particular disease state, future costs and outcomes are not discounted.

2.8 Assumptions

For purposes of analysis of the use of monotherapy versus combination therapy in the treatment of pelvic inflammatory disease, the following major assumptions are made:

a) It is estimated that of those women presenting with signs and symptoms of pelvic inflammatory disease, 86% will have a bacterial infection, 6% will have non-bacterial infection, and 8% will have other diagnoses (12).
b) Clinical success rates (i.e. alleviation of symptoms) are a more relevant indicator of response to treatment as opposed to bacteriological success rates, as it is the symptoms which prompt patients to seek medical care.

3.0 RESULTS

Refer to **Appendix A** for listings of individual results.

3.1 Outcomes of Interest

The major findings of the clinical trial are summarized in the following tables and figures:

Table 3.1 Age comparisons for the moxifloxacin treatment group and ofloxacin/metronidazole treatment group

	Mean age	**Range**
Moxifloxacin	29 yrs	18 – 50 = 32
Ofloxacin/metronidazole	30 yrs	18 – 50 = 32

The two treatment groups were comparable at baseline for age (mean age 29 years, range 18 - 50 years for moxifloxacin group; 30 years, range 18 - 50 years for ofloxacin/metronidazole group).

Table 3.2 Clinical Response comparisons for the moxifloxacin treatment group and ofloxacin/metronidazole treatment group

	Moxifloxacin		**Ofloxacin/metronidazole**	
Clinical Response	**Frequency**	**Percentage**	**Frequency**	**Percentage**
Clinical Resolution	72	65	80	72
Clinical Improvement	32	29	23	21
Clinical Failure	3	3	4	4
Indeterminate	4	4	4	4

Table 3.3 Detailed comparison of the proportions of patient populations and their outcomes

Clinical Outcome	**Moxifloxacin**	**Ofloxacin/metronidazole**
Clinical Resolution	72/111	80/111
Adverse Events	39/72	58/80
Drug-related adverse events	27/39	44/58
Non-drug related adverse events	12/39	14/58
No Adverse Events	33/72	22/80
Clinical Improvement	32/111	23/111
Adverse Events	16/32	12/23
Drug-related adverse events	14/16	10/12
Non-drug related adverse events	2/16	2/12
No Adverse Events	16/32	11/23
Clinical Failure	3/111	4/111
Indeterminate	4/111	4/111

χ^2- tests confirmed equivalence between the two groups with regard to their clinical outcomes.

Clinical Resolution:

In the moxifloxacin group, 72 patients displayed clinical resolution. Of those 72 patients, 39 patients experienced adverse events, 27 were related to moxifloxacin and 12 were not related to the study drug. In the moxifloxacin group, 33 patients who displayed clinical resolution experienced no adverse events.

In the ofloxacin/metronidazole group, 80 patients displayed clinical resolution. Of those 80 patients, 58 patients experienced adverse events, 44 were related to ofloxacin/metronidazole and 14 were not related to the study drug. In the ofloxacin/metronidazole group, 22 patients who displayed clinical resolution experienced no adverse events.

Clinical Improvement:

In the moxifloxacin group, 32 patients displayed clinical improvement. Of those 32 patients, 16 patients experienced adverse events, 14 were related to moxifloxacin and 2 were not related to the study drug. In the moxifloxacin group, 16 patients who displayed clinical improvement experienced no adverse events.

In the ofloxacin/metronidazole group, 23 patients displayed clinical improvement. Of those 23 patients, 12 patients experienced adverse events, 10 were related to ofloxacin/metronidazole and 2 were not related to the study drug. In the ofloxacin/metronidazole group, 11 patients who displayed clinical improvement experienced no adverse events.

Clinical Failure:

In the moxifloxacin group 3 patients displayed clinical failure and were therefore switched to an alternate treatment. No adverse events were experienced by these patients.

In the ofloxacin/metronidazole group 4 patients displayed clinical failure and were therefore switched to an alternate treatment. No adverse events were experienced by these patients.

Indeterminate

In the moxifloxacin group 4 patients displayed results that could not be assessed. No drug related adverse events were experienced by these patients.

In the ofloxacin/metronidazole group 4 patients displayed results that could not be assessed. No adverse events were experienced by these patients.

Table 3.4 Summary of clinical findings

Outcome measure	**Moxifloxacin monotherapy**	**Ofloxacin/ metronidazole combination therapy**
Patients enrolled (ITT population)	111	111
Patients completed study (PP population)	101	100
Clinical improvement at TOC	32	23
Clinical resolution at TOC	72	80
Clinical failures at TOC	3	4
Indeterminate at TOC	4	4
Proportion with adverse effects	55	70
Proportion requiring additional antibiotic therapy due to re-infection	1	1
Withdrawals due to:		
Consent withdrawn	4	3
Lost to follow up	2	2
Adverse drug reaction	2	2
Patient noncompliance	2	2
Protocol violation	1	1
Other	0	1

Key:

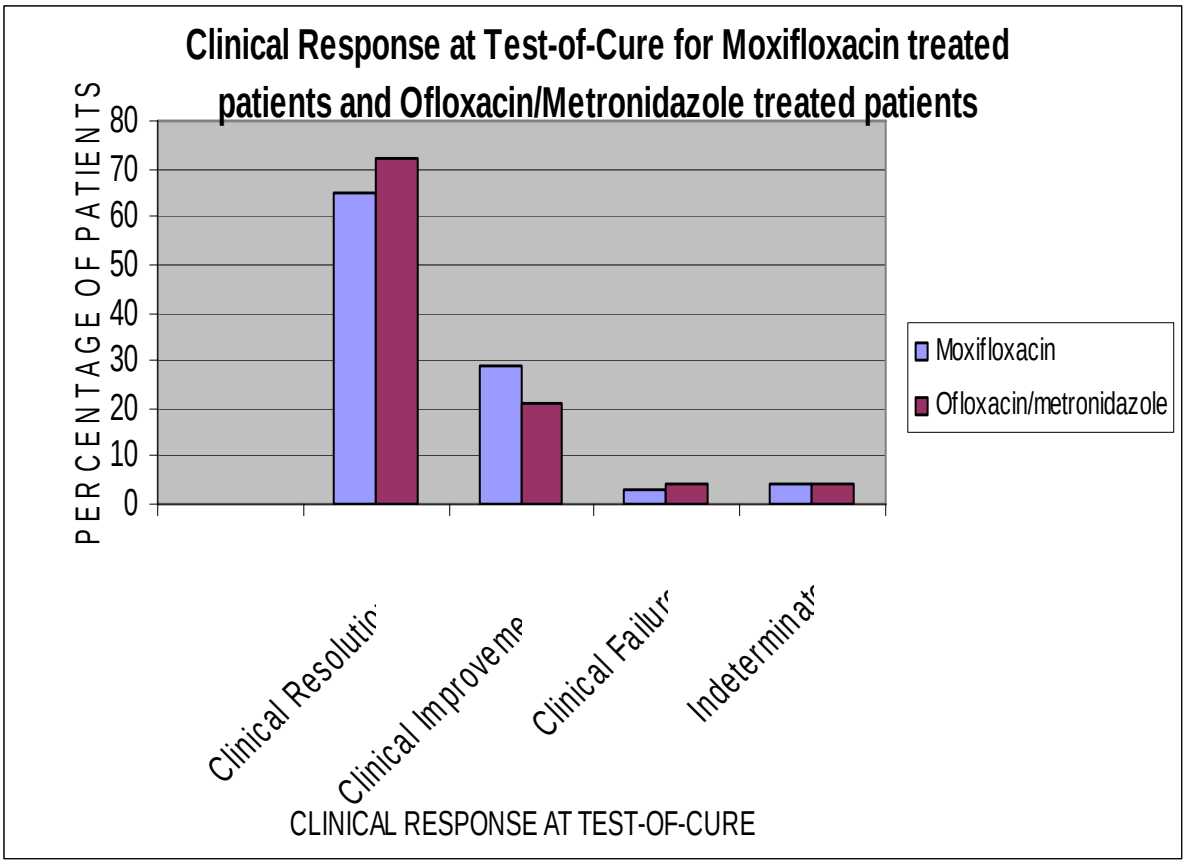
ITT – Intent-to-treat

PP – Per Protocol

TOC – Test of Cure visit

Analysis of clinical efficacy (clinical improvement or clinical resolution) on the basis of intention-to-treat revealed no significant difference between treatments in clinical efficacy at test-of-cure ($p>0.05$), with 94% and 93% efficacy for the moxifloxacin group and ofloxacin/metronidazole group respectively.

Figure 3.1 Clinical Responses at Test-of-Cure



3.2 Acquisition Costs

Daily treatment acquisition costs:

Avelon 400 mg (moxifloxacin) once daily : R28.28 per patient per day

Zanocin 400 mg (ofloxacin) bd + Metazol (metronidazole) 400 mg bd : (R15.12 x 2) + (R0.11 x 2) = R30.62 per patient per day.

The incremental primary medical cost for ofloxacin/metronidazole versus moxifloxacin was R2.34 per patient.

14-Day treatment acquisition costs:

Avelon 400 mg once-daily : R395.92

Zanocin 400 mg bd + Metazol 400 mg bd : R428.68

Monotherapy is therefore less costly by R32.76 for a 14 day treatment duration compared to combination therapy with ofloxacin/metronidazole. This price difference could possibly influence the results of the pharmacoeconomic analysis to be in favour of moxifloxacin monotherapy. This bias is minimised by performing a break-even analysis and varying the cost of moxifloxacin.

3.3 Support Medicine Cost

One patient in each group required further antibiotic therapy to treat re-infection. Forty-seven versus fifty-eight patients in the moxifloxacin group versus ofloxacin/metronidazole group respectively were treated for treatment related adverse events.

3.4 Additional Physician Consultations

Treatment modifications necessitated by inadequate treatment and adverse events generated 107 additional physician consultations (48 for moxifloxacin group and 59 for ofloxacin/metronidazole group).

3.5 Overall Cost Effectiveness

Standard costs are outlined in **Table 3.5**. To ensure consistency, most costs were estimated from a single source. Specifically, costs are derived from: Orderwise, September 2004 (11), and Pricing Regulations published in August 2004 (Act 101 of 1965 as amended).

Table 3.5 Standard Costs used in the analysis of moxifloxacin monotherapy versus ofloxacin/ metronidazole combination therapy in the treatment of pelvic inflammatory disease

Variable	**Value**
Initial visit to physician	R155
Revisit with side effects or persistent symptoms	R155
Revisit for recurrent infection	R155
Daily cost, moxifloxacin 400mg od	R28.28
Daily cost, ofloxacin + metronidazole	R30.62

The pharmacoeconomic analysis was performed on 222 patients. Analysis was on an intention-to-treat basis. There were no statistically significant differences in demographic variables between treatment groups. The majority of adverse events requiring economically significant treatment consisted of nausea, vomiting, vaginitis, arthralgias and blood dyscrasias. No significant differences in clinical outcomes were detected.

The cost analysis is a cost minimisation analysis that uses the Average Cost Effective Ratio (ACER) to determine the cost per successfully treated patient. This is depicted in the table below.

	Ofloxacin/metronidazole	Moxifloxacin
ACQUISITION COST	R44489.58	R40835.92
ADDITIONAL PHYSICIAN VISITS	R12090.00	R9610.00
ADDITIONAL TREATMENT: switching to alternate antibiotic	R210.07	R1843.79
TREATMENT OF MEDICATION related adverse events	R9727.55	R4865.83
TREATMENT OF non MEDICATION related adverse events	R482.65	R188.67
TOTAL COST OF TREATMENT FOR ALL PATIENTS ENROLLED IN THE CLINICAL TRIAL (adding all of the above)	R 66 999.85	R 57 344.21
COST OF TREATMENT PER PATIENT	R 603.60	R 516.61
SUCCESS RATES	93 % *	94 % *
COST PER SUCCESSFULLY TREATED PATIENT	R 649.03	R 549.59

* 95 % Confidence intervals for Success Rates:
Moxifloxacin (89.6%; 98.4%)
Ofloxacin/metronidazole (88.3%; 97.7%)

Tables 3.6 to Table 3.9 outline the cost of treating adverse events for individual patients in the two groups. The adverse event treatment is broken down into Drug Related Adverse Events (i.e. related to the study drug) and Non-Drug Related Adverse Events (i.e. not related to the study drug). The decision on whether an adverse event was drug related or not was left with the study investigator.

Table 3.6: Treatment of Adverse Events: Moxifloxacin Group – Clinical Resolution

TREATMENT OF ADVERSE EVENTS: MOXIFLOXACIN GROUP – CLINICAL RESOLUTION					
SUBJECT NUMBER	ADVERSE EVENT	TREATMENT OF DRUG RELATED ADVERSE EVENTS		TREATMENT OF NON-DRUG RELATED ADVERSE EVENTS	
		MEDICATION TO TREAT ADVERSE EVENTS	TOTAL COST	MEDICATION TO TREAT ADVERSE EVENTS	TOTAL COST
101008	HEARTBURN	GELUSIL	R 158.76		
101022	ANEMIA, HYPOKALEMIA, SYPHILIS, INCR SGOT	SLOW-K	R 72.90	BENZATHINE PENICILLIN	R 5.72
		IRON SULPHATE	R 10.78		
		MULTIVITE	R 0.82		
101023	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101026	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101028	OTITIS EXTERNA, LEUCOPENIA, THROMBOPENIA	PANADO 500MG	R 3.36		
101032	HEARTBURN	GELUSIL	R 25.20		
101034	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101035	SYPHILIS	BRUFEN	R 56.70		
101038	SOFT TISSUE INJURY	BRUFEN	R 6.75		
101041	FLU, SYPHILIS	BRUFEN	R 13.50	BENZATHINE PENICILLIN	R 5.72
101044	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101046	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101053	HEADACHE	PARACETAMOL	R 2.40		
		VITAMIN B-COMPLEX	R 1.46		
		BRUFEN 400MG	R 16.20		
101059	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101061	NAUSEA	MAXOLON	R 17.28		
101064	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101075	SYPHILIS, DENTAL ABCESS	CODIS	R 8.46	BENZATHINE PENICILLIN	R 5.72
101078	DYSFUNCTIONAL UTERINE BLEEDING	NUR-ISTERATE	R 224.28		
101079	NAUSEA, NEUTROPENIA, ARMPIT ABCESS, MENSTRIAL IRREG	DEPO-PROVERA	R 6.48		
101081	CONJUNCTIVITIS	CHLOROMYCETIN	R 32.65		
102010	INFLUENZA,NAUSEA	MED-LEMON	R 1.17		
		FLUTEX CAPSULES	R 63.42		
102037	HEADACHE,DIARRHOEA	GRANDPA	R 1.40		
102058	MENSTRUAL IRREGULAROTIES	DEPO PROVERA	R 84.60		
103001	DYSPNOEA	VENTOLIN	R 23.32		
103007	ANEMIA	FERROUS SULPHATE	R 63.84		
		FOLIC ACID	R 1.72		
103013	HYPERTENSION,SYPHILIS,NEUTROPENIA	ENALAPRIL	R 59.64	BENZATHINE PENICILLIN	R 34.03
		BRUFEN	R 24.30		
103015	LAPAROTOMY,ANEMIA,INCR SGOT	BRUFEN	R 5.40		
103016	STOMACHCRAMPS,ARTHRALGIA,SYPHILIS,DIARRHOEA, ANEMIA	MULTIVITAMIN	R 0.82	BENZATHINE PENICILLIN	R 34.03
		VITAMIN B-COMPLEX	R 1.46		
		FERROUS SULPHATE	R 127.68		
		BRUFEN	R 54.00		
103020	BACKACHE	BRUFEN	R 5.40		
		MAINTELYTE	R 67.62		
103026	ANEMIA	FOLIC ACID	R 1.72		
		IRON	R 0.90		
103031	SYPHILIS			BENZATHINE PENICILLIN	R 34.03
104008	NAUSEA,VAG THRUSH	MAXOLON	R 21.60		
		CANESTAN	R 47.75		
		PANADO	R 4.80		
104012	TIREDNESS,BACKACHE	BRUFEN	R 113.40		
105007	HEADACHE,DIZZINESS,CANDIDA VAGINITIS,SYPHILIS	BRUFEN	R 56.70	BENZATHINE PENICILLIN	R 11.44
		DENOREX	R 22.06		
		AQUEOUS CR	R 2.95		
105008	GENERAL BODY PAINS,LOWER ABD PAIN,UTI,CANDIDA VAGINITIS,ELEV CREATININE,ELEV ALKPHOS,ELEV ALT	ZINACEF, FLAGYL	R 768.48		
105010	HEADACHE, CANDIDA	CANESTEN	R 47.75		
		PARACETAMOL	R 26.88		
105013	LOOSE STOOLS,NAUSEA,INTEMITTENT HEADACHES	GRANDPA	R 0.70		
107001	EXACERBATION OF ABD PAIN	ZINACEF	R 649.82		
TOTAL COST OF TREATMENT			R3009.28		R170.73

Table 3.7: Treatment of Adverse Events: Moxifloxacin Group – Clinical Improvement

TREATMENT OF ADVERSE EVENTS: MOXIFLOXACIN GROUP – CLINICAL IMPROVEMENT					
SUBJECT NUMBER	ADVERSE EVENT	TREATMENT OF DRUG RELATED ADVERSE EVENTS		TREATMENT OF NON-DRUG RELATED ADVERSE EVENTS	
		MEDICATION TO TREAT ADVERSE EVENTS	TOTAL COST	MEDICATION TO TREAT ADVERSE EVENTS	TOTAL COST
102001	SORE THROAT, BODY ACHE	IBUPROFEN	R 148.50		
		PARACETAMOL	R 7.20		
102006	NAUSEA,HEADACHE, CONSTIPATION	IBUPROFEN	R 162.00		
		CYCLIZINE	R 13.20		
		FYBOGEL	R 97.44		
102012	HYDRO TUBO OVARIAN MASS,NAUSEA, BODY ACHE	MAXOLON	R 6.30		
		VOLTAREN IMI	R 36.82		
		DOLOROL FORTE	R 29.39		
102018	CANDIDA	CANESTEN	R 72.81		
102031	HEADACHE	BRUFEN	R 37.80		
102060	CANDIDA ALBICANS	MULTIVITAMIN	R 1.64		
104002	FLU,CONSTIPATION	STOPAYNE TAB	R 65.94		
104011	SLIGHT DIZZINESS,VAG THRUSH	CANESTAN	R 47.75		
104013	TERMINATION OF PREGNANCY			MISOPROSTIL	R17.94
104016	CANDIDIASIS VAG INFECTION	CANESTAN	R 47.75		
105004	VOMITING,NAUSEA,ANEMIA,RASH,CONSTIPATION,INCR ESR,RAISED PLATELET, PAIN	OMNOPON	R 9.09		
		PANADO	R 26.88		
		STEMETIL IV	R 49.80		
		SENOKOT	R 2.40		
		STEMETIL TAB	R 92.31		
105014	ELEVATED ESR,ANEMIA, PAIN	PANADO	R 12.96		
		FERROUS SULPHATE	R 63.84		
105020	HEADACHE	PANADO	R 2.40		
105022	CONJUNCTIVITIS, PAIN	PANADO	R 12.00		
		CHLOROMYCETIN	R 32.65		
		IBUPROFEN	R 16.20		
106002	VAGINAL INFECTION	GENTAMICIN	R 291.24		
		FLAGYL	R 470.24		
TOTAL COST OF TREATMENT			R1856.55		R17.94

Table 3.8: Treatment of Adverse Events: Ofloxacin/metronidazole Group – Clinical Resolution

TREATMENT OF ADVERSE EVENTS: OFLOXACIN/METRONIDAZOLE GROUP – CLINICAL RESOLUTION					
SUBJECT NUMBER	ADVERSE EVENT	TREATMENT OF DRUG RELATED ADVERSE EVENTS		TREATMENT OF NON-DRUG RELATED ADVERSE EVENTS	
		MEDICATION TO TREAT ADVERSE EVENTS	TOTAL COST	MEDICATION TO TREAT ADVERSE EVENTS	TOTAL COST
101005	NAUSEA, FLU, SYPHILIS , BODY ACHE	CODIS	R 17.82	BENZATHINE PENICILLIN	R 11.44
		NORMAL SALINE	R 8.00		
101009	HERPES ZOSTER			AMITRYPTYLINE	R 208.32
				TEGRETOL	R 22.08
				CALAMINE	R 4.58
101021	NAUSEA, CONJUNCTIVITIS, RASH	SPERSALLERG	R 23.83		
		ALLERGEX	R 0.78		
		PANADO	R 0.24		
		MAXOLON TABS	R 21.60		
101024	GASTRITIS, SYPHILIS	BRUFEN 200MG	R 5.40	BENZATHINE PENICILLIN	R 5.72
		GELUSIL	R 52.92		
101025	CONJUNCITIVITIS, PAIN	CHLOROMYCETIN	R 32.65	BENZATHINE PENICILLIN	R 5.72
		PANADO	R 1.44		
101027	SYPHILIS, IRREG VAG BLEED			BENZATHINE PENICILLIN	R 5.72
					R 3.84
101030	DIZZINESS, NAUSEA, SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101031	ANEMIA, NEUTROPENIA, PAIN THROMBOCYTOPENIA	BRUFEN 200MG	R 9.45		
		IRON SULPHATE	R 63.84		
		FOLIC ACID	R 1.72		
101036	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101039	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101040	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101042	SYPHILIS, NEUTROPENIA			BENZATHINE PENICILLIN	R 5.72
101043	NAUSEA, NEUTROPENIA	VALOID	R 19.80		
101045	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101049	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101052	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101056	ABN LIVER ENZ, SYPHILIS, PAIN	BRUFEN 400MG	R 13.50	BENZATHINE PENICILLIN	R 5.72
101060	RASH	ALLERGEX	R 1.56		
101062	HEADACHE	CODIS	R 26.70		
101063	NAUSEA, SYPHILIS	MAXOLON TABS	R 12.96	BENZATHINE PENICILLIN	R 5.72
101066	CONSTIPATION, VAG ITCH, CRAMPS	SENOKOT	R 100.80		
		BUSCOPAN	R 53.04		
		DIFLUCAN	R 61.87		
101068	NAUSEA, SYPHYLIS, ANEMIA, INCR ESR			BENZATHINE PENICILLIN	R 5.72
101072	NAUSEA, HEARTBURN, BACKACHE				
		VITAMIN B-COMPLEX	R 1.46		
		MAXOLON	R 17.28		
		GELUSIL-S	R 26.88		
		BRUFEN	R 9.45		
		METHYLSALICYLATE	R 2.42		
101074	HAEMORROIDS, FLU	BRUFEN	R 8.10		
		SCHERIPROCT	R 90.41		
		METHYLSALICYLATE	R 2.42		
101076	NAUSEA	MAXOLON	R 30.24		
101077	SYPHILIS			BENZATHINE PENICILLIN	R 5.72
101080	BACK ACHE, RELAPSE	BRUFEN	R 113.40		
		DOXYCYCLINE	R 2.12		
		CIPROBAY	R 9.81		
101082	SYPHILIS, MENSTRUAL IRREG	DEPO PROVERA	R 5.64		
102002	NAUSEA,VOMITING	MAXOLON	R 2.88		
102004	NAUSEA,PELVIC PAIN	MAXOLON	R 12.96		
		COMPRAL	R 1.02		
102011	GENERAL BODY ACHE	IBUPROFEN	R 16.20		
		DOLOROL FORTE	R 42.41		
		VOLTAREN	R 22.14		
102016	SYPHILIS	PARACETAMOL	R 0.16		
102056	CANDIDA ALBICANS, ANEMIA	FERROUS SULPHATE	R 63.84		
103003	BACKACHE	BRUFEN	R 0.90		
103004	ANEMIA ,PAIN	FERROSULPHATE	R 63.84		

		FOLIC ACID	R 1.72		
		BRUFEN	R 14.40		
103012	PAIN	BRUFEN	R 8.10		
103017	APPENDISECTOMY,ANEMIA	BRUFEN	R 10.80		
103018	NAUSEA, PAIN	BRUFEN	R 5.40		
		MAINTELYTE	R 35.68		
104005	HYPERTENSION,THRUSH,HYPERNATREMIA	COVERSYL	R 79.80		
		CANESTAN VAG CR	R 47.75		
104007	NAUSEA,IRREG MENS BLEED,VOMITING	NORETHISTERONE	R 51.24		
104014	PERSISTENTLY ELEVATED ESR, HOSPITALISATION	ZINACEF, FLAGYL, MAINTELYTE	R 3,734.01		
105003	ANEMIA,CANDIDA VAGINITIS	GYNO-PEVARYL	R 555.41	DIFLUCAN	
105005	MENSTRUAL IRREG	NUR ISTERATE	R 1,679.16		
105009	CANDIDA VAGINITIS,ANEMIA,PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY,MENINGITIS,PULM TB,AIDS,UTI,INCR ESR	PARACETAMOL	R 101.44		
		DEPO PROVERA	R 4.48		
		GYNO-PEVARYL	R 101.44		
		IRON SULPHATE	R 1.35		
		MANNITOL	R 49.42		
		MACRODANTIN	R 85.40		
		HEPARIN	R 945.60		
		PYRIDOXINE	R 2.52		
105012	CANDIDA VAGINITIS, INFLUENZAE,NEUTROPENIA,ABD PAIN	PANADO	R 12.00		
		GYNO-PEVARYL	R 101.44		
		DRIXINE NASAL	R 24.42		
105015	SYPHILIS	PANADO	R 3.84		
105017	VOMITING,SYPHILIS,DYSURIA			BICILLIN	5.72
105019	HEADACHE	PANADO	R 13.44		
105023	CANDIDA VAGINITIS	PANADO	R 12.80	DIFLUCAN	
		TRIPHASIL	51.24		
		GYNO-PEVARYL	R 101.44		
106001	CANDIDA VAGINITIS,TASTE PERVERSION,ABD CRAMPS,CYST RIGHT OVARY	GYNO-PEVARYL	R 101.44		
		PARACETAMOL	R 2.56		
		IBUPROFEN	R 10.80		
		PARACETAMOL	R 4.80		
		MULTIVITAMIN	R 0.40		
TOTAL COST OF TREATMENT			9031.64		341.78

Table 3.9: Treatment of Adverse Events: Ofloxacin/metronidazole Group – Clinical Improvement

TREATMENT OF ADVERSE EVENTS: OFLOXACIN/METRONIDAZOLE GROUP – CLINICAL IMPROVEMENT					
SUBJECT NUMBER	ADVERSE EVENT	TREATMENT OF DRUG RELATED ADVERSE EVENTS		TREATMENT OF NON-DRUG RELATED ADVERSE EVENTS	
		MEDICATION TO TREAT ADVERSE EVENTS	TOTAL COST	MEDICATION TO TREAT ADVERSE EVENTS	TOTAL COST
102024	BITTER TASTE,VAGINAL CANDIDIASIS,PAIN,	BRUFEN	R 113.40		
		CANESTEN	R 47.75		
102053	VAGINAL CANDIDIASIS	CLOTRIMAZOLE	R 47.75		
103008	HYPERTENSION,ANEMIA, PAIN	HYDROCHLOROTHIAZIDE	R 11.13		
		FERROUS SULPHATE	R 191.52		
		ATENOLOL	R 175.56		
		BRUFEN	R 13.50		
104003	HYPOKALEMIA			HYDROCHLORTHIAZIDE	R 22.26
104015	PAIN	PARACETAMOL	R 1.12		
		IBUPROFEN	R 18.90		
105018	NAUSEA,SYPHILIS,ANEMIA, PAIN			DOXYCYCLINE	R 29.68
		PANADO	R 26.88	FLAGYL	R 67.68
				CIPROFLOXACIN	R 9.81
				BICILLIN	R 5.72
106003	SYPHILIS			BICILLIN	R 5.72
107002	INCR MONOCYTE,INCR WBC,NEUTROPHILS ABSENT,NAUSEA,HEADACHE,WEAK NESS	METOCLOPRAMIDE	R 43.20		
		PARACETAMOL	R 4.80		
		MULTIVITAMIN	R 0.40		
TOTAL COST OF TREATMENT			R695.91		R140.87

Clinical Resolution:

In the moxifloxacin group, 72 patients displayed clinical resolution. Of those 72 patients, 39 patients experienced adverse events, 27 were related to moxifloxacin and 12 were not related to the study drug. In the moxifloxacin group, 33 patients who displayed clinical resolution experienced no adverse events. The total cost of treating patients with moxifloxacin (drug acquisition cost) was R9615.20 + R3789.52 + R12726.00= R26130.32 for the proportion that displayed clinical resolution. This was calculated according to the number of doses of moxifloxacin taken. In this group of patients, R3009.28 was spent on treating adverse events that were due to moxifloxacin (namely: gastritis, blood dyscrasias, heartburn, skeletal muscle pain, nausea, anemia) and R170.73 was spent on treating adverse events that were not related to the study drug (e.g. for the treatment of syphilis that developed during the clinical study). Additional physician visits were required due to patients experiencing adverse events (either moxifloxacin related or not related to moxifloxacin therapy). These additional physician visits incurred a total cost of R4185.00 + R1860.00 = R6045.00. Total treatment cost for the proportion of patients displaying clinical resolution was therefore R16809.00 + R5820.00 + R12726.00 = R35355.00

In the ofloxacin/metronidazole group, 80 patients displayed clinical resolution. Of those 80 patients, 58 patients experienced adverse events, 44 were related to ofloxacin/metronidazole and 14 were not related to the study drug. In the ofloxacin/metronidazole group, 22 patients who displayed clinical resolution experienced no adverse events. The total cost of treating patients with ofloxacin/metronidazole (drug acquisition cost) was R14728.22 + R8420.50 + R9308.48 = R32457.20 for the proportion that displayed clinical resolution. This was calculated according to the number of doses of ofloxacin/metronidazole taken. In this group of patients, R9031.64 was spent on treating adverse events that were due to ofloxacin/metronidazole (namely: nausea, flu, allergies, pain, gastritis, anemia, constipation, blood dyscrasias, candidiasis) and R341.78 was spent on treating adverse events that were not related to the study drug (e.g. for the treatment of syphilis and herpes zoster infections that developed during the clinical study). Additional physician visits were required due to patients experiencing adverse events (either ofloxacin/metronidazole related or not related to ofloxacin/metronidazole therapy). These additional physician visits incurred a total cost of

R6820.00 + R2170.00 = R8990.00. Total treatment cost for the proportion of patients displaying clinical resolution was therefore R30580.00 + R10932.00 + R9308.00 = R50820.00

Clinical Improvement:

In the moxifloxacin group, 32 patients displayed clinical improvement. Of those 32 patients, 16 patients experienced adverse events, 14 were related to moxifloxacin and 2 were not related to the study drug. In the moxifloxacin group, 16 patients who displayed clinical improvement experienced no adverse events. The total cost of treating patients with moxifloxacin (drug acquisition cost) was R5542.88 + R791.84 + R6391.28= R12726.00 for the proportion that displayed clinical improvement. This was calculated according to the number of doses of moxifloxacin taken. In this group of patients, R1856.55 was spent on treating adverse events that were due to moxifloxacin (namely: nausea, headache, pain, candidiasis) and R17.94 was spent on treating adverse events that were not related to the study drug (e.g. for misoprostol treatment during the clinical study for pregnancy termination). Additional physician visits were required due to patients experiencing adverse events (either moxifloxacin related or not related to moxifloxacin therapy). These additional physician visits incurred a total cost of R2170.00 + R310.00 = R2480.00. Total treatment cost for the proportion of patients displaying clinical improvement was therefore R9569.00 + R1120.00 + R6391.00 = R17080.00

In the ofloxacin/metronidazole group, 23 patients displayed clinical improvement. Of those 23 patients, 12 patients experienced adverse events, 10 were related to ofloxacin/metronidazole and 2 were not related to the study drug. In the ofloxacin/metronidazole group, 11 patients who displayed clinical improvement experienced no adverse events. The total cost of treating patients with ofloxacin/metronidazole (drug acquisition cost) was R3092.62 + R1714.72 + R4715.48 = R9522.82 for the proportion that displayed clinical improvement. This was calculated according to the number of doses of ofloxacin/metronidazole taken. In this group of patients, R695.91 was spent on treating adverse events that were due to ofloxacin/metronidazole (namely: nausea, vomiting, candidiasis, anemia, hypertension, headache, blood dyscrasias) and R140.90 was spent on treating adverse events that were not related to the study drug (e.g. for the treatment of syphilis that developed during the clinical

study). Additional physician visits were required due to patients experiencing adverse events (either ofloxacin/metronidazole related or not related to ofloxacin/metronidazole therapy). These additional physician visits incurred a total cost of R1550.00 + R310.00 = R1860.00. Total treatment cost for the proportion of patients displaying clinical improvement was therefore R5339.00 + R2166.00 + R4715.00 = R12220.00

Clinical Failure:

In the moxifloxacin group 3 patients displayed clinical failure and were therefore switched to an alternate treatment. No adverse events were experienced by these patients. The total cost of treating patients with moxifloxacin (drug acquisition cost) was R1187.76 for the proportion that displayed clinical failure. This was calculated according to the number of doses of moxifloxacin taken. In this group of patients, R1082.31 was spent on switching to alternate antibiotic therapy. Additional physician visits were required due to patients experiencing clinical failure. These additional physician visits incurred a total cost of R465.00. Total treatment cost for the proportion of patients displaying clinical failure was therefore R2375.00

In the ofloxacin/metronidazole group 4 patients displayed clinical failure and were therefore switched to an alternate treatment. No adverse events were experienced by these patients. The total cost of treating patients with ofloxacin/metronidazole (drug acquisition cost) was R1714.72 for the proportion that displayed clinical failure. This was calculated according to the number of doses of ofloxacin/metronidazole taken. In this group of patients, R210.07 was spent on switching to alternate antibiotic therapy. Additional physician visits were required due to patients experiencing clinical failure. These additional physician visits incurred a total cost of R620.00. Total treatment cost for the proportion of patients displaying clinical failure was therefore R2545.00

Indeterminate

In the moxifloxacin group 4 patients displayed results that could not be assessed. No drug related adverse events were experienced by these patients but failure of therapy resulted in an additional cost of R761.48 for alternate therapy. The total cost of treating patients with moxifloxacin (drug acquisition cost) was R791.84 for the proportion that displayed results that

could not be assessed. This was calculated according to the number of doses of moxifloxacin taken. Additional physician visits incurred a cost of R620.00. Total treatment cost for the proportion of patients displaying results that could not be assessed was therefore R2173.00.

In the ofloxacin/metronidazole group 4 patients displayed results that could not be assessed. No adverse events were experienced by these patients. The total cost of treating patients with ofloxacin/metronidazole (drug acquisition cost) was R791.84 for the proportion that displayed results that could not be assessed. This was calculated according to the number of doses of ofloxacin/metronidazole taken. Additional physician visits incurred a cost of R620.00. Total treatment cost for the proportion of patients displaying results that could not be assessed was therefore R1412.00.

Refer to:
Table 3.10 Outcome costs associated with consequences of moxifloxacin treatment
Table 3.11 Outcome costs associated with consequences of ofloxacin/metronidazole treatment

Table 3.10 Outcome costs associated with consequences of moxifloxacin treatment

Path no.	Clinical Outcome	Drug Acquisition Cost	Cost of Treating Adverse Events or Clinical Failures	Cost of Additional Physician visits incurred due to Adverse Events or Clinical Failures	Total Cost in Rands for all patients receiving moxifloxacin
1	Clinical Resolution Drug-related Adverse Events	9615.20	3009.28	4185.00	16809.00
2	Clinical Resolution Non-drug related Adverse Events	3789.52	170.73	1860.00	5820.00
3	Clinical Resolution No Adverse Events	12726.00	-	-	12726.00
4	Clinical Improvement Drug-related Adverse Events	5542.88	1856.55	2170.00	9569.00
5	Clinical Improvement Non-drug related Adverse Events	791.84	17.94	310.00	1120.00
6	Clinical Improvement No Adverse Events	6391.28	-	-	6391.00
7	Clinical Failure	1187.76	1082.31	465.00	2735.00
8	Indeterminate	791.84	761.48	620.00	2173.00

Note: Each arm of the decision tree is broken down into the different paths that are numbered chronologically from 1 to 8 for the moxifloxacin portion of the decision tree.

Table 3.11 Outcome costs associated with consequences of ofloxacin/metronidazole treatment

Path no.	Clinical Outcome	Drug Acquisition Cost	Cost of Treating Adverse Events or Clinical Failures	Cost of Additional Physician visits incurred due to Adverse Events or Clinical Failures	Total Cost in Rands for all patients receiving Ofloxacin/ metronidazole
9	Clinical Resolution Drug-related Adverse Events	14728.22	9031.64	6820.00	30580.00
10	Clinical Resolution Non-drug related Adverse Events	8420.50	341.78	2170.00	10932.00
11	Clinical Resolution No Adverse Events	9308.48	-	-	9308.00
12	Clinical Improvement Drug-related Adverse Events	3092.62	695.91	1550.00	5339.00
13	Clinical Improvement Non-drug related Adverse Events	1714.72	140.90	310.00	2166.00
14	Clinical Improvement No Adverse Events	4715.48	-	-	4715.00
15	Clinical Failure	1714.72	210.07	620.00	2545.00
16	Indeterminate	791.84	-	620.00	1412.00

Note: Each arm of the decision tree is broken down into the different paths that are numbered chronologically from 9 to 16 for the ofloxacin/metronidazole portion of the decision tree.

3.5.1 Interpreting the Decision Trees

The decision trees are used as a tool for sensitivity analysis. This analysis is important as a means of testing the robustness of the Average Cost Effective Ratio (ACER) method. This decision analysis is important as it is used to proportionately calculate the average cost of treating a patient by taking the success rates, failure rates and cost of treating adverse events into account. This information would be lost by doing a simple cost minimization analysis. The decision trees are read from right to left. The total cost of treatment for all patients receiving a particular treatment option are listed in chronological order on the right. This is reflected as path numbers in Table 3.10 and 3.11. Each path refers to a clinical outcome i.e.

Moxifloxacin portion of the decision tree:

1. Drug related adverse events encountered in patients who showed Clinical Resolution
2. Non-drug related adverse events encountered in patients who showed Clinical Resolution
3. No adverse events encountered in patients who showed Clinical Resolution
4. Drug related adverse events encountered in patients who showed Clinical Improvement
5. Non-drug related adverse events encountered in patients who showed Clinical Improvement
6. No adverse events encountered in patients who showed Clinical Improvement
7. Failure (switch to alternate treatment)
8. Indeterminate

Ofloxacin/metronidazole portion of the decision tree:

9. Drug related adverse events encountered in patients who showed Clinical Resolution
10. Non-drug related adverse events encountered in patients who showed Clinical Resolution
11. No adverse events encountered in patients who showed Clinical Resolution
12. Drug related adverse events encountered in patients who showed Clinical Improvement
13. Non-drug related adverse events encountered in patients who showed Clinical Improvement
14. No adverse events encountered in patients who showed Clinical Improvement
15. Failure (switch to alternate treatment)
16. Indeterminate

Each branch of the respective decision trees is used to depict the proportionate value of the total cost as listed on the right. The choice nodes (depicted by circles) provide a cost value that is calculated from the preceding total costs and form the new totals for the next level of the decision. These in turn are used to proportionately calculate new totals. At the terminal node (depicted by squares), the figures under each outcome (Clinical Resolution, Clinical Improvement, Clinical Failure, Indeterminate) are added together to provide the final cost per patient.

3.5.1 a. Decision Analysis: Calculations for Cost Analysis as outlined in the Moxifloxacin Portion of the Decision tree

Refer to:

Table 3.3 Detailed comparison of the proportions of patient populations and their outcomes

Table 3.10 Outcome costs associated with consequences of moxifloxacin treated patients with pelvic inflammatory disease

Figures 3.2 Decision Analysis: Results of moxifloxacin portion of the decision tree

Clinical Resolution
Path 1 and 2:
(0.69 x R16809) + (0.31 x R5820) = R13402
Path 2 and 3:
(0.54 x R13402) + (0.46 x R12726) = R13091
TOTAL COST:
(0.65 x R13091) = R8509

Clinical Improvement
Path 4 and 5:
(0.88 x R9596) + (0.13 x R1120) = R8566.6
Path 5 and 6:
(0.5 x R85666) + (0.5 x R6391) = R7479
TOTAL COST:
(0.29 x R7479) = R2169

Clinical Failure
Path 7 TOTAL COST:
(0.03 x R2735) = R82

Indeterminate
Path 8 TOTAL COST:
(0.04 x R2173) = R87

Total Cost of Treatment per Patient as per Decision Analysis for the Moxifloxacin portion of the decision tree:
R8509 + R2169 + R82 + R87 = R10 847.00

3.5.1 b Decision Analysis: Calculations for Cost Analysis as outlined in the Ofloxacin/Metronidazole Portion of the Decision tree

Refer to:
Table 3.3 Detailed comparison of the proportions of patient populations and their outcomes

Table 3.11 Outcome costs associated with consequences of ofloxacin/metronidazole treated patients with pelvic inflammatory disease

Figures 3.3 Decision Analysis: Results of ofloxacin/metronidazole portion of the decision tree

Clinical Resolution
Path 9 and 10:
(0.76 x R30580) + (0.24 x R10932) = R25865
Path 10 and 11:
(0.73 x R25865) + (0.28 x R9308) = R21488
TOTAL COST:
(0.72 x R21488) = R15471

Clinical Improvement
Path 12 and 13:
(0.83 x R5339) + (0.17 x R2166) = R4800
Path 13 and 14:
(0.52 x R4800) + (0.48 x R4715) = R4759
TOTAL COST:
(0.21 x R4759) = R999

Clinical Failure
Path 15 TOTAL COST:
(0.04 x R2545) = R102

Indeterminate
Path 16 TOTAL COST:
(0.04 x R1412) = R57

Total Cost of Treatment per Patient as per Decision Analysis for the Ofloxacin/ metronidazole portion of the decision tree:
R15471 + R1000 + R102 + R57 = R16 630.00

Figure 3.2 Decision Analysis: Results of moxifloxacin portion of the decision tree

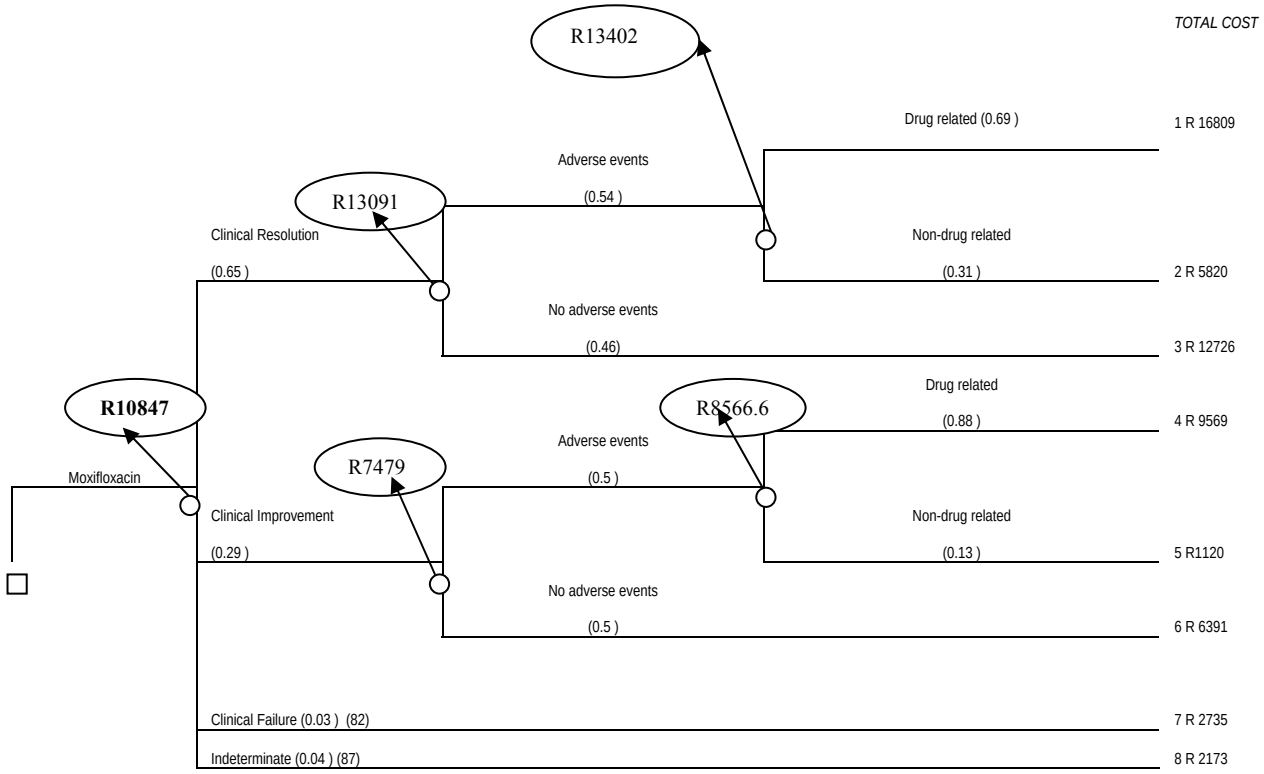
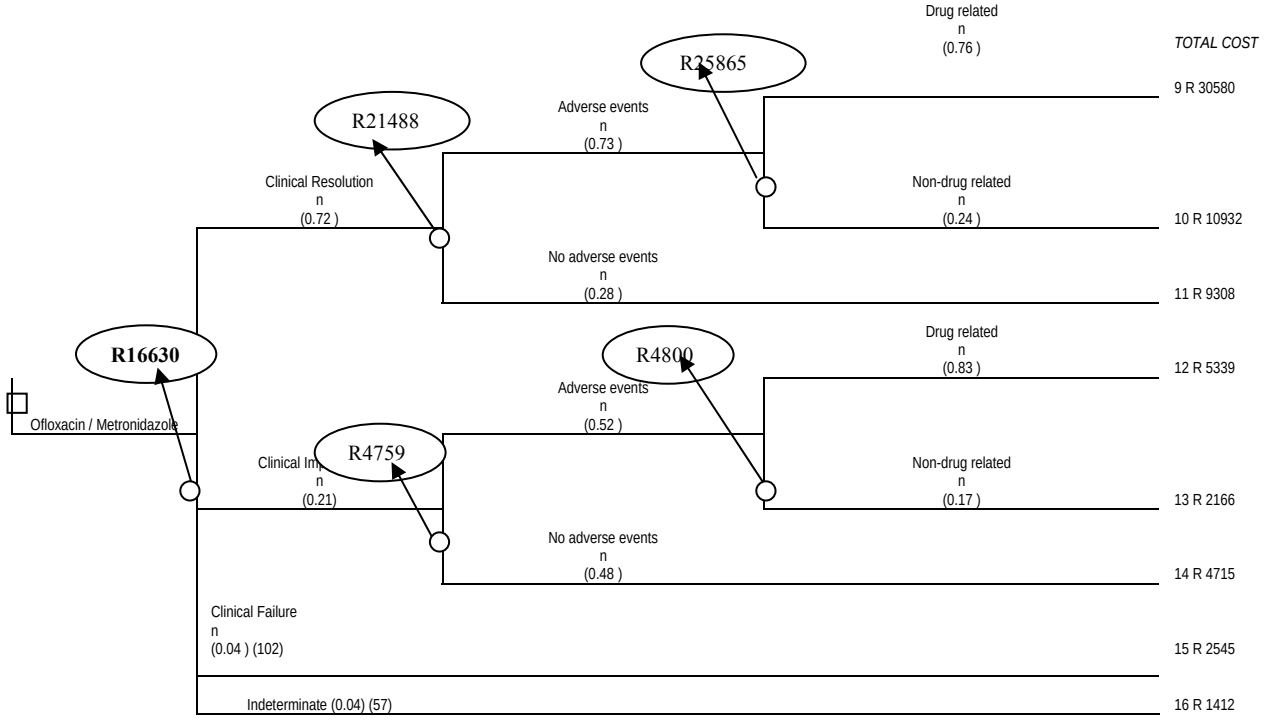


Figure 3.3 Decision Analysis: Results of ofloxacin/metronidazole portion of the decision tree



3.6 Sensitivity Analyses

The decision analysis itself as outlined in the decision trees serves as a sensitivity analysis. This sensitivity analysis tests the robustness of the methods used to calculate the cost per successfully treated patient.

3.6.1 Cost Estimates

Differences in drug acquisition cost and success rates

Treatment Option	Cost	Success rate	Incremental cost
Moxifloxacin	28.28	0.94	-2.34
Ofloxacin/metronidazole	30.62	0.93	

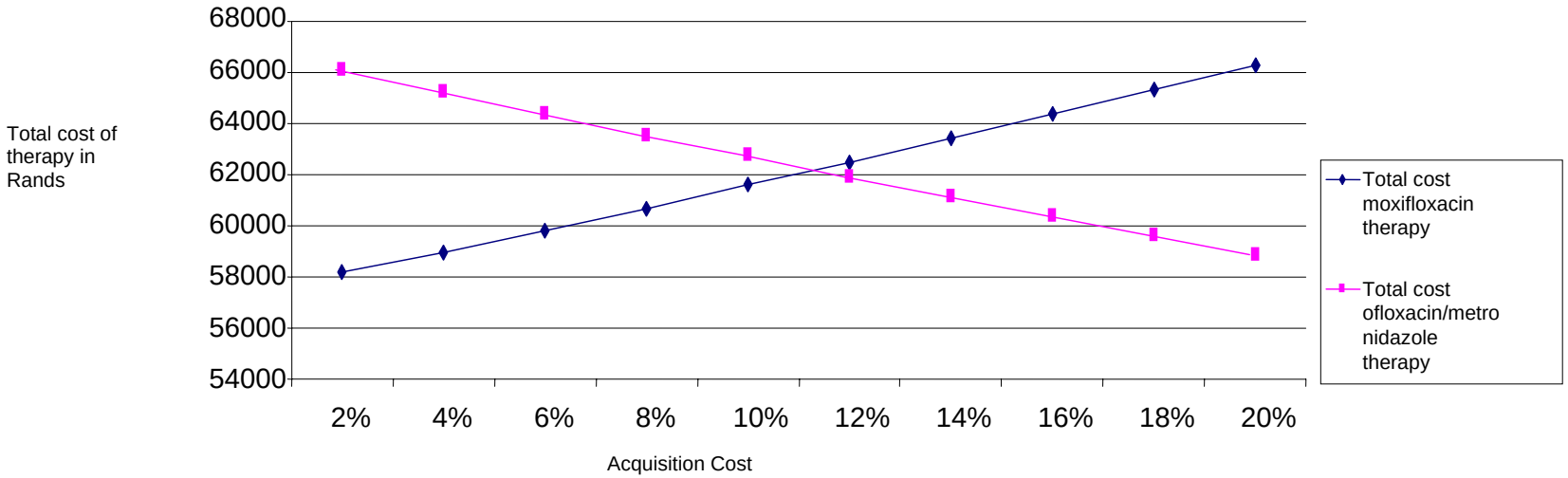
The cost per patient of moxifloxacin therapy was R10847 and the cost of ofloxacin/metronidazole therapy was R16630 when a sensitivity analysis was performed. As our results led to a clear cost saving in favour of moxifloxacin, they may be considered robust.

A break-even analysis using the ROSA method (Rank Order Stability Analysis) was performed. The acquisition cost of moxifloxacin was increased in increments of 2 % over 2-20 %. Similarly, the acquisition cost of ofloxacin/metronidazole was decreased over the same range. The results showed that although the cost figures differed over the stipulated range, the findings are consistent, hence, indicating that moxifloxacin has a cost advantage over ofloxacin/metronidazole.

Table 3.12: Break-even analysis: Increasing the Acquisition Cost of Moxifloxacin in 2% increments over the range 2-20%												
	Ofloxacin/ Metronidazole	Moxifloxacin: Increasing Acquisition Cost in 2% increments										
		0%	2%	4%	6%	8%	10%	12%	14%	16%	18%	20%
Acquisition costs	44489.58	40835.92	41652.64	42485.69	43335.40	44202.11	45086.15	45987.87	46907.63	47845.78	48802.70	49778.75
Physician visits	12090.00	9610.00	9610.00	9610.00	9610.00	9610.00	9610.00	9610.00	9610.00	9610.00	9610.00	9610.00
Additional treatment: switching to alternate antibiotic	210.07	1843.79	1843.79	1843.79	1843.79	1843.79	1843.79	1843.79	1843.79	1843.79	1843.79	1843.79
Treatment of medication related adverse events	9727.55	4865.83	4865.83	4865.83	4865.83	4865.83	4865.83	4865.83	4865.83	4865.83	4865.83	4865.83
Treatment of non-medication related adverse events	482.65	188.67	188.67	188.67	188.67	R188.67	188.67	188.67	188.67	188.67	188.67	188.67
TOTAL	R 66 999.85	R 57 344.21	58160.93	58993.98	59843.69	60710.40	61594.44	62496.16	63415.92	64354.07	65310.99	66287.04

Table 3.13: Break-even analysis: Decreasing the Acquisition Cost of Ofloxacin/metronidazole in increments of 2% over the range 2-20%											
	Ofloxacin/ Metronidazole	Ofloxacin/metronidazole: Decreasing acquisition cost in increments of 2%									
		20%	18%	16%	14%	12%	10%	8%	6%	4%	2%
Acquisition costs	44489.58	36351.23	37093.09	37850.09	38622.54	39410.75	40215.05	41035.77	41873.23	42727.79	43599.79
Physician visits	12090.00	12090.00	12090.00	12090.00	12090.00	12090.00	12090.00	12090.00	12090.00	12090.00	12090.00
Additional treatment: switching to alternate antibiotic	210.07	210.07	210.07	210.07	210.07	210.07	210.07	210.07	210.07	210.07	210.07
Treatment of medication related adverse events	9727.55	9727.55	9727.55	9727.55	9727.55	9727.55	9727.55	9727.55	9727.55	9727.55	9727.55
Treatment of non-medication related adverse events	482.65	482.65	482.65	482.65	482.65	482.65	482.65	482.65	482.65	482.65	482.65
TOTAL	R 66 999.85	58861.5	59603.36	60360.36	61132.81	61921.02	62725.32	63546.04	64383.50	65238.06	66110.06

Figure 3.4 Break-even analysis: Effect of Increasing the Acquisition Cost of Moxifloxacin in 2% increments over the range 2-20%
and Decreasing the Acqusition Cost of Ofloxacin/Metronidazole in 2% increments over the range 2-20%



4.0 DISCUSSION

It is important to re-iterate that this pharmacoeconomic study is a costing out of a clinical trial. The results of other trials are not relevant to this particular study. However, in discussion, it is worthwhile to mention other available therapies in the treatment of PID:

PID is a polymicrobial condition, and, although *E. coli* and *C. trachomatis* are major pathogens, therapy should also be active against *Neisseria gonorrhoea, M. hominis, coliforms* and the non-sporing anaerobes.When a drug regimen is chosen, there are concerns about toxicity, cost, compliance and the potential effect on the microbial environment. The three conventional and most often cited effective antimicrobial agents in the treatment of *chlamydial* infections are: Doxycycline, Oxytetracycline and Erythromycin.

Tetracyclines:

Tetracyclines have been the mainstay of PID therapy. Current treatment guidelines in South Africa recommend the following for the treatment of PID:

Doxycycline, oral, 200 mg immediately, then 100 mg 12 hourly (with meals) for 10 to 14 days. The current widely used alternatives to oral doxycycline is erythromycin, usually recommended as erythromycin base 500 mg 6-hourly for 7 days. However, a large number of patients will experience gastrointestinal side effects on this regimen. Another option is to give erythromycin as the stearate 500 mg bd for ten days. The incidence of gastrointestinal side effects with either the tetracyclines or erythromycin is a cause of concern, resulting in unreliable compliance. Furthermore, although the eradication of *C. trachomatis* approaches 100%, the clinical cure rate is approximately 80%. A disquieting observation has been that some isolates of *Chlamydia* demonstrate in vitro or in vivo resistance to tetracyclines and to erythromycin. Azithromcyin has been a major advance in the treatment of *Chlamydia trachomatis* in studies with reasonable follow-up, azithromycin has provided efficacy equivalent to that of doxycycline with a single oral dose. Effectiveness would be even better taking into account the compliance issues.

Penicillins:

The use of penicillins for *chlamydial* infections continues to be controversial. Amoxycillin is used in a dose of 500 mg orally tds for 7 to 10 days but usually for pregnant women with *chlamydial* infection who are unable to tolerate erythromycin. Other pencillins, and all cephalosporins, have no role in the management of *chlamydial* infections. Penicillins are however used in the treatment of *Neisseria gonorrhoea* related PID. The South African EDL recommends for more severe cases:

Amoxycillin, oral, 250 mg 8 hourly for at least 3 days

PLUS

Metronidazole, oral, 400 mg 8 hourly, if there is no vomiting, otherwise per rectum 500 mg 8 hourly initially for 3 to 5 days.

This treatment has been incorporated into the EDL due to its cost effectiveness and successful clinical outcome.

Macrolides:

The macrolides: roxithromycin, azithromycin and clarithromycin are all effective in *chlamydial* and *non-chlamydial*, *nongonococcal*, lower genital tract infections when given in standard doses twice daily for 7 to 10 days. A single 1 g oral dose of azithromycin is of equivalent efficacy to oral doxcycline 100 mg bd for seven days, and is recommended for uncomplicated urethral, cervical and rectal *chlamydial* infection. In the UK the approximate cost of 1g azithromycin is £7 - £9, compared with £3 - £5 for a week's course of doxycycline (100 mg bd). However, Carlin and Barton (17) looked not only at drug costs, but also the cost of follow-up clinic visits. They found that for every 100 patients there was an overall saving of £360 in the azithromycin-treated group compared with the doxycyline-treated group. The syndromic approach to treating nongonococcal urethritis with azithromycin was addressed by Stamm and colleagues (18). As expected, eradication of *C. trachomatis* was similar in the azithromycin-treated and doxycycline-treated groups, although it is noteworthy that three patients in the former group, apparently clear of the organism at two weeks' follow-up, were infected at week five, raising the possibility of suppression rather than eradication of the organism. Despite good in vitro activity of both azithromycin and doxycycline against *U. urealyticum*, overall microbiological cure rates were only 45% and 47% respectively.

Quinolones:

The clinical efficacy of older quinolones (such as ciprofloxacin, norfloxacin and lomefloxacin) has been somewhat disappointing. Ofloxacin, which is only twice as active as ciprofloxacin in vitro, is highly effective in eradicating *C. trachomatis*. While the use of a single dose of 400 mg ofloxacin for treating gonorrhoea is acceptable, 400 mg bd for 7 days for *chlamydial* infection is recommended. Further studies are required to confirm the ideal regimen, particularly with regard to the efficacy of single daily dosage, the length of course, and prolonged follow up with particular emphasis on clinical cure in contrast to organism eradication. The spectrum of activity of the newer quinolones suggests that they may play a role in the treatment of PID. PID is a polymicrobial condition, and, although *C. trachomatis* is the major pathogen, therapy should also be active against *Neisseria gonorrhoea, M. hominis, coliforms* and the non-sporing anaerobes. Therefore, only the most recently developed quinolones are likely to be effective (moxifloxacin, gatifloxacin).

The main finding of this economic analysis of the MAIDEN trial was that the use of moxifloxacin 400 mg od instead of ofloxacin 400mg/metronidazole 400mg bid for the treatment of pelvic inflammatory disease led to net economic benefits in the study population. A crucial factor in pharmacoeconomic analyses is the ability to generalize the results and apply the economic decision to routine clinical practice. Patients eligible for this economic study appear to be similar to the majority of patients with PID. However, we should not loose sight of the fact that the analysis was based on the results of a controlled clinical trial. Sensitivity analyses usually facilitates extrapolation of economic data to routine clinical practice. In this trial, decision analysis was used as a tool to test the sensitivity of the cost outcomes.The cost per patient of moxifloxacin therapy was R10847 and the cost of ofloxacin/metronidazole therapy was R16630 when a sensitivity analysis was performed. As our results led to a clear cost saving in favour of moxifloxacin, they may be considered robust. For this economic analysis, total direct medical cost savings to South Africa were calculated based on the actual trial usage of the medications by treating physicians. However, treatment durations and the number of consultations are often higher in a clinical trial than in day to day medical practice. In this study, a treatment duration of 14 days was set to ensure that patients with PID would receive an appropriate duration of treatment. The variation in treatment length

between the artificial duration of this trial and day to day clinical experience highlights a problem that must be faced when undertaking and interpreting an economic evaluation using clinical trial data. However, this bias is minimized by the use of incremental analysis because most of the additional costs are common to both the active treatment and control groups and cancel out when comparisons are made. A minimum of three physician visits were required for evaluation of each case whereas in routine clinical practice a patient would probably return only if treatment failed or the patient experienced major adverse events.

It would have been preferable to have included direct nonmedical, indirect and intangible costs and benefits in this study but these could not be evaluated with sufficient accuracy. The savings calculated therefore could represent an underestimate to society but from a funder perspective, the savings would be appropriate. In addition, the unquantified costs of inconvenience associated with combination therapy versus monotherapy, as well as the more frequent administrations of ofloxacin/metronidazole, may be important to patients and caregivers.

5.0 CONCLUSION

1. The clinical trial did not establish any difference among the two study groups i.e. moxifloxacin versus ofloxacin/metronidazole, in terms of efficacy when administered for pelvic inflammatory disease.
2. In 14-day treatment regimens, much of the difference in the acquisition cost of monotherapy versus combination therapy is offset by the higher cost of treating adverse effects which occurred when combination therapy was used. Sensitivity analysis of most of the areas of uncertainty or variation had little impact on the conclusions derived from the model.
3. Limitations of this analysis include: data availability limitations (i.e. no direct comparisons or effectiveness data to other treatment options available), difficulties in measuring indirect costs such as loss of productivity and wages, artificial constraints of the clinical trial.

From a pharmacoeconomic perspective, the data accumulated from this cost analysis shows that an economically attractive empirical regimen is one that provides the patient with broad spectrum antibacterial coverage, has minimal adverse effects and does not require additional antibacterials in the course of treatment. Such a regimen, is cost effective in the long run because it would not require additional antibacterials and it could be discontinued relatively quickly in the responding patient. Moxifloxacin 400mg od has shown to be a more economically attractive regimen in the treatment of pelvic inflammatory disease compared to conventional combination therapy (ofloxacin plus metronidazole) in the context of this clinical trial.

APPENDIX A

Listing of Individual Results

	Page
Group A (moxifloxacin) – combined results	47-50
Group A (moxifloxacin) – Clinical Resolution	51- 53
Group A (moxifloxacin) – Clinical Improvement	54- 55
Group A (moxifloxacin) – Clinical Failure	56
Group A (moxifloxacin) – Indeterminate	57
Group B (ofloxacin/metronidazole) – combined results	58- 61
Group B (ofloxacin/metronidazole) – Clinical Resolution	62- 64
Group B (ofloxacin/metronidazole) – Clinical Improvement	65
Group B (ofloxacin/metronidazole) – Clinical Failure	66
Group B (ofloxacin/metronidazole) - Indeterminate	67

APPENDIX B

Calculations

B.1 Sample size calculation for moxifloxacin group:

$n = \pi(1-\pi)(1.96/a)^2$
$= 0.94\ (1-0.94)\ (1.96/0.04)^2$
$= 111$

For the moxifloxacin group, the study on 111 patients revealed that the treatment provided clinical success (clinical improvement + clinical resolution) in 104 (94%) of patients to within 4% with a probability of 95%. The sample size of 111 patients was therefore sufficient.

B.2 95% Confidence interval for success rates:

95% Confidence interval (Moxifloxacin group):

$(0.94 - 1.96 \cdot \sqrt{0.94(1-0.94)/111}\ ;\ 0.94 + 1.96 \cdot \sqrt{0.94(1-0.94)/111})$

$= (0.896; 0.984)$

95% Confidence interval (Ofloxacin/metronidazole group):

$(0.93 - 1.96 \cdot \sqrt{0.93(1-0.93)/111}\ ;\ 0.93 + 1.96 \cdot \sqrt{0.93(1-0.93)/111})$

$= (0.883; 0.977)$

B.3 Gc statistic – Success Rates

The following results reflect the numbers of clinical successes and failures in the comparative study on 222 patients:

	Moxifloxacin	Ofloxacin/metronidazole	Total
Clinical Success	104	103	207
Clinical Failure	3	4	7
Total	107	107	214

The success rates with the two treatments were compared statistically at the 5% level.

1. H0: $\pi 1 = \pi 2$

   H1: : $\pi 1 \neq \pi 2$

2. $\alpha = 0.05$

3. Test statistic: $\dfrac{n(|ad - cb - n/2|)^2}{(a+c)(b+d)(a+b)(c+d)} \sim \chi^2(1)$

4. Reject H0 if gc > 3.841

5: gc = $\dfrac{214(|104x4 - 3x103 - 214/2|)^2}{(107)(107)(207)(7)} \sim \chi^2(1)$

= 0

6. Since 0 is not in the rejection region, H0 is not rejected. The two sample proportions, namely 94% and 93% therefore do not differ significantly.

B4. Test for a difference between two independent proportions (normal distribution);

CLINICAL IMPROVEMENT:

	Group A	Group B
ITT	n1 = 111	n2=111
Clin improvement	x1 = 32	x2 = 23
Proportion of clinical improvement	p1 = 0.288	p2 = 0.207

1. H0: $\pi 1 = \pi 2$; H1: $\pi 1 \neq \pi 2$
2. $\alpha = 0.01$
3. Test statistic: $Z = \dfrac{P1 - P2 - (\pi 1 - \pi 2)}{\sqrt{P(1-P)(1/n1 + 1/n2)}} \sim n(0;1)$

4. Reject H0 if $z \leq -2.58$ or ≥ 2.58
5. $p = \dfrac{32 + 23}{111 + 111} = 0.248$

$$z = \frac{0.288 - 0.207 - 0}{\sqrt{0.248(1-0.248)(1/111 + 1/111)}} = 1.397$$

6. Since 1.397 is not > 2.58, H0 cannot be rejected. The conclusion is that the two sample proportions do not differ significantly with regard to clinical improvement

CLINICAL RESOLUTION:

	Group A	Group B
ITT	n1 = 111	n2=111
Clin resolution	x1 = 72	x2 = 80
Proportion of clinical resolution	p1 = 0.649	p2 = 0.721

1. H0: $\pi 1 = \pi 2$; H1: $\pi 1 \neq \pi 2$
2. $\alpha = 0.01$
3. Test statistic: $Z = \dfrac{P1 - P2 - (\pi 1 - \pi 2)}{\sqrt{P(1-P)(1/n1 + 1/n2)}} \sim n(0;1)$

4. Reject H0 if $z \leq -2.58$ or ≥ 2.58
5. $p = \dfrac{72 + 80}{111 + 111} = 0.685$

$$z = \frac{0.649 - 0.721 - 0}{\sqrt{0.685(1-0.685)(1/111 + 1/111)}} = -1.154$$

6.Since -1.154 is not < -2.58, H0 cannot be rejected. The conclusion is that the two sample proportions do not differ significantly with regard to clinical resolution

CLINICAL FAILURE:

	Group A	Group B
ITT	n1 = 111	n2=111
Clin failure	x1 = 3	x2 = 4
Proportion of clinical failure	p1 = 0.027	p2 = 0.036

1. H0: $\pi 1 = \pi 2$; H1: $\pi 1 \neq \pi 2$
2. $\alpha = 0.01$
3. Test statistic: $Z = \dfrac{P1 - P2 - (\pi 1 - \pi 2)}{\sqrt{P(1-P)(1/n1 + 1/n2)}} \sim n(0;1)$

4. Reject H0 if $z \leq -2.58$ or ≥ 2.58
5. $p = \dfrac{3 + 4}{111 + 111} = 0.0315$

$$z = \frac{0.027 - 0.036 - 0}{\sqrt{0.0315(1-0.0315)(1/111 + 1/111)}} = -0.383$$

6. Since -0.383is not < -2.58, H0 cannot be rejected. The conclusion is that the two sample proportions do not differ significantly with regard to clinical failure

CLINICAL RESOLUTION: DRUG RELATED ADVERSE EVENTS

	Group A	Group B
Adverse Events in Clin Resol group	n1 = 39	n2=58
Drug related AE	x1 = 27	x2 = 44
Proportion of Drug related AE	p1 = 0.692	p2 = 0.759

1. H0: $\pi 1 = \pi 2$; H1: $\pi 1 \neq \pi 2$
2. $\alpha = 0.01$
3. Test statistic: $Z = \dfrac{P1 - P2 - (\pi 1 - \pi 2)}{\sqrt{P(1-P)(1/n1 + 1/n2)}} \sim n(0;1)$

4. Reject H0 if $z \leq -2.58$ or ≥ 2.58
5. $p = \dfrac{27+44}{39+58} = 0.835$

$$z = \frac{0.692 - 0.759 - 0}{\sqrt{0.835(1-0.835)(1/39 + 1/58)}} = -0.872$$

6.Since -0.872 is not < -2.58, H0 cannot be rejected. The conclusion is that the two sample proportions do not differ significantly with regard to drug related adverse events in the clinical resolution group

CLINICAL IMPROVEMENT: DRUG RELATED ADVERSE EVENTS:

	Group A	Group B
Adverse Events in Clin Improvement group	n1 = 16	n2=12
Drug related AE	x1 = 14	x2 = 10
Proportion of Drug related AE	p1 = 0.875	p2 = 0.833

1. H0: $\pi 1 = \pi 2$; H1: $\pi 1 \neq \pi 2$
2. $\alpha = 0.01$
3. Test statistic: $Z = \dfrac{P1 - P2 - (\pi 1 - \pi 2)}{\sqrt{P(1-P)(1/n1 + 1/n2)}} \sim n(0;1)$

4. Reject H0 if $z \leq -2.58$ or ≥ 2.58
5. $p = \dfrac{14 + 10}{16+12} = 0.857$

$$z = \frac{0.875 - 0.833 - 0}{\sqrt{0.857(1-0.857)(1/16 + 1/12)}} = 0.313$$

6.Since 0.313 is not > 2.58, H0 cannot be rejected. The conclusion is that the two sample proportions do not differ significantly with regard to drug related adverse events in the clinical improvement group

B5. Test for a difference between two independent proportions (χ^2 distribution);

CLINICAL IMPROVEMENT:

	Group A	Group B	Total
Clin improvement	x1 = 32	x2 = 23	55
Rest of group	n1-x1 = 79	n2-x2 = 88	167
Total	n1 = 111	n2=111	222

1. H0: $\pi 1 = \pi 2$

   H1: : $\pi 1 \neq \pi 2$

2. $\alpha = 0.05$

3. Test statistic: $\dfrac{n(|ad - cb - n/2|)^2}{(a+c)(b+d)(a+b)(c+d)} \sim \chi^2(1)$

4. Reject H0 if gc > 3.841

5: gc = $\dfrac{222(|32x88 - 79x23 - 222/2|)^2}{(32+79)(23+88)(32+23)(79+88)} \sim \chi^2(1)$

$= \dfrac{222 \times (888)^2}{113168385}$

$= 1.55$

6.Since 1.55 is not in the rejection region, H0 is not rejected. The two sample proportions for clinical improvement therefore do not differ significantly.

CLINICAL RESOLUTION:

	Group A	Group B	Total
Clin resolution	x1 = 72	x2 = 80	152
Rest of group	39	31	70
Total	111	111	222

1. H0: $\pi 1 = \pi 2$

   H1: : $\pi 1 \neq \pi 2$

2. $\alpha = 0.05$

3. Test statistic: $n(|ad - cb - n/2|)^2 \quad \sim \chi^2(1)$

   $(a+c)(b+d)(a+b)(c+d)$

4. Reject H0 if gc > 3.841

5: gc = $222(|72x31 - 39x80 - 222/2|)^2 \quad \sim \chi^2(1)$

   $(111)(111)(152)(70)$

   = $\frac{222 \times (999)^2}{131095440}$

   = 1.69

6. Since 1.69 is not in the rejection region, H0 is not rejected. The two sample proportions for clinical resolution therefore do not differ significantly.

CLINICAL RESOLUTION: DRUG RELATED ADVERSE EVENTS

	Group A	Group B	Total
Drug related AE in clin resol group	x1 = 27	x2 = 44	71
Rest of group	12	14	26
Total	39	58	97

1. H0: $\pi 1 = \pi 2$

   H1: : $\pi 1 \neq \pi 2$

2. $\alpha = 0.05$

3. Test statistic: $n(|ad - cb - n/2|)^2 \quad \sim \chi^2(1)$

   $(a+c)(b+d)(a+b)(c+d)$

4. Reject H0 if gc > 3.841

5: gc = $97(|27x14 - 12x44 - 97/2|)^2 \quad \sim \chi^2(1)$

   $(39)(58)(71)(26)$

   = $\frac{97 \times (198.5)^2}{4175652}$

   = $\frac{3822018.25}{4175652}$

   = 0.92

6. Since 0.92is not in the rejection region, H0 is not rejected. The two sample proportions for drug related adverse events in the clinical resolution group therefore do not differ significantly.

CLINICAL IMPROVEMENT: DRUG RELATED ADVERSE EVENTS:

	Group A	Group B	Total
Drug related AE in clin resol group	x1 = 14	x2 = 10	24
Rest of drug related AE	2	2	4
Total	16	12	28

1. H0: $\pi 1 = \pi 2$

   H1: : $\pi 1 \neq \pi 2$

2. $\alpha = 0.05$

3. Test statistic: $n(|ad - cb - n/2|)^2 \sim \chi^2(1)$

   $(a+c)(b+d)(a+b)(c+d)$

4. Reject H0 if gc > 3.841

5: gc = $28(|14x2 - 2x10 - 28/2|)^2 \sim \chi^2(1)$

$(16)(12)(24)(4)$

$= \frac{28 \times (6)^2}{18432}$

= 0.055

5. Since 0.055 is not in the rejection region, H0 is not rejected. The two sample proportions for drug related adverse events in the clinical improvement group therefore do not differ significantly.

APPENDIX C

Protocol Approval

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PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM

Trial No.: **10995**

Title of Protocol: **Prospective, randomized, double-blind, multicenter, multinational study comparing efficacy and safety of moxifloxacin 400 mg po od for 14 days with ofloxacin 400 mg po bid plus metronidazole 400 mg po bid for 14 days in patients with uncomplicated pelvic inflammatory disease (PID).**

Investigator Name:
Investigator Address:
Investigator Telephone No:
Centre No.:

SPONSOR: BAYER (Pty) Ltd, P O Box 198, ISANDO, 1600 on behalf of Bayer Vital GmbH, Germany

You are being invited to take part in a research study. The reason it is considered "research" is because the medicine, moxifloxacin, has not been approved by the Medicines Control Council (MCC)of South Africa for treating pelvic inflammatory disease (PID). Therefore, this medicine is considered experimental or investigational. Before you decide to participate, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with the study staff / personnel if anything is unclear or there are words or phrases you do not understand. If you would feel more comfortable, also discuss the study with your family and general practitioner if you wish.

What is the medicine that is being tested ?

Moxifloxacin is a new antibiotic which has been approved in tablet form (oral formulation) in South-Africa **for** treating respiratory tract infections.

What is the purpose of the study?

The Sponsor's test antibiotic, moxifloxacin, is being tested at approximately 65 study centers in 12 countries to determine if this medicine is safe and effective in treating adult females with PID (Infection of the internal female organs). In total 632 patients will participate world-wide and approximately 200 patients will be recruited in South-Africa. The centre at your local hospital will recruit not more than 40 patients. The recruitment period for this study will be approximately 17 months.
Your active individual involvement in the study will be 6-8 weeks (you will have an additional 24-month follow-up with regular phone contacts). Other antibiotics already approved for the treatment of PID, namely ofloxacin and metronidazole, will also be used in the study and will be compared to moxifloxacin.

Do I have to participate in the study ?

It is up to you to decide whether or not to take part in this study. Your participation is completely voluntary. If you decide not to take part there will be no penalty or loss of benefits that you are entitled to. You are also free to withdraw at any time, without your medical care

or legal rights being affected. If you decide to participate you will be given this information sheet to keep and be asked to provide your signature indicating your consent. Should you have any questions now or during the course of the study about study procedures or the medication being tested, your study doctor will be glad to answer them at any time.

Who should <u>not</u> participate in this study?
You should not take part if you took part in another study within the past 30 days. If you have suffered or are suffering particular diseases which prevent the use of any of the study medication or may influence the outcome of your PID, you should not take part in this study. In addition, your doctor will check your current medicines to avoid any non-permissible medication during the study. Please inform your doctor of your full medical history and other medication so that he can evaluate whether you are eligible for participation in the study.

It is possible that if the test medicine is given to a pregnant woman it will harm the unborn child. Pregnant or breast feeding women, therefore, must not take part in this study, nor should women who plan to become pregnant during the study period. If you choose to take part, you must agree to have pregnancy testing performed (initially urine and to be confirmed with a blood test) and to also use adequate hormonal contraception to prevent pregnancy during the study. In addition, a condom should be used to prevent you from contracting any possible re-infection from your partner during the study period.

What will happen to me if I participate?

If you decide to participate, you should understand that this study is designed as a "randomized" and "double-blind" trial. "Randomized" means that a computer has already determined which of the two treatment regimen you will receive (like flipping a coin); the test medicine, moxifloxacin, or the registered medicines, ofloxacin and metronidazole (in combination). There are an equal number of patients randomized to the two treatment groups, so you have a 50% chance of receiving the investigational medicine and a 50% chance of receiving ofloxacin and metronidazole.

"Double-blind" means that the Sponsor has packaged the medicine in a manner so that neither you nor the study staff will know which medicine you are receiving. The Sponsor study monitor or representative that will be reviewing your study records will also not know which medicine you are receiving. This allows everyone involved in this research study to evaluate the safety and effectiveness of the test medicine in a fair way. If necessary, however, the clinic staff can find out which medicine you are taking, in case of any emergency or, where, for some reason, this could be in your best medical interest.

In addition to today's clinic visit, you will be required to come back to the clinic three more times; once during the time you are taking your medication (between days 4 and 7 of treatment); once after you complete your medication (between 7 and 14 days <u>after</u> you stop your medication); and once at a follow-up visit (between 28 and 42 days <u>after</u> you stop your medication). You will be reimbursed for each follow up visit you attend to cover your travel expense. In addition, your doctor will interview you by telephone every 6 months for an approximate duration of 2 years following your treatment. These follow-up telephone calls will be designed to collect information on your pregnancy(ies), if any, on potential recurrent PID episodes or pelvic pain you may experience during this period of time.

Today and at all other visits, the doctor will examine you to assess the signs and symptoms of your condition. This will include an abdominal, pelvic and speculum (vaginal) examination.

You will be asked to give information on pain that you experienced and general health status, by completing a short questionnaire. Your temperature will be recorded at each visit, and in addition, your blood pressure and pulse will be measured at today's visit, and again at all other visits. At today's visit a sample of your urine will be requested to perform a pregnancy test. Blood specimens will be obtained for laboratory testing, including a pregnancy test and syphilis (a type of sexually-transmitted disease) test. An additional blood sample will be taken at the "visit after completion of all medication" (3rd visit) and if necessary, again at the follow-up visit (4th Visit) in case your doctor would like to make sure that abnormalities observed at the post therapy visit (3rd Visit) have returned to normal. The blood will be taken with a needle from a vein in your arm; the amount taken will be approximately 25 ml (about 5 teaspoons full). At today's visit, a complete medical history will also be taken and a scan, called a pelvic ultrasound, will be done to rule out any complication of your infection which would need a specific medical management. Based on the results, your doctor will decide if you will be able to participate. This examination could be repeated during the course of study if your doctor thinks it is necessary for your health. If your doctor considers a laparoscopy (a small tube inserted into your abdomen to directly assess the condition of your internal female organs) has to be performed, this can be done, but it is not an examination required in the study. Smears from the endocervix (in your vagina) will be obtained at today's visit for a microbiological examination to identify the bacteria (germs) responsible for your infection. This examination will be repeated at the post therapy (3rd Visit) and follow up (4th Visit) visits to make sure you are completely cured.

Today's visit will take approximately one hour. Each of your return visits will require approximately 30 minutes of your time. Each telephone interview will take approximately 10 minutes of your time.

If you or the doctor decides to stop your participation in the trial for any reason, you will be required to return to the clinic for a physical examination, and to have blood and vaginal smear samples obtained. Also, if it appears that the study medication you are taking is not working as expected, the same procedures will be performed before an alternative antibiotic is prescribed for you.

What do I have to do?

"You must give your doctor your exact address and phone number so that he can contact you during the 2-year follow-up period.

You must take your study medication twice a day, that is two capsules and one tablet in the morning and again two capsules and one tablet in the evening. The medication must be taken with at least ½ a glass of water, and may be taken with or without food. Your medication should be stored at room temperature, and you should take all medication daily for the entire 14 days. You must bring any unused medication to your second clinic visit, and your completed (empty) dosing card to your third clinic visit. If there is a need to reschedule a clinic visit, please call the study nurse as soon as possible at phone number ……..

Consequences (i.e. other conditions or symptoms) resulting from PID can be seen if the infection is not totally cured. Therefore, it is important that you return to your doctor for all visits so that he can make sure you have been adequately treated.

In case you report experiencing a new onset of pelvic pain during the telephone contacts at follow-up, you will be urged to return to your doctor to determine if you have possibly again developed PID.

It is also important that, at all times during the study, you tell your doctor about any other medicine you are taking or wish to take. This includes any over the counter medication, vitamins, herbal supplements or dietary supplements. You must also tell him about anything unusual that is happening with your health, including any worsening of existing medical conditions. If you have to see another doctor or are admitted into hospital, please let them know that you are taking part in this study and show them the medication card and this leaflet. You must notify the study staff as quickly as possible of these types of events at phone number …….

What risks or discomforts might occur if I participate?

During the course of the study, blood samples will be taken at three different times (visits) at most (total of approximately 75 ml i.e. 15 teaspoons full). There may be temporary discomfort and/or slight bruising around the needle puncture area.

The use of antibiotics may cause side effects. Because of the "double-blind" design of the study, any of the undesirable effects listed below are possible since you will not know which active medicine you will receive.

More than 13,000 patients have been treated in studies with different doses of moxifloxacin either by mouth or intravenously (given into a vein). The results have shown that moxifloxacin is generally as well tolerated by patients as other antibiotics used to treat PID.
The more frequently reported adverse medicine reactions (side-effects), reported with moxifloxacin are:
Headache, abdominal pain, nausea, vomiting, diarrhoea, dyspepsia (indigestion), prolongation of the QT interval (an abnormality of the heart rhythm) especially if the level of potassium (a type of salt) in the blood is low, abnormal liver function tests (tests performed on the blood to determine how well the liver is functioning), dizziness, and an altered sense of taste. In addition, numerous other side effects have been uncommonly or rarely reported. These include potentially life-threatening complications such as serious abnormalities of the heart rhythm and allergic reactions. A full list of these complications, together with other known complications of fluorquinolione antibiotics (to which class of antibiotics moxifloxacin belongs) is available from your study doctor.

Some of the more commonly reported side-effects of ofloxacin are:- nausea, stomach cramps, diarrhoea, vomiting, skin rash or bruising and increased sensitivity to sunlight.

Metronidazole may cause the following side=effects:- nausea, loss of appetite, a metallic taste in the mouth, stomach cramps, vomiting and diarrhoea.

A full list of side-effects associated with ofloxacin and metronidazole appears in the package inserts of these registered medications, copies of which can be obtained from your study doctor.

As it may be the case when taking any kind of medication, unexpected or unknown side effects may occur.
Your ability to drive or operate machinery might be impaired, particularly in conjunction with alcohol. In addition, the consumption of alcohol is not allowed during study treatment since this may cause some adverse reactions (hot flushes, vomiting, fast pulse rate) when associated with metronidazole.

Sometimes during the course of a study, significant new information becomes available about the test medicine that may affect your willingness to continue to take part. If this happens, we will discuss this with you and you will have the opportunity to decide if you want to continue in the study. It may also be your doctor's decision to end your participation. In either case, your doctor will make arrangements for your continued medical care. If your participation in the study does continue after being informed of any new information, you will be asked to sign an updated consent form.

What are the possible benefits of participating?

All clinic visits, examinations and medical tests specifically required for this study will be provided to you free of charge for the duration of your participation. You will be actively treated for your PID with antibiotics, although no cure or improvement can be guaranteed in your case.

The information we receive from this study may help us to better treat future patients with PID.

Will there be any cost to me if I participate?

The Sponsor, will supply the investigational antibiotic moxifloxacin and comparator medicines to you free of charge. The Sponsor will pay for all costs of procedures and consultations as specified in the protocol.
You will not be paid to participate in this trial except for re-imbursement for travel expenses while meeting study commitments.

Can I use alternative treatment should I decide not to participate?

If you do not wish to take part in this clinical study, there are a number of registered antibiotics ***(for example, a*** *combination of ciprofloxacin, doxycycline and metronidazole) which can be used for the treatment of your infection.*
If you wish, your doctor will discuss these options, their benefits and risks, with you in detail.

What if something goes wrong or if I have problems while I am in the study?

Your doctor and his staff are available to answer any further questions arising in connection with this trial. They will also be happy to answer any questions concerning your rights as a patient and participant in this trial.
The occurrence of undesirable effects during the use of medicines can not be, excluded with absolute certainty. Damage claims in the case of an injury, are therefore safeguarded through an insurance provided for by legal regulations. For the duration of the study, an insurance has been taken out with ***Gerling Konzern, Von Werth Str. 4-14, 50597 Koln, Germany.*** *You may ask your doctor or the study co-ordinator should you like to have a copy of the insurance certificate.*
Compensation for any injury caused by taking part in this study will be in accordance with the Association of British Pharmaceutical Industry (ABPI). Copies of these guidelines are available on request. The conduct of this study will be according to ICH guidelines and the Declaration of Helsinki (updated 2000).
For insurance reasons, it is necessary that, except for emergency situations, changes in therapy are only made with the consent of your doctor. An injury to your health, which might have occurred as a consequence of the study must be reported immediately to your doctor and the insurance company. Your doctor will then inform the Sponsor which will then channel information to the insurance company. It is also important that you follow the instructions of your doctor and his staff exactly during the course of the study, in order to protect your rights to compensation. Failure to inform your study staff of your full medical history or to take medication not authorized by your study doctor (except in case of emergency) could jeopardize your insurance cover.

In case of health injury, every possible measure, independent of costs, will be used to limit the extent of the injury. The insurance company will offer a financial compensation that is fair and reasonable for injury.

Excluded from the insurance coverage are injuries of already existing illnesses which would have occurred or continued to exist even without taking part in the study, as well as injuries caused by intentionally disobeying explicit instructions in context with the study.

For further information on the insurance coverage, please ask your doctor. He will provide you with the documented insurance conditions.

Every effort will be made to prevent any injury that could result from this study. You understand that complications may arise during the course of therapy either due to your disease or due to treatment.

Please inform your referring/family practitioner and your life insurer of your study participation.

What happens when the study stops/is completed?

Your doctor will collect further information on your well-being, fertility status and possible recurrent PID or pelvic pain during a 2-year period after you have finished your study medication. This information will be limited to what would be relevant for the study medicine and its effectiveness. By providing your signature on the consent, you agree that after the final visit this information may be collected and recorded in the context of this research study.

Can I be withdrawn from the study without my permission?

As your participation in this study is entirely voluntary, you may withdraw from the study at any time that you wish even without stating your reasons. If you withdraw from the study, this will not effect your future treatment.

Under certain circumstances it is possible that your doctor or the Sponsor decide to take you off the study without asking your permission. Possible reasons for that may be:

- *you do not fulfil the necessary criteria*
- *you get another illness*
- *your doctor no longer considers your participation in the study helpful for you*
- *the sponsor decides to stop the study.*

Will my participation in this study be kept confidential?

If you consent to take part in this study, your signature provides permission for your medical records to be directly accessed and reviewed by authorised individuals from the Sponsor or Sponsor's representatives (auditors/monitors), by medicines regulatory authorities, or by the ethics committee. The purpose of the records inspection is to ensure the information collected for this research study is accurate and that the study protocol has been carried out correctly. Records which reveal your identity will be kept confidential by these parties except that, in rare instances, revealing your identity to another party may be required by law or judicial process. Information from the study may be published, but this will not include your name.

What will happen to the results of the study?

The results of this study will be used to support applications to international health authorities to approve the investigational medicine for prescription use for PID. It is possible that these results are used in countries in addition to and other than those where the study was specifically conducted. Patients data most likely will be transferred from a European Member State to a non-European country, e.g., to allow study results being used for international submission to Health Authorities. If this happens, the patient's identity will remain confidential. The parties responsible for the processing of data is clearly identified, for example, Bayer AG, their subsidiaries or contractors.

It is also planned that the results of this study will be published in a medical journal and/or they may be presented at a scientific conference or symposium. If this happens, the data will remain anonymous. If you require additional details about this, ask your doctor.

Who is organising and funding the study?

The pharmaceutical company Bayer Vital GmbH is the sponsor of the study. Bayer Vital GmbH is also organising and funding the study.

Who has reviewed the study?

The details of this study have been reviewed and approved by …….. University of…….. If you require details about this committee, these are available from your doctor.

If you want any information regarding your rights as a research participant, or complaints regarding this research study, you may contact……., which is an independent committee established to help protect the rights of research participants at……

Contact for further information

If you have a question about the study or need to report a study-related illness or injury, please call Dr ……

South African Medicines Control Council

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at: The Registrar, SA Medicines Control Council, Department of Health, Private Bag X828, PRETORIA, 0001, Fax: (012) 323-4474, e-mail: labusa@health.gov.za

Thank you for participating in this research study. You will be given a copy of the information sheet and a signed consent form to keep for your records

To be signed by the patient or a legally acceptable representative:

1. I confirm that I have read and understand the patient information sheet (dated 24 March 2003, version 6 for the above study, the study has been explained to me, and I have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that refusal to participate will involve no penalty or loss of benefits that I am entitled to. I also understand that I am free to withdraw at any time, without my medical care or legal rights being affected.
3. I understand that study records and my medical records may be looked at by authorized individuals from Bayer or representatives of Bayer, by regulatory authorities or by the ethics committee where it is relevant to my participation in the study. I give permission for these individuals to have direct access to my records and understand such information will be treated as confidential.
4. I understand I have the right to access my medical records and correct information I believe is inaccurate (*as applicable, per country and regulatory requirements; may be deleted otherwise*).
5. I agree to participate in this study.

Patient:

Full Name (print) .....

Signature ..... Date .....

To be completed by the qualified individual executing consent:

I confirm that I have explained and discussed with the patient the nature, purpose, requirements and risks of the study. I have also discussed alternative therapies or treatments and will ensure a copy of this PI/IC is provided to the patient.

Full Name (print) ..... Position .....

Signature ..... Date .....

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