A COMPARISON OF THE RELATIVE COSTS OF CONTINUOUS VERSUS INTERMITTENT INFUSION OF CEFEPIME IN PATIENTS WITH CHRONIC PSEUDOMONAL PULMONARY DISEASE

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DECLARATION

I, Fihlani Norman Mavukani declare that this research report is my own work. It is being submitted for the degree of Master of Science (Medicine) (Pharmaceutical Affairs) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signature:.....

Date: 06 NOVEMBER 2012

ABSTRACT

Pharmacoeconomic research describes and analyses the costs and consequences of pharmaceutical products and services and their impact on individuals, healthcare systems and society. Its application in clinical practice can serve as a clinical management tool. A clinical study was initiated to study the effects of continuous versus intermittent cefepime on the development of bacterial resistance, colony forming units pre- and post-therapy in cystic fibrosis patients with chronic pseudomonal pulmonary disease. Cefepime is a fourth generation cephalosporin antibiotic with a broad spectrum of activity against Gram-negative and Gram-positive pathogens including *Pseudomonas aerugunosa.* Cystic fibrosis is an inherited disease of the exocrine glands, primarily affecting the gastro-intestinal and respiratory systems, and usually characterized by a triad of chronic obstructive pulmonary disease, exocrine pancreatic insufficiency, and abnormally high sweat electrolytes.

This cost evaluation study was used to determine the cost of conducting the clinical study and to compare the relative costs of continuous infusion (CI) and intermittent therapy (IT). It was postulated that CI administration may result in improved efficacy and reduced development of resistance, and this would be a strong recommendation for its use in any patient likely to be infected with organisms of high resistance potential such as in the intensive care units (ICU) and Oncology Units.

Cystic fibrosis patients who were admitted for 14 days of therapy every 4 months were randomised either to receive continuous infusions (CI) or standard intermittent therapy (IT) of cefepime 4 g per day (50 mg/kg twice daily) at the time of their periodic admissions. Sixteen eligible patients were recruited from the paediatric and adult cystic fibrosis clinics.

The partial cost of the study for the clinician perspective was R462 534; study drug constituted the major cost input. The results offer approximations to be made for similar study costings conducted in similar settings. For the hospital perspective the total costs for the CI group which ranged from R645 158 to R723 259 were higher than those for the IT group (range: R469 495 to R522 225), and for both groups they were driven by hospitalization. Remarkable numerical cost differences were observed in favour of the IT group in terms of cefepime usage and personnel time.

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The parent clinical study was partly funded by Bristol-Myers Squib (the manufacturer of cefepime), but otherwise controlled by the Chief Investigator (Investigator Originated Proposal); the current costing evaluation generated cost data directly from the parent study and as such there was no specific funding involved for this 'piggy-back' study.

Dr Gareth J. Lowndes reviewed and commented on the draft protocol of this 'piggy-back' study and the current report.

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ABBREVIATIONS

Abbreviation	**Definition**
AFB	Acid Fast Bacilli
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
CEA	Cost-effectiveness Analysis
CFU	Colony-forming Units
CI	Continuous Infusion
CLS	Contract Laboratory Services
CMID	Clinical Microbiology and Infectious Diseases
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
EUCAST	The European Committee on Antimicrobial Susceptibility Testing
GGT	Gamma Glutamyl Transferase
ICU	Intensive Care Unit
IT	Intermittent Therapy
MC & S	Microscopy, Culture & Sensitivities
MIC	Minimum Inhibitory Concentration
NCCLS	National Council for Clinical Laboratory Standards
NHLS	National Health Laboratory Service
NRPL	National Reference Price List
PMB	Prescribed Minimum Benefit
PTT	Partial Thromboplastin Time
QOL	Quality of Life
SEP	Single Exit Price/Pricing
fT > MIC	Time of Free Drug Above MIC
UPFS	Uniform Patient Fee Schedule
VAT	Value-Added Tax
WCC	White Cell Count

1.0 INTRODUCTION

The cost of pharmaceutical products and pharmaceutical services has become an important issue to patients, third party payers and governments. Changes in healthcare policy around the world are focusing on the goal of ensuring that the provision of medical care occurs in a fiscally rational manner [1]. South Africa is no exception: for instance, the government has drawn up a series of measures to curtail medical inflation and excessive medicine utilization. These are embodied in the National Drug Policy as well as the Medicines and Related Substances Control Amendment Act, 1997 (Act 90 of 1997) and Regulations thereto [2, 3, 4].

Thus, it has become necessary to value the costs and consequences of drug therapy. However, despite the general evidence supporting the use of pharmaceuticals, few data exist regarding the actual costs and benefits attributed to specific drug therapies [1].

Pharmacoeconomic research describes and analyses the costs (i.e., the resources consumed) and consequences (i.e., clinical and humanistic) of pharmaceutical products and services and their impact on individuals, healthcare systems and society [1].

A cost-effectiveness analysis (CEA) is an approach used for identifying, measuring and comparing the significant costs and consequences of alternative interventions. Net costs are calculated as production costs plus induced resources minus induced resource savings. Production costs are the costs of the resources used to actually provide an intervention. Induced resource losses are the resources consumed in tests and treatments undertaken as a consequence of the initial intervention (e.g., to diagnose and treat adverse effects). Induced resource savings are resource expenditures that are averted as a consequence of improved health.

CEA is applied to health matters where a program's inputs can be readily measured in monetary terms, and the program's outputs are more appropriately stated in terms of health improvements created (e.g., clinical efficacy). This technique is designed to assist a decision maker in identifying a preferred choice among possible alternatives [1].

1.1 Drug profile

Cefepime (Maxipime, Bristol-Myers Squibb) is a fourth generation cephalosporin antibiotic with a broad spectrum of activity against a wide range of Gram-positive and Gram-negative pathogens including *Pseudomonas aeruginosa*. It is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. It is highly resistant to hydrolysis by a number of beta-lactamases, has a low affinity for chromosomally encoded beta-lactamases, and exhibits rapid penetration into Gram-negative bacterial cells [5].
Cefepime is currently registered with the South African Medicines Control Council.

1.2 Cystic fibrosis

Cystic fibrosis[6, 7] is an inherited disease of the exocrine glands, primarily affecting the gastro-intestinal and respiratory systems, and usually characterized by a triad of chronic obstructive pulmonary disease, exocrine pancreatic insufficiency, and abnormally high sweat electrolytes. In the treatment of cystic fibrosis, a comprehensive and intensive program is essential, directed by an experienced physician with the services of personnel in nursing, physical and respiratory therapies, and counseling. The goals of therapy include the maintenance of adequate nutritional status, prevention or aggressive therapy of pulmonary complications, encouragement of physical activity, and provision of psychosocial support.
For severe pulmonary exacerbations, especially in patients colonized with *Pseudomonas*, treatment with parenteral antibiotic therapy is advised. This usually requires hospital admission, but in older patients may be carried out safely at home. Antibacterial treatment is given for at least two weeks, and may be required for up to one year. The goal of treating pulmonary infections should be to improve the clinical picture sufficiently so that continuous use of antibiotics is unnecessary; however, in some ambulatory patients with frequent pulmonary exacerbations, long-term use of antibiotics may be indicated.

P. aeruginosa [8] is one of the more common and clinically difficult-to-treat causes of hospital-acquired infections [9]. It is the major pathogenic species in the family Pseudomononadaceae and is readily identified as a gram-negative straight or slightly

curved rod with a length ranging from 1 to 3 μm. Colonies of *P. aeruginosa* can have a highly varied morphology, with typical colonies appearing to spread over the plate, lie flat with a metallic sheen, and frequently produce gelatinous appearance, particularly in areas of heavy growth. *P. aeruginosa* is able to grow on a wide variety of media, ranging from minimal to complex, and can metabolize a large array of carbon sources [8].

1.3 Review of previous research

The appropriate and judicious use of antimicrobial treatment in ICU settings is a constant clinical challenge for healthcare professionals due to the appearance and spread of new multiresistant pathogens and the need to update knowledge of factors involved in the selection of multiresistance and in the patient's clinical response. In order to optimize the efficacy of empirical antibacterial treatments and to reduce the selection of multiresistant pathogens, different strategies have been advocated, including de-escalation therapy and pre-emptive therapy as well as measurement of pharmacokinetic and pharmacodynamic parameters for proper dosing adjustment. Although the theoretical arguments of all these strategies are very attractive, evidence of their effectiveness is scarce [10].

Prolonged or continuous infusion therapy has improved microbiological responses in pathogens with MICs at or 2-4 fold higher than existing European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints in pre-clinical studies. However, at present, the clinical evidence base for prolonged or continuous infusion therapy is insufficiently strong to support widespread use [11].

Although continuous infusion is a rational method to optimize the time during which the free drug exceeds the MIC of the organism (fT > MIC) it is not always realistic for multiple reasons. For example an intravenous line or lumen of intravenous catheter must be dedicated for infusion of the antibiotic, and this is not always practical, especially for patients who have limited intravenous access or patients who require multiple daily infusions [12].

In the current practice of economic evaluations, unit costs are determined for the specific setting and often depend on the availability of data [13]. Thus, for a pharmacoeconomic

evaluation to be relevant it should be conducted based on local data. Analyses performed overseas will often not be suitable because of major differences in the measurement and valuation of costs, sophistication of a healthcare practice's accounting system and the way in which healthcare is funded (e.g., inclusion of incidental costs).

Against this background, a literature search on the relative costs of cefepime therapy in patients with chronic *Pseudomonal* pulmonary disease in the local setting was conducted. This produced a nil result. The database PubMed (which links to Medline and Pre-Medline) was screened for articles added to it and published to date. Search parameters identified as keywords included permutations of "cefepime", "pulmonary disease", "cost", "cost-effectiveness", "pharmacoeconomic evaluation/analysis". Through the literature searches no pharmacoeconomic studies could be identified evaluating the benefit of continuous infusion versus intermittent therapy in cystic fibrosis patients, nor could studies on the relative costs of cefepime therapy in the South African setting.

In compiling the inputs (resources and services) for this cost evaluation, the following considerations were made:

(a) Costs of inpatient hospitalization are frequently the main drivers of treatment costs, and their unit cost can markedly affect the outcomes of an economic evaluation;
(b) Direct costs (i.e., costs that are booked directly to the medical and nursing departments, e.g. wages and medical materials) would be derived from the medical accounts of the hospital and classified accordingly;
(c) Indirect costs such as accommodation would be calculated from the final cost centres (i.e., the departments providing the healthcare services to patients, such as nursing department) and tied to the number of inpatient days[13].

1.4 Hypothesis

From the clinical perspective it was postulated that continuous infusion (CI) administration of cefepime may result in improved efficacy and reduced development of resistance and this would be a strong recommendation for its use in any patient likely to

be infected with organisms of high resistance potential such as in the intensive care units (ICUs) and Oncology Units.

Insofar as the costing evaluation is concerned, it was postulated that CI administration of cefepime may result in less cost than intermittent therapy (IT) administration (i.e., CI may be more cost effective than IT administration).

1.5 Rationale of the study

Two of the most important parameters that affect the efficacy of an antimicrobial agent are the minimum inhibitory concentration (MIC) of the infecting pathogen to the therapeutic agent and the magnitude of the exposure of the organism to the drug [14].

Beta-lactam antibiotics (i.e., penicillins, cephalosporins, carbapenems, monobactams) and the glycopeptides (i.e., vancomycin) show little concentration-dependent bactericidal activity. Apparently, once the concentration exceeds a critical value, which appears to be about two to four times above their MIC for a given organism, killing proceeds at a zero-order rate, and increasing drug concentration does not change the microbial death rate. [14].

This is in contrast to aminoglycosides (i.e., tobramycin, gentamicin), fluroquinolones (i.e. ciprofloxacin, levofloxacin), and amphotericin B, which eliminate microorganisms most rapidly when their concentrations are appreciably above the MIC of the targeted microorganism(s). Hence, their type of killing is referred to as concentration-dependent or dose-dependent killing [14].

Beta-lactam antibiotics exhibit time-dependent or concentration-independent killing; in other words time above minimum inhibitory concentration (MIC) determines the kill rate. Hence, the duration of the concentration of the drug above its MIC for the suspected or proven pathogens at the site of infection should be the best predictor of clinical outcome. This would indicate that these agents should be administered by continuous infusion (CI) in order to potentially enhance the efficacy of treatment or allow less drug to be used on a daily basis [15].

Data exists in terms of concentration-dependant antibiotics, that area under the inhibitory curve over MIC influences the development of resistance. What has not been investigated is whether CI would reduce the tendency for resistance to develop in the concentration independent groups such as β-lactams, in other words a mutant prevention concentration. Resistance in the ICU and other areas where antibiotic use is high and in patients requiring chronic antibiotic therapy is a major problem. Any intervention that would ameliorate this would be of value.

Because ICU patients rotate and the populations of organisms vary, it was decided to study a group of patients with cystic fibrosis who were permanently colonized with *P. aeruginosa* and who were admitted every four months for antibiotic therapy.

In addition, if colony forming units (CFUs) are reduced in sputa in the CI group this may have important implications in terms of delaying relapse in patients chronically colonized with *Pseudomonas.*

2.0 AIMS AND OBJECTIVES

The aims of this study were:

a) Clinician perspective: to determine upon study completion the total cost of conducting this clinical study (original estimate: 3rd quarter 2004);
b) Hospital perspective: to collate the total costs upon study completion and determine whether continuous infusion (CI) of was more cost-effective than intermittent therapy (IT)

The study objectives were as follows:

- Clinician perspective: monitoring and collection of the following costs of IT and CI therapy at four monthly intervals: molecular fingerprinting, bacteriology, blood tests, and antibiotic costs;
- Hospital perspective: measurement and estimation of the use of the following routine and ancillary (medical) services at four monthly intervals: hospital stay (including dietary and laundry), personnel time, supplies, cefepime, antibiotic concomitant medication, radiology, and laboratory tests. Since the routine services are standard across all patient days, the average daily cost applied to each day; the ancillary services varied by patient.

3.0 MATERIALS AND METHODS

3.1 Study population

Cystic fibrosis patients who were admitted for 14 days of therapy every 4 months were randomized either to receive continuous infusions (CI) or standard intermittent therapy (IT) of cefepime 4 g per day (50 mg/kg twice daily) at the time of their periodic admissions. Sputa were taken pre-therapy, during and post-therapy and examined for CFUs and sensitivity of the organism. In both groups drug levels and MIC were measured and where applicable continuous therapy was altered to achieve a continuous

level above MIC and at a drug level of at least 3 μg/ml. Please refer to Appendix 8.2 for the schedule of investigations done per admission and resources/services consumed (hospital stay, personnel time, supplies, concomitant medication, radiology, and laboratory tests). DNA fingerprinting utilizing pulsed field gel electrophoresis was performed to confirm that the colonizing *Pseudomonas* was the same strain on each subsequent patient visit. All sputa Microscopy, Culture and Sensitivities (MC & S) were performed according to National Council for Clinical Laboratory Standards (NCCLS) criteria and standards for the purpose of direct therapy. Only strains of *P. aeruginosa* were labelled (date of culture, patient and number). Sixteen patients comprising 8 each in the CI and IT groups were recruited from the paediatric and adult cystic fibrosis clinics. *P. aeruginosa* was isolated from 14 of these patients. All or some of the isolates from 13 patients could be analysed. The disposition of patients enrolled into the study is summarized in Appendices 8.1a and 8.1b. The data has been anonymised.

3.2 Structure

Any study that looks at costs offers little or no information of relevance for improving the efficiency of resource allocation [16]. Charges (patient bills) may bear little resemblance to economic cost and use of charges as a basis for economic cost may lead researchers to draw unwarranted conclusions about economic efficiency [17].

Therefore, a CEA was considered an appropriate pharmacoeconomic evaluation technique for this study since the two dosing regimens were postulated to produce different clinical outcomes, and it was anticipated that there would be a difference in the health resources consumed in delivering the treatment.

3.2.1 Perspectives

In this costing evaluation, two perspectives were adopted, namely:

3.2.1.1 Public/academic hospital perspective

A public/academic hospital perspective was adopted since the parent clinical study was being conducted within Johannesburg General Hospital (now called Charlotte Maxeke Johannesburg Academic Hospital), a hospital setting which fits this perspective. It was

considered that a cost effectiveness analysis within this perspective would be useful to the hospital management to guide future decisions regarding the overall impact of cefepime in the hospital's formulary system and for budgeting purposes. Additionally, this perspective was scheduled to capture important direct and indirect cost data elements arising from the interdisciplinary group nature of the study which would not otherwise be captured from the clinician perspective since they were provided at zero charge in the latter perspective, viz., medical supplies, personnel time, hospitalisation, routine radiology and routine laboratory tests.

For the hospital perspective, the cost-effectiveness of IT and CI therapy were compared based on the costs within the healthcare sector. The costs were scheduled to be valued at the baseline year in which the study commenced (i.e. 2003) and adjusted for their differential timing (i.e. discounted) at 5 %.

3.2.1.2 Clinician perspective

The relative costs of IT and CI therapy were scheduled to be monitored and compared, including resources consumed due to protocol-mandated care and testing. It was deemed necessary to consider the clinician perspective separately from the hospital perspective in order to monitor and compare costs (including significant trial-induced cost, e.g.; DNA fingerprinting) which, although important as part of the clinical study protocol, would prevent an accurate measurement of costs that would occur in a natural situation (i.e., in the routine management of cystic fibrosis).
The costs were valued at the actual year in which they were incurred.

3.2.2 Billing structure

A billing structure entitled Uniform Patient Fee Schedule (UPFS) is in operation at Johannesburg General Hospital. The UPFS has been developed by the national Department of Health to provide a simpler charging mechanism for publicly funded hospitals. It was adopted as policy by the Department in November 2000 [18]. The UPFS provides a sliding scale for billing patients who have chosen to use State facilities either

by agreement with their medical scheme or because they could afford to pay cash; whilst indigent patients are charged subsidized rates.

For both the trial-specific and CEA costings, a common baseline was adopted for the costing, viz., private rates were used to value the relevant resources/services consumed (Subsidized state rates, which are themselves "one-off" of "flat" charges per month, are unsuitable for this purpose lest they introduce an artificial skew in the costing).

The cefepime drug price included for both the clinician and hospital perspectives were based on the single exit price (SEP) as quoted by the drug manufacturer. It should be noted that the single exit pricing for medicines on the private market in SA had remained unchanged from 2003 to 2006 [19]. The fixed SEP was due to the policy of administered pharmaceutical pricing currently in force in South Africa in terms of which the SA Ministry of Health had not authorized pharmaceutical manufacturers to implement any SEP increases for pharmaceutical products from 2003 to 2006. At the time of data collection, Regulations relating to SEP increase were still in draft for comment prior to finalization [20, 21].

3.2.3 Discounting

Discounting refers to the valuation of the net present value of a commodity. It is performed in order to adjust future costs and effects for their differential timing, thereby allowing a decision maker to compare them on the same temporal baseline [22].

This study was scheduled to run for one year in which case it was originally deemed unnecessary to discount either the costs or the benefits of the study since no differential timing of costs was foreseen. The study timing was dependent on the ability to enroll patients within a reasonable time frame. However, it was anticipated that the parent clinical study would face a challenge in recruiting an adequate number of qualified subjects within the one-year timeframe. And so one area beyond the author's control was the inherent uncertainty of the timing of completion of the clinical study and its attendant bearing on the availability of the costing information (hence the completion of the costing evaluation). As it turned out the clinical protocol's intentions fell short of practical outcomes with regard to the recruitment rate: the clinical study ran beyond the one-year schedule and the last patient admission was in August 2005.

It therefore became necessary to discount the resource (service) consumption. For the purpose of this report the choice of the discount rate was based on that used in a recent cystic fibrosis study [7].

3.2.4 Sensitivity analysis

A sensitivity analysis tests the numerical assumptions and enables the impact of best- and worst-case scenarios to be determined. In other words, it often identifies whether choosing different assumptions leads to a different conclusion regarding cost effectiveness [23]. The outcome of a sensitivity analysis gives an indication of the robustness of the results when changes are made to specific assumptions in the study. Areas of imprecise data in clinical study costing studies typically include: length of hospital stay, cost of hospitalization, drug costs, and choice of discount rate.

In this study, the sensitivity analysis of the numerical assumptions in the hospital perspective was scheduled to be assessed in univariate analysis by varying the values for the following variable, which is associated with imprecise data:

- duration (minutes) per day spent on a single patient (best- and worst-case scenarios).

3.3 Methods of data collection

The best measure of a resource's value is its opportunity cost, defined as the cost of using resources for some purpose, measured as their value in their next best alternative use [1]. It is used to estimate prices for resources that have no prices.

Cost data for the resources defined in the protocol was collected from the hospital's records as well as study-specific documents in cooperation with personnel from the Cystic Fibrosis ward, the Paediatric ward, the National Health Laboratory Service (NHLS), and Administration of the Johannesburg General Hospital; the Contract Laboratory Services (CLS) of the Wits Health Consortium (Pty) Ltd; and the Wits Infection Control Unit (CMID). The rand values for bacteriology testing were derived from the records of the NHLS, the CLS and the CMID as well as study-specific documents, while the rand values for routine and medical resources were derived from

the Johannesburg General Hospital's records and study-specific documents. The hospital records and study-specific documents included trial master files, patient files, original recordings from automated instruments, laboratory notes, etc. In order to document the magnitude of resource consumption for personnel time, the various personnel were asked to estimate the average time per day spent on a single patient (including best- and worst-case scenarios where practicable). Costs were calculated by multiplying the time per inpatient day with hourly rates of the relevant personnel involved.
This database was considered sufficient to permit a substantive review of the resource consumption.

3.4 Time schedule

The study commenced in June 2003 and was scheduled to continue for one year. However, as it turned out it ran beyond the one-year schedule and the last patient admission was in August 2005. Since then, full recruitment was not achievable and it was decided to terminate the study in 2006.

4.0 RESULTS

Sixteen eligible patients were drawn from the paediatric and adult cystic fibrosis clinics. Two patients were not included in the costing study: one patient from the CI group was deceased after visit 1; the other patient from the IT group tested negative for *Pseudomonas* and was therefore not enrolled. Records for 7 patients from each treatment group were accessible for costing purposes and the results are presented below.

4.1 Clinician perspective

Molecular fingerprinting costs:

Cost per isolate$^{(A)}$ = R150.00
Total number of isolates = 140

Total molecular fingerprinting cost = R22 500.00 ..... (A)

Note: The cost per isolate is inclusive of consumables, sample storage and labour; the labour cost given for this study was at a discounted hourly rate for a Senior Scientist.

Cost of bacteriology (MIC tests & CFUs)[(i)]

.....(B)

Cost of blood test (cefepime levels) [(ii)]

R7 669.28.....(C)

Blood test (procalcitonin) [(i)]

.....(D)

Cefepime antibiotic costs:

2 grams BD x 662 days = 2648 grams
Cefepime SEP (5 x 2 g vials) (ref BMS Price List, 2005) = R1 632.82
Therefore unit cost = R163.28 per gram
Total cefepime cost: R432 365.00.....(E)

Partial cost of study: (A) + (C) + (E) = R462 534.28
Total cost of study[(i)]: (A) + (B) + (C) + (D) + (E) = R...

Notes:
(i) Partial results were collated and therefore are not being presented here: for procalcitonin neither the NHLS nor the hospital's finance department could provide the full cost data; for bacteriology only typical data was available showing how the billing was charged for various patients but not the full data.
(ii) Drug levels were performed twice at each visit.

4.2 Hospital perspective

The cost results for the hospital perspective are shown in Tables 4.2.1 and 4.2.2 below and are a summation of: the level of resource/service consumption multiplied by the monetary value per time interval incurred for each patient as reflected in Appendix 8.2.

The only concomitant medication scheduled to be captured in this study were anti-infectives used to deal with microbial resistance. Concomitant medicines outside of this classification would be excluded since aspects such as the fact that patients had the option to bring their own medicines into the hospital would skew the analysis.

Table 4.2.1 Costs incurred in treatment of cystic fibrosis when personnel time calculated at minimum level

COST CATEGORY	**CI GROUP (n = 7)**	**IT GROUP (n = 7)**
Routine Services		
Hospital stay, dietary and laundry	R283 962	R205 086
Medical Services		
Personnel time (including administration)	R116 370	R87 619
Supplies	R1921	R1407
Cefepime	R240 247	R173 875
Antibiotic concomitant medication[ii]	Not calculated	Not calculated
Radiology	R2658	R2508
Laboratory tests[ii]	Not calculated	Not calculated
Total Costs	R645 158	R469 495

Notes:

(i) The costs were valued at 2003 prices and discounted at 5 %; the minimum/maximum personnel time refers the estimated shortest/longest time per day spent on a single patient (i.e., best- and worst-case scenarios), respectively.

(ii) Partial results were collated and therefore are not being presented here.

Table 4.2.2 Costs incurred in treatment of cystic fibrosis when personnel time calculated at maximum level

COST CATEGORY	CI GROUP (n = 7)	IT GROUP (n = 7)
Routine Services		
Hospital stay, dietary and laundry	R283 962	R205 086
Medical Services		
Personnel time (including administration)	R194 471	R139 349
Supplies	R1921	R1407
Cefepime	R240 247	R173 875
Antibiotic concomitant medication[ii]	Not calculated	Not calculated
Radiology	R2658	R2508
Laboratory tests[ii]	Not calculated	Not calculated
Total Costs	R723 259	R522 225

Notes:

(i) The costs were valued at 2003 prices and discounted at 5 %; the minimum/maximum personnel time refers the estimated shortest/longest time per day spent on a single patient (i.e., best- and worst-case scenarios), respectively.

(ii) Partial results were collated and therefore are not being presented here.

Cost Effectiveness Analysis

$$CER_{CI} = \frac{\text{Total CI Resource Cost}}{\text{Reported CI Effectiveness}}$$

$$CER_{IT} = \frac{\text{Total IT Resource Cost}}{\text{Reported IT Effectiveness}}$$

If the actual CEA result was obtained (please refer to Table 4.2.3 below), an inference would be made as to which modality should be given relative priority (i.e. the one with a lower CER). In other words, the treatment that represented the best value for money would be regarded as the primary therapeutic option for the management of cystic fibrosis. However, since clinical results (bacterial eradication or clinical efficacy) were not available in this study a cost-effectiveness analysis was not practicable and is not being presented in this report.

Table 4.2.3 Cost-effectiveness of two independent treatment modalities [(i)]

Modality	Cost (Rand)[C]		Health Effect (% Bacterial eradication or Clinical efficacy) [E]	Cost-effectiveness ratio [C/E] (Rand/% Bacterial eradication or Clinical efficacy)	
	At minimum personnel time	At maximum personnel time		At minimum personnel time	At maximum personnel time
CI					
IT					

(i) Clinical results (bacterial eradication or clinical efficacy) were not available in this study.

Sensitivity analysis

Under this section, the writer had scheduled to document what would occur when the least favourable (i.e. maximum) values for personnel time were used, and whether or not the additional cost per unit of effect remained acceptable. However, a sensitivity analysis was not practicable and is not being presented in this report since clinical results were not available in this study.

5.0 LIMITATIONS

- The study experienced a delayed recruitment rate and consequent inability to obtain enough patients for the study. In the end, the Chief Investigator advised

that it was impossible to measure the success of the continuous infusion (CI) technique as per the hypothesis. For this reason, clinical results (by way of bacterial eradication or clinical efficacy) were not available at the end of the parent study.

- The clinical study population was drawn from the paediatric and the adult cystic fibrosis wards. There was variability of clinical record-keeping between the two wards. Information regarding the following aspects was not available from the paediatric clinic for costing purposes: routine laboratory tests performed and concomitant medicine administered during the study. This precluded the author from valuing these costs in terms of the hospital perspective.
- The author was not able to collate the cost data for some of the patients due to them having withdrawn from the clinical study before reaching the scheduled end date.
- Incomplete cost data was availed to the author in relation to the following tests: bacteriology (MIC & CFUs) and blood test (viz., procalcitonin). For this reason, partial cost-of-study results are presented in terms of the clinician perspective.

6.0 DISCUSSION

The combined postulate for this study from the hospital perspective was that, when administered by CI, cefepime may fall into quadrant B in Table 6.1 below, thus making it dominantly acceptable for use in any patient likely to be infected with organisms of high resistance potential such as in the ICU and Oncology Unit as shown in Table 6.1 below.

Table 6.1 Dominance and tradeoffs in economic evaluation: costs and effects of new intervention relative to comparison [16]

Costs of CI	**Effectiveness of CI**	
	Higher than IT	**Lower than IT**
Higher than IT	A: Tradeoff	C: Dominance to reject
Lower than IT	B: Dominance to accept	D: Tradeoff

A standardized format was followed for data collection between the enrolled patients from the Cystic Fibrosis ward and the Paediatric ward and the author believes that this has controlled the potential source of variation between these patient groups [24].

Disaggregated data regarding service provision (resource utilization), unit prices and costs are presented in this report, thereby enabling conclusions to be drawn regarding the determinants for costs of the two therapies, for instance, what percentage of the total costs were attributable to hospitalization.

There is a current drive of antimicrobial stewardship programmes and dosing of antibiotics based on their pharmacokinetic and pharmacodynamics parameters, hence interest in the clinical utility of continuous infusion therapy with concentration-independent antibiotics such as cefepime.

The results of the current study show the partial cost of the study for the clinician perspective at R462 534. The lack of cost results regarding bacteriology and procalcitonin precludes information on the total cost of the study to be provided. However, since the tests done do not form part of the standard clinical treatment requirements these will vary from study to study. For instance the cost of bacteriology per visit depends on the number of isolates per specimen (i.e. what grows in the culture) and therefore would vary from patient to patient. These available results do offer approximations to be made for similar study costings conducted in similar settings.

For the hospital perspective the total costs for the CI group which ranged from R645 158 R 723 259 (depending on whether personnel time is calculated at minimum or maximum level, respectively) are higher than those for the IT group (R469 495 to R522 225 at minimum or maximum personnel time level, respectively), and for both groups they are driven by hospitalization. The results indicate a remarkable numerical cost differences in favour of the IT group in terms of cefepime usage (a difference of R66 372) and personnel time (a difference ranging from R28 751 to R55 122 at minimum or maximum

personnel time level, respectively), followed by supplies and radiology although the difference for these two services is less pronounced.

Since the clinical study protocol made provision for cefepime therapy to be altered to achieve a continuous level above MIC, the much higher cost for cefepime in the CI group points to this having been the case. However, without information on the clinical success of this technique it is impossible to make any tentative inferences in relation to cost-effectiveness. From a theoretical viewpoint, since hospitalization is the main driver of costs in both groups, it would be interesting to know whether this could be offset by a reduction in admissions (for instance by increasing the admission interval from 12 weeks to 16 weeks) even if this meant infusing a higher drug loading of cefepime via CI on each occasion, the attendant increased personnel time notwithstanding. The reduced infusion interval would result in a reduction in supply consumption (e.g. line drips, etc).

Oostenbrink *et al* (2003) reported that missing data resulting from premature clinical study withdrawal pose a common problem in the analysis of longitudinal data [25]. This was a case in point in this evaluation: the author was not able to collate cost data for some of the patients due to them having withdrawn from the clinical study before reaching the scheduled end date. Having considered the five different methods discussed by Oostenbrink *et al* (ibid) to deal with cost data of patients who withdraw in a clinical trial, the linear extrapolation method, notwithstanding its theoretical limitation for bias, was scheduled to be used to deal with the cost data of the withdrawn patients in preference to the 4 other methods described. The following considerations were taken into account in selecting this method: the low numerical sample size of this study would make the complete case analysis method unfavourable; the hot decking method would be impractical since the parent clinical study did not avail stratified patient variables; the multi-departmental sources of the costing data in the current study would introduce great complexity to the costing calculations if the predicted mean or multiple imputation methods were to be pursued. Pursuant to the linear extrapolation method, the costs of the withdrawn patients would be extrapolated to the 1 year study duration by dividing the observed costs of a patient by the actual number of days that particular patient remained

in the study and multiplying the result by 56 (i.e., the planned number of admission days as per the clinical protocol). In the end the extrapolation was, however, not conducted for the withdrawn patients since it has turned out that a CEA calculation is not practicable in this study due to the absence of the clinical efficacy results. There is a theoretical limitation to using such a retrospective analysis as the linear extrapolation method, viz., it perhaps overestimates the mean costs, because it extrapolates cumulative costs which may be strongly influenced by one or two periods with very high costs. Although it is impossible to exclude confidently the possibility that this shortcoming would somewhat hamper the interpretation of the data, the author does not believe that this approach would significantly jeopardize the integrity of the final results, and the basis for the tentative cost-effectiveness conclusions made in the study would be defensible.

A second challenge in this costing study has been the fact the clinical study spanned various departments and institutions, including the Cystic Fibrosis ward, Paediatric ward, National Health Laboratory Service, and Administration of the Johannesburg General Hospital, the Contract Laboratory Services (CLS) of the Wits Health Consortium (Pty) Ltd, and the Wits Infection Control Unit (CMID). This meant that the author has had to collate and compile a number of cost data sets into a single integrated analysis.

Adoption of a societal perspective in pharmacoeconomic studies is recommended, capturing patient's total use of healthcare resources, both within and outside of a clinical trial in order to reflect the interdependent relationship between hospitalization, outpatient care and medication use [7], [27]. For instance, inclusion of patient indirect expenditures for travel to the hospital, domestic help as well as loss of school hours and work hours if the patients are employed or attend school/university would be a useful exercise with the potential to enhance the generalisability of the results. However, this was not deemed practicable in this exploratory study due mainly to the following considerations:
Health care funding in South Africa is drawn from three main sources, namely, public sector budget, medical insurance and private out-of-pocket expenditure. In terms of the Medical Schemes Act, medical schemes are legally obliged to pay in full for medical services for 25 diseases gazetted with the treatment guidelines, which are referred to as

prescribed minimum benefit (PMB) conditions [26]. The medical schemes are allowed to stipulate that the patient must obtain the medical services for a PMB condition from a designated service provider in order to enjoy medical aid cover. The medical schemes may also restrict such cover to certain medicines listed in a formulary.
The essential implication of such is that the design of a prospective cost-effectiveness evaluation trial to a societal perspective would pose major methodological difficulties such as careful attention to pre-established, systemic written procedures with regard to the collation of the cost inputs in order to exclude the artificial confounding factors that such a complex funding structure as described above would pose.
A case in point is cystic fibrosis which, although not listed in the chronic disease list for PMB cover, is on an "extended" list of some medical schemes. This means that medical cover for a patient has to be motivated for by the treating clinician on a case-by-case basis, and exclusions, restrictions or waiting periods on payments are possible.

7.0 CONCLUSIONS AND RECOMMENDATIONS

Out of the two finalized costings from the clinician perspective, the study drug usage constitutes the major cost in the study. The following inputs were provided at zero charge and are therefore excluded from the calculation: medical supplies, personnel time, hospitalization, routine radiology and routine lab tests.

From the hospital perspective about 40% of the total costs are attributable to hospitalization. Study drug usage is the second driver of costs followed by personnel costs. In relative cost terms, continuous infusion (CI) costs are much higher than those for intermittent therapy (IT). This result may be related to the higher hospital resource usage of the CI group. However, it is not possible to draw any conclusions from this with regard to cost-effectiveness this study in the absence of relative clinical efficacy results as explained under sections on Limitations and Discussion.

Further research involving larger studies and a broader perspective would generate a substantial database to enable unequivocal general recommendations to be made, which would potentially address such economic considerations as the following:

1. Is the benefit meaningful for the wider population?
2. For whom is the improved modality most appropriate?
3. Patient's quality of life (QOL) supported by validated measurement instruments, since health interventions affect QOL in several ways claims.

For a study of this nature, a multicentre setting is recommended as an attempt to enhance the recruitment rate.

8.0 APPENDICES

Appendix 8.1a: visit record summary sheet – continuous infusion (CI) group

Patient Code	Hospitalisation		Concomitant medicines administered
	Dates hospitalized (dd/mm/yy)	Number of days hospitalized (excl date discharged)	
JB496001	Visit 1: 23/06/03 – 04/07/03	11	Nil
	Visit 2: 06/11/03 – 07/11/03	1	Nil
	Visit 3: 01/03/04	0	Nil
	Visit 4: 02/07/04 – 16/07/04	14	Nil
MD496004	Visit 1: 13/07/03 – 29/07/03	16	Nil
	Visit 2: 10/11/003 – 25/11/03	15	Nil
	Visit 3: 23/03/04 – 06/04/04	14	Nil
	Visit 4:02/08/04 – 16/08/04	14	Nil
TNG496005	Visit 1: Dates unavailable	N/A	N/A
	No Visits 2 – 4 (Deceased)	-	-
NS496006	Visit 1: 01/09/03 – 16/09/03	15	Tobramycin 320 I.V./day
	Visit 2: 03/11/03 – 25/11/03	22	Tobramycin 320 I.V./day
	Visit 3: 29/01/04 – 04/03/04	34	Tobramycin 320 I.V./day plus Ciprobay 200 mg I.V./b.d.
	No visit 4 (Deceased)	-	-
CLM496007	Visit 1: 19/04/04 – 05/05/04	16	Tobramycin 420 I.V. plus cloxacillin p.o.x 6 hourly, for 2 weeks
	Visit 2: 08/07/04 – 23/07/04	15	Nil
	Visit 3: 17/10/04 – 28/10/04	11	Nil
	Visit 4: 17/01/05 – 01/02/05	15	Nil
JAP496008	Visit 1: 26/05/04 – 09/06/04	14	Tobramycin 320 I.V./day plus cloxacillin p.o.x 6 hourly, for 2 weeks
	Visit 2: 18/08/04 – 01/09/04	14	Nil
	Visit 3: 23/11/04 – 14/12/04	21	Nil
	Visit 4: 09/03/05 – 23/03/05	14	Nil
KP496009	Visit 1: 20/07/04 – 03/08/04	14	Tobramycin 320 I.V./day plus cloxacillin p.o. x 6 hourly, for 2 weeks
	Visit 2: 15/10/04 – 28/10/04	13	Nil
	Visit 3: 14/01/05 – 28/01/05	14	Nil
	Visit 4: 11/04/05 – 25/04/05	14	Nil
JDT496011	Visit 1: 03/11/04 – 17/11/04	14	Tobramycin 320 mg I.V./day plus cloxacillin 2g p.o. x 6 hourly, for 2 weeks
	Visit 2: 09/02/05 – 24/02/05	15	Nil
	Visit 3: 20/05/05 – 03/06/05	14	Nil
	Visit 4: 05/08/05 – 19/08/05	14	Nil

Appendix 8.1b: visit record summary sheet – intermittent therapy (IT) group

Patient Code	Hospitalisation		Concomitant medicines administered
	Dates hospitalized (dd/mm/yy)	Number of days hospitalized (excl. date discharged)	
ML496002	Visit 1: 07/07/03 – 24/07/03	17	Nil
	Visit 2: 22/09/03 – 23/11/03	1	Nil
	Visit 3: 23/02/04 -27/02/04	4	Nil
	Visit 4: 31/05/04 – 14/06/04	14	Nil
HPK496003	Visit 1: 14/07/03 – 21/07/03	7	Tobramycin 420 I.V. plus cloxacillin 2g p.o.x6 hourly
	Visit 2: 03/11/03 – 07/11/03	4	Nil
	Visit 3: 21/03/04 – 25/03/04	4	Nil
	Visit 4:16/06/04 – 30/06/04	14	Nil
BLH496010	Visit 1: 18/10/04 – 29/10/04	11	Tobramycin 420I.V. plus cloxacillin 2g p.o.x6 hourly
	Visit 2: 17/01/05 – 02/02/05	16	Nil
	Visit 3: 09/05/05 – 17/05/05	8	Nil
	No visit 4 (Withdrawn due to resistance)	-	-
28401KLS	Visit 1: 12/08/03 – 28/08/03	16	Details unavailable from records
	Visit 2: 25/11/03 – 09/12/03	14	Details unavailable from records
	Visit 3: 30/03/04 – 13/04/04	14	Details unavailable from records
	Visit 4: 06/07/04 – 16/07/04	10	Details unavailable from records
28402JD	Visit 1: 12/08/03 – 28/08/03	16	Details unavailable from records
	Visit 2: 04/02/04 – 18/02/04	14	Details unavailable from records
	No visit 3 and 4	-	-
284003CR	Visit 1: 27/08/03 – 10/09/03	14	Details unavailable from records
	Visit 2: 02/12/03 – 15/12/03	13	Details unavailable from records
	Visit 3: 30/03/04 – 13/04/04	14	Details unavailable from records
	Visit 4: 30/07/04 – 06/08/04	7	Details unavailable from records
284004GTH	Visit 1: 09/09/03 – 23/09/03	14	Details unavailable from records
	Visit 2: 09/12/03 – 23/12/03	14	Details unavailable from records
	Visit 3: 02/03/04 – 16/03/04	14	Details unavailable from records
	No visit 4	-	Details unavailable from records
284005BNN	Visit 1: 23/09/03 Not enrolled (tested negative for *Pseudomonas*)	-	-

Notes:
Cystic fibrosis ward patient coding: 496-series
Paediatric ward patient coding: 284-series
For the paediatric ward patients, actual dates of hospitalization were unavailable. The author has had estimate these based on laboratory result order forms and invoice dates

Appendix 8.2 Resource and medical service cost structure: private rates[(i)]

Resource/service (magnitude of consumption)	Monetary value		
	FY2003	**FY2004**	**FY2005**
Hospital stay, dietary, laundry:	R772.00 per day	R772.00 per day	R772.00 per day
Personnel:			
Medical officer/pulmonologist (day 1; day 2 – 14; min 15 minutes, max 1 hour)	Day 1: R380.00 Day 2 – 14: R200.00 per day	Day 1: R380.00 Day 2 – 14: R200.00 per day	Day 1: R480.00 Day 2 – 14: R250.00 per day
Pathologist (day 1, 7 and 14)	Included in table 6.2 costs	Included in table 6.2 costs	Included in table 6.2 costs
Dietician (day 1 consult on average; min 30 minutes, max 1 hour)	R170.00 per hour	R180.00 per hour	R195.00 per hour
Physiotherapist (every day from day 1 – 14, weekdays only; min 30 minutes, max 1 hour)	Estimated:R105.70 per day	R111.92 per day	Estimated: R121.24 per day
Registered nurse (daily; min 1 hour, max 3 – 4 hours)	R43.40 per hour (R65.10 per hour Sundays & public holidays)	Estimated: R44.74 (R75.78 per hour Sundays & public holidays)	R46.08 per hour (R86.46 per hour Sundays & public holidays)
Admin clerk (on admission and discharge; min 15 minutes, max 30 minutes)	Estimated: R3850/month	Estimated: R3850/month	R3850/month
Supplies			
Long line drip & accessories (average 4 lines per 14 days)	R2.67 (I.V. line) R7.18 (dial a flow) R2.16 (Jelco) 17cents (needle) R1.32 (syringe)	R2.67 (I.V. line) R7.18 (dial a flow) R2.16 (Jelco) 17cents (needle) R1.32 (syringe)	R2.67 (I.V. line) R7.18 (dial a flow) R2.16 (Jelco) 17cents (needle) R1.32 (syringe)
Oxygen cylinder (3 l per minute for 18 hrs)	Included as part of daily charge	Included as part of daily charge	Included as part of daily charge
Oxygen mask (one every 14 days)	R2.32 each	R2.32 each	R2.32 each
Oxygen tubing (one every 14 days)	R11.89 (10 m)	R11.89 (10 m)	R11.89 (10 m)
Nebuliser mask (one every 14 days)	R4.70 each	R4.70 each	R4.70 each
Cefepime (per dosage regimen)[(ii)]	R181.26 per vial	R181.26 per vial	R181.26 per vial
Concomitant medication (per dosage regimen) [(iii), (iv)]	Tobramycin: R10.53 (estimated) Cloxacillin: R4.48 (estimated)	Tobramycin: R11.14 per vial Cloxacillin: R4.82	Tobramycin: R11.75 per vial Cloxacillin: R5.10
Radiology (3 chest X-rays per admission):	R36.00 each	R36.00 each	R36.00 each
Lab tests excl pathology:	Refer to Appendix 8.3 – 8.5 below	Refer to Appendix 8.3 – 8.5 below	Refer to Appendix 8.3 – 8.5 below

Notes:

(i) Resource/service cost structure constructed based on hospital records, standard NHLS/CMS rates and personnel interviews

(ii) Cefepime 2 g vial cost unchanged from 2003 – 2005

(iii) Tobramycin 40 mg/ml injection (2 ml)

(iv) Cloxacillin 250 mg oral capsules

Appendix 8.3 Bacteriology: NHLS rates

			NHLS Costs (incl. VAT)		
Tests	**NHLS Code**	**NHLS Description**	**NHLS 2003**	**NHLS 2004**	**NHLS 2005**
Sputum AFB (Acid Fast Bacilli)	0464	Micro TB Misc Fluor	R 24.93	R 28.04	R 29.50
	0443	Fluid Prep for TB Microscopy	R 16.62	R 17.20	R 18.10
Sputum MCS (No Growth)	0331	Microscopy Only Stained Prep	R 24.93	R 28.04	R 29.50
	0240	Culture Aerobic	R 33.24	R 36.12	R 37.90
Sputum MCS (Growth)	0331	Microscopy Only Stained Prep	R 24.93	R 28.04	R 29.50
	0240	Culture Aerobic	R 33.24	R 36.12	R 37.90
	0245	Culture Anaerobic	R 24.93	R 25.80	R 27.10
	0160	Automated Bld Cult Aerobic Growth	R 58.17	R 79.64	R 83.60
	0170	Automated Blood Cult Anaerobic Growth	R 58.17	R 79.64	R 83.60
	0326	Biochem ID Bacterium Abridged	R 16.62	R 18.06	R 19.00
	0327	Biochem ID Bacterium Extended	R 66.48	R 71.64	R 75.20
	0025	Disc Sensitivity (per organism)	R 41.55	R 45.84	R 48.10
	0015	Beta Lactamase Test	R 24.93	R 25.80	R 27.10
	0080	MIC MBC Kill	R 63.71	R 66.99	R 73.60
C-Reactive Protein (CRP)	2801	C-Reactive Protein	R 19.39	R 20.40	R 21.30

Appendix 8.4 Bacteriology: CMS rates

			CMS Costs (incl. VAT)		
Tests	**CMS Code**	**CMS Description**	**BHF 2003**	**NRPL 2004**	**CMS 2005**
Sputum AFB (Acid Fast Bacilli)	3867	Miscellaneous (body fluid*	R 30.33	R 32.60	R 34.30
	3881	Mycobacteria	R 18.57	R 20.00	R 21.00
Sputum MCS (No Growth)	3867	Miscellaneous (body fluid*	R 30.33	R 32.60	R 34.30
	3893	Bacteriological Culture: Miscellaneous	R 39.00	R 42.00	R 44.10
Sputum MCS (Growth)	3867	Miscellaneous (body fluid*	R 30.33	R 32.60	R 34.30
	3893	Bacteriological Culture: Miscellaneous	R 39.00	R 42.00	R 44.10
	3909	Anaerobe culture: limited procedure	R 27.86	R 30.00	R 31.50
	4651	Non- radiometric automated blood cultures	R 86.04	R 92.60	R 97.40
	4651	Non- radiometric automated blood cultures	R 86.04	R 92.60	R 97.40
	3923	Biochemical Identification of Bacterium: Abridged	R 19.50	R 21.00	R 22.10
	3924	Biochemical Identification of Bacterium: Extended	R 77.38	R 83.30	R 87.60
	3887	Antibiotic susceptibility test: per organism	R 49.52	R 53.30	R 56.00
	3911	Beta Lactamase Assay	R 27.86	R 30.00	R 31.50
	3903	Antibiotic level: biological *	R 72.42	R 77.90	R 82.00
C-Reactive Protein (CRP)	3947	C-Reactive Protein	R 22.28	R 24.00	R 25.20

Appendix 8.5 Chemical tests: NHLS rates

NHLS Test Description	NHLS Costs (incl. VAT)		
	NHLS 2003	**NLHS 2004**	**NHLS 2005**
WCC	R65.00	R69.90	R73.60 (R73.40)
Hb	Imputed = R44.60	R48.00	Imputed = R50.44
Platelets	R30.33	R32.60	R34.23 (R34.30)
CRP	CRP = R22.28 Imputed (Quantitative protein estimation) = R51.19 Protein: total = R19.25	CRP = R24.00 (Quantitative protein estimation) = R55.10 Protein: total = R20.70	CRP = R25.20 R57.86 (R57.90) R21.80
ESR	R15.48	R16.70	Imputed = R17.55
Blood culture (Fungal culture)	R27.86	R30.00	R31.50
Sodium, potassium chloride	R98.05	R105.50	R110.78 (R111.00)
Creatinine	R22.41	R24.10	R25.31 (R25.40)
Total bilirubin	R29.53	R31.80	R33.40
Bilirubin conjugated	R22.41	R24.10	R25.40
Albumin	R29.71	R32.00	R33.60
Alkaline phosphatase	R32.06	R34.50	R36.30
Gamma GT (glutamyl transferase)	R33.43	R36.00	R37.80
ALT	R33.43	R36.00	R37.80
AST	R33.43	R36.00	R37.80
Corr. Calcium	R22.41	R24.10	Imputed = R25.33
Magnesium	R22.41	R24.10	Imputed = R25.33
Phosphate	R22.41	R24.10	Estimated = R25.33

NHLS Test Description	NHLS Costs (incl. VAT)		
	NHLS 2003	NLHS 2004	NHLS 2005
PTT (partial thromboplastin time)	Imputed = R36.24	R39.00	R41.00
Aspergillus (fungus identification)	R51.38	R55.30	R58.07 (R58.10) Fungus culture: R31.50
Vitamin A	Imputed = R39.03	R42.00	R44.10
Vitamin D	Estimated = R39.03	Estimated = R42.00	Estimated = R44.10
Vitamin E (tocopherol)	Imputed = R22.28	Imputed = R23.98	R25.20
Glucose	Imputed = R22.44	R24.10	R25.40
Sputum AFB	1= R19.50 (R77.38) 2 = R154.76	1 = R21.00 (R83.30) 2 = R166.60	1 = R22.05 (R87.60) 2 = R174.94 3 = R262.41
Sputum mycology (mycobacteria)	R18.57 (R30.33)	R20.00	R21.00
Sputum culture	R39.00	R42.00	R44.10
Sputum sensitivity	R49.52	R53.30	R55.97 (R56.00)
Prothrombin index	Imputed = R37.16	R40.00	R42.00
Non-radiometric blood cultures	Imputed = R88.11	R92.60	R97.23
Drug level (biological fluid)	Imputed = R66.80	R71.90	R75.50 (R75.70)
Hormone concentration quantitation	Imputed = R77.03	R82.70	Imputed = R86.90

Notes:

(i) Cost structure constructed based on selected NHLS invoices for medical aid patients spanning 2003 – 2005. Multiple cost entries alongside specific tests reflect varying invoice amounts observed

(ii) Where invoice amount unavailable for specific test, average cost increase 2003 to 2004 calculated at 7.63 % for imputation purposes

(iii) Where invoice amount unavailable for specific test, average cost increase from 2004 to 2005 calculated at 5.09 % for imputation purposes

Appendix 8.6 Ethics clearance certificate number

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