South African National Essential Medicines List
Adult Hospital Level Medical Review
Component: HIV and AIDS

Flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV infected adults

Health Economics and Budget Impact Analysis

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Tables and Figures

Table of Abbreviations

5FC	Flucytosine
AmBd	Amphotericin B
ART	Antiretroviral therapy
ARVs	Antiretrovirals
CD4	Differentiated cells
CM	Cryptococcus meningitis
FBC	Full blood count
Flu	Fluconazole
HIV	Human immunodeficiency virus
K	Potassium
LOS	Length of stay
Mg	Magnesium
PLHIV	Persons living with HIV
SC	Standard of care
VL	Viral Load

Glossary of Terms

For a glossary of health economics terms the following weblink from the Health Economics Centre, University of York can be used:

https://www.yhec.co.uk/tools-resources/glossary/

Executive Summary

Background and Introduction

Although in recent years the number of cases of CM has decreased in South Africa from 7140 cases in 2016 to 6636 cases in 2017 and the incidence per 100 000 HIV infected people has dropped from 102/100 000 (95%CI 100-105) in 2016 to 93 (95%CI 91-96) in 2017, the in-hospital case fatality ratio has remained unchanged (p=0.44). The current standard of treatment for cryptococcal meningitis is a 2 week induction course of amphotericin B and fluconazole. Although flucytosine has been considered an alternative treatment by the WHO concerns around lack of availability and high prices have limited access, especially in low to middle income countries.

In 2018 a clinical review of more recently published clinical trial data on flucytosine from the ACTA trial and an updated Cochrane Review and meta-analysis conducted by the Adult Review Committee of the NEMLC prompted a request for an updated cost-effectiveness and budget impact analysis.

The aim of this analysis was to determine the cost-effectiveness and budget impact of introducing flucytosine as induction therapy for cryptococcal meningitis in HIV infected adults in a public sector setting in South Africa in order to inform whether flucytosine should be included on the Essential Medicines List

Method

A cost-effectiveness decision analysis model was developed based on survival estimates from the ACTA trial at 2 and 10 weeks. The model included 4 treatment arms:

- **2wk AmBd/Flu (SC)** - 2 week course of fluconazole/amphotericin B (current standard of care)
- **1wk Flu/5FC** - 1 week short course flucytosine/amphotericin B
- **2wk AmBd/5FC** - 2 week course flucytosine/amphotericin B
- **Oral** - 2 week oral flucytosine/fluconazole

For the survival base-case the ACTA trial outcomes at 10 weeks were selected and then extrapolated to 1 year based on an 11.2% mortality rate at 12 months followed by an annual mortality rate for HIV infected individuals of 0.65% pa until the end of the model. The time horizon of 25 years for this model was based on the average life expectancy of an HIV-infected patient at 35 years of age who is receiving ART in South Africa. Due to the well-known toxicities associated with amphotericin B, the probabilities of patients experiencing adverse drug reaction were included in the analysis. The pharmacoeconomic outcomes for this study were presented as Incremental Cost-effectiveness Ratios (ICERs) of Cost/LYGs and Cost/QALYs.

The cost/QALY outcome was based on the QALYs accumulated over 25 years life expectancy.

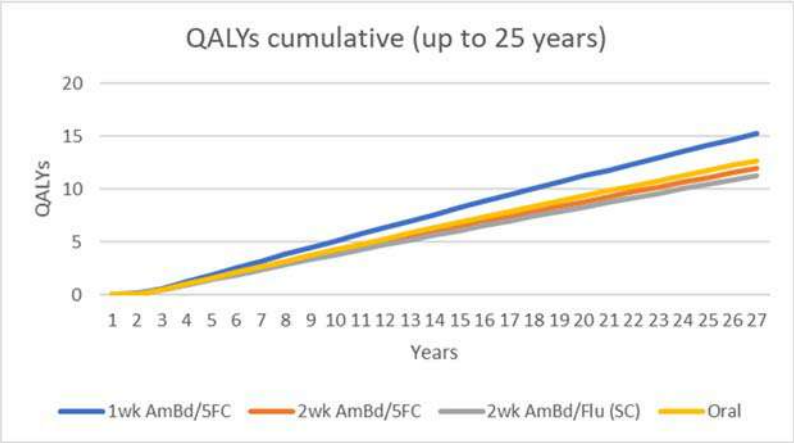


Figure 1. Accumulated QALYs per year for each treatment arm

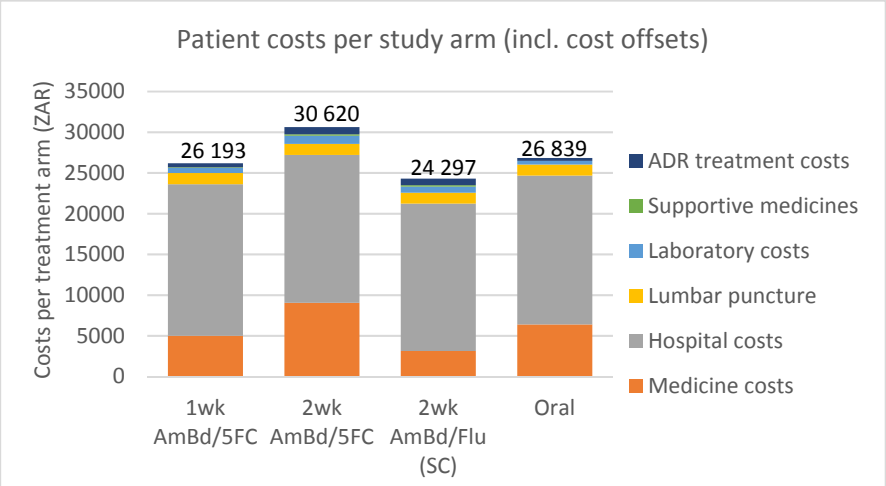
Costs

Costs were determined for 2018. Medicine prices were taken from the Master Procurement Catalogue where available. The current price of flucytosine was based on a buy-out price obtained from the Western Cape. Generally, there is no vial sharing for Amphotericin B for patients, so it was assumed that 2 vials per dose were used. This was based on an estimated patient weight of 60kg at a dose of 1mg/kg/day. The ACTA trial fluconazole dosing regimen of 1200mg per day differs slightly from the WHO guidelines of 800mg per day. In this analysis, the ACTA trial dosing was used as the base-case and a sensitivity analysis was conducted to determine the impact of using the WHO dosing guidelines instead. In the ACTA trial all patients received pre-emptive hydration and electrolyte supplementation. This was considered in the study with utilisation based on the current WHO guidelines, pre-emptive hydration (daily saline prior to AmBd infusions) and electrolyte supplementation (KCL injections prior to AmBd infusions, 1-2 KCL tablets daily and 500mg magnesium oral twice daily if available).

In addition to infusion fees, laboratory costs, lumbar puncture procedures and the cost of adverse drug reactions, the base-line hospital costs were determined for a Level 2 facility with an in-patient stay of 17 days as per the ACTA trial. This took into consideration additional length of stay in a proportion of patients due to ADRs or failure to respond to treatment.

Results

When the proportion of patients alive in each arm is taken into consideration, the highest medicine costs were in the 2 week AmBd/5FC arm followed by the 2 week oral regimen, then the 1 week AmBd/5FC with the lowest medicines cost in the standard of care arm. However, the total cost of the 2 week SC is not much lower than the highest cost because of infusion fees at approx. R202 pd. Monitoring costs are highest in the 2 week Am/5FC arm followed by the 2 week SC. Supportive medicine costs are lowest in 1 week with no additional costs for the oral regimen.



As expected the 1 week flucytosine arm has the highest numbers of LYGs and QALYs, followed by the oral regimen, then the 2 week flucytosine arm with the lowest in the standard of care arm.

Discounted

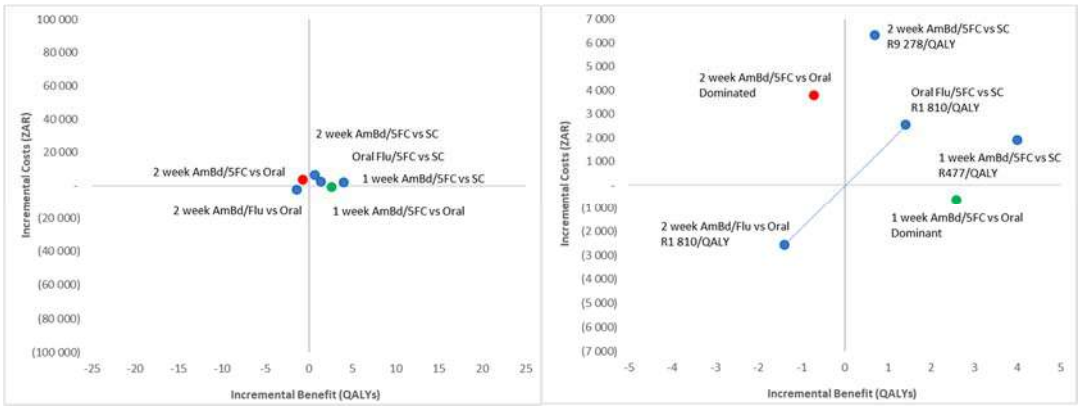
	LYG	QALY	Cost
1 week AmBd/5FC	16.22	15.27	26 196
2 week AmBd/5FC	12.71	11.97	30 620
2 week AmBd/Flu	11.99	11.29	24 294
Oral 5FC/Flu	13.48	12.69	26 839

The ICERs for the different treatment arms compared to standard of care show that the 1 week flucytosine course is most cost-effective with an ICER of less than R500/QALY although none of the ICERs are more than R10 000/QALY which is considered to be very cost-effective. For the comparator to the oral regimen, the 1 week flucytosine course dominates with better clinical benefits (QALYs) and lower costs, whereas the 2 week flucytosine course is dominated with poorer clinical outcomes and higher costs. Compared to the oral regimen, the 2 week standard of care has poorer clinical outcomes but lower costs.

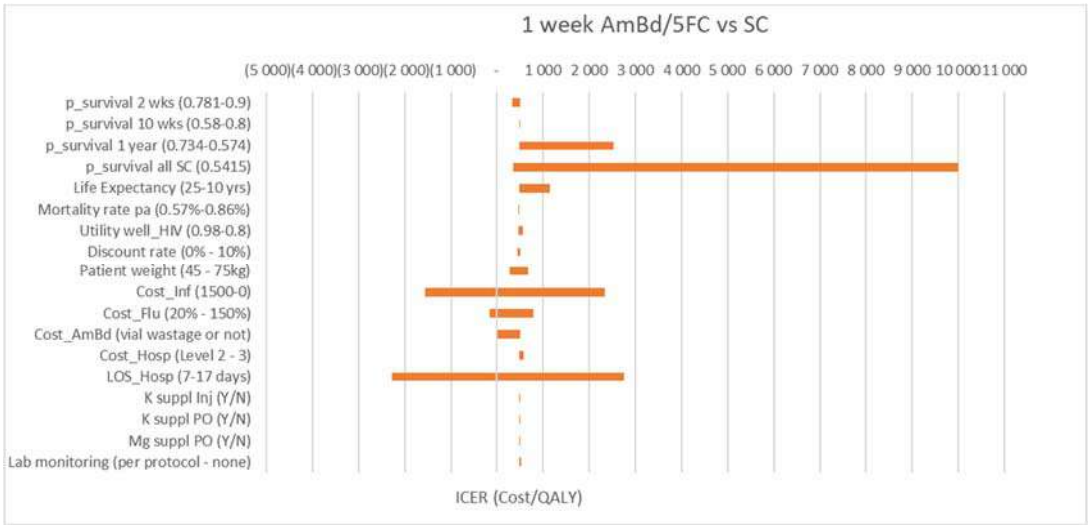
Discounted	**incr LYG**	**incr QALY**	**incr Cost**	**ICER (R/LYG)**	**ICER (R/QALY)**
vs 2 week AmBd/Flu (SC)					
1 week AmBd/5FC	4.23	3.99	1 902	450	477
2 week AmBd/5FC	0.72	0.68	6 326	8 759	9 278
Oral 5FC/Flu	1.49	1.41	2 545	1 708	1 810

Discounted	**incr LYG**	**incr QALY**	**incr Cost**	**ICER (R/LYG)**	**ICER (R/QALY)**
vs Oral regimen					
1 week AmBd/5FC	2.73	2.58	- 643	- 235	Dominant
2 week AmBd/5FC	- 0.77	- 0.72	3 781	- 4 922	Dominated
2 week AmBd/Flu (SC)	- 1.49	- 1.41	- 2 545	1 708	1 810

When plotted on a cost-effectiveness plan, the outcomes are arranged very closely together even though some of the ICERs are in the dominant quarters. When viewed on a smaller scale the difference between the ICERs can be seen more clearly.



When a sensitivity analysis was conducted to assess the uncertainty in the model it was found that varying most parameters did not have a substantial impact on the outcomes. The model is most sensitive to hospital length of stay, Infusion fees and the cost of flucytosine.



Even when the survival rate is fixed to be the same as the standard of care for each arm (i.e. survival probability at 2 weeks for all arms is 0.781), the ICERs do not shift much and the flucytosine regimens are still cost-effective compared to the standard of care. It is only if the survival rate for all arms is equivalent to the standard of care at 12 months that the oral and 2 week flucytosine regimens are no longer cost effective with ICERs of R99 935/QALY and R544 326/QALY respectively.

The inclusion of costs for treatment of anaemia (blood transfusions) or neutropenia (antibiotics) does not impact substantially on the ICER outcomes, nor for the inclusion or exclusion of use of potassium or magnesium supplementation.

The model is sensitive to the price of flucytosine with the oral arm becoming cost saving at a 50% price discount and when price is discounted to 50% the 1 week flucytosine course also becomes cost saving although the 2 week flucytosine course still has an ICER of R2 260/QALY. The price at which the 1 week regimen is cost-neutral is around R1 450 per pack and R1 218 per week of treatment.

When the cost of infusion fees is increased (R500 up to R1500), the 1 week flucytosine and oral course become dominant although not at the cost of level 3 infusion fees (R233 per infusion) where there is still a small ICER for all 3 arms compared to SC. Although other published cost-effectiveness analyses included an infusion fee as a separate cost item, in South Africa it most likely included in the hospital

daily rate. The impact of excluding the infusion fee cost was assessed and found to increase the ICERs slightly but not to more than R10 000/QALY for any arm. The impact of a higher infusion fee may be relevant in the private sector setting where infusion fees are likely to be higher and charged as a separate item on the hospital bill. In that case, the oral regimen is clearly favourable and becomes cost saving at around R500 per infusion fee.

Due to the trial protocol in ACTA the average LOS in the trial was 17 days regardless of which treatment arm they were in. It is possible that patients who are well enough to be discharged may leave sooner if they are on the 1 week AmBd/5FC or oral regimen. This has a substantial impact on the model so that if the length of stay in hospital is reduced to 10 or 7 days for either the 1 week or oral flucytosine course, the ICERs become increasingly dominant in those arms.

Increasing or reducing the number of therapeutic lumbar punctures either in the comparator arms or standard of care does not have much impact on the ICERs. Varying the number of laboratory tests only slightly increases the ICERs if the lab monitoring is reduced.

Budget Impact Analysis

Assuming the base case inputs, including the same LOS (17 days) for all treatment arms, the greatest total and incremental budget impact for 2018 is with the 2 week AmBd/5FC course of treatment, followed by the oral regimen, then the 1 week course and the current standard of care having the lowest budget impact.

Total Costs	**1wk AmBd/5FC**	**2wk AmBd/5FC**	**2wk AmBd/Flu (SC)**	**Oral**
Budget Impact (2018)				
Medicine costs	21 024 705	38 008 704	13 127 540	26 832 427
Hospital costs	78 060 260	76 171 543	75 970 616	76 714 047
Lumbar puncture	5 764 090	5 624 624	5 609 787	5 664 683
Laboratory costs	2 648 768	4 230 882	3 131 652	1 839 471
Supportive medicines	262 024	714 782	712 897	-
ADR treatment costs	2 132 805	3 698 911	3 361 008	1 539 055
Total	**109 892 651**	**128 449 446**	**101 913 499**	**112 589 682**

If all patients were switched to the flucytosine regimens, the average additional cost per patient (total costs) over what is currently spent on standard of care would be R1 902 and R2 545 per patient per year for the 1 week and oral course respectively.

Total Inc. impact (2018)	**Total Inc cost**	**Ave Inc cost per pt**
vs 2wk AmBd/Flu (SC)		
1wk AmBd/5FC	7 979 152	1 902
2wk AmBd/5FC	26 535 947	6 326
Oral	10 676 184	2 545

As the price of flucytosine is reduced so the incremental budget impact decreases until at a 50% price reduction the oral regimen becomes cost saving and at a 75% price reduction both the 1 week flucytosine arm and oral regimen are cost saving. The 1 week course becomes cost saving at a pack price of around R1 450 (R1 218 per week of treatment).

In addition, the model is sensitive to the whether an infusion fee is included or not with the incremental budget increasing for the 1 week course and the oral regimen as the cost of treatment in the 2 week courses is reduced. As the infusion fee increases so these increase and the oral and 1 week courses become cost saving.

The greatest impact is seen when the LOS is reduced for the 1 week and oral regimens assuming that patients are able to be discharged sooner. If the LOS is reduced to 10 days or 7 days the 1 week and oral courses become increasingly cost-saving.

Conclusion and Recommendation

This updated cost-effectiveness analysis confirms that the addition of flucytosine as induction therapy in the treatment of cryptococcal meningitis in patients infected with HIV is cost-effective regardless of whether it is used as a 1 week, 2 week or oral regimen. As to be expected the 1-week flucytosine course is most cost-effective with an ICER of less than R500/QALY, followed by the oral regimen compared to the standard of care. The model is most sensitive to changes in costs rather than outcomes with the greatest impact seen where cost-savings can be achieved by reducing the price of flucytosine, reducing the infusion fee costs and reducing the hospital length of stay.

However, the outcomes and resource utilisation in a general clinical practice setting such as that in the public sector in South Africa may differ. It is recommended that if flucytosine is included on the Essential Medicines List, a study is conducted to verify these outcomes and costs.

Although the incremental budget impact of flucytosine compared to current standard of care is in the region of R8 million per annum, savings could be achieved with early discharge of patients as well as a reduction in the price of flucytosine.

It is recommended that negotiations are conducted with the manufacturer to reach a cost-neutral price (approx. 50% reduction) for the 1 week induction treatment course.

1. Introduction and Background

Although in recent years the number of cases of CM has decreased in South Africa from 7140 cases in 2016 to 6636 cases in 2017 and the incidence per 100 000 HIV infected people has dropped from 102/100 000 (95%CI 100-105) in 2016 to 93 (95%CI 91-96) in 2017, the in-hospital case fatality ratio has remained unchanged (p=0.44) (1)

Treatment of cryptococcal meningitis (CM) in HIV infected patients in South Africa comprises either a combination of amphotericin B+fluconazole or amphotericin B as monotherapy. South African guidelines (2) currently recommend an induction-phase treatment of Amphotericin B (1mg/kg/day IV) + fluconazole (800mg/day PO). Fluconazole and amphotericin B have been the mainstay of treatment for many years, however increasing evidence has shown that the use of flucytosine is more effective and less toxic. In 2018 the WHO updated their guidelines to include recommendations for the short-course (1 week) flucytosine/Amphotericin B regimen as well as an alternative 2 week oral course of flucytosine and fluconazole. This was based evidence of increased superiority of the regimens over current treatment recommendations (3).

Lack of availability of flucytosine is a common problem, especially in low-middle income countries however a major concern is also around the cost of this medicine as it is likely to be unaffordable at current international prices (4) (5).

In 2018 a clinical review of more recently published clinical trial data from the ACTA trial (6) and an updated Cochrane Review (7) and meta-analysis conducted by the Adult Review Committee of the NEMLC (8) prompted a request for an updated cost-effectiveness and budget impact analysis.

2. Aims and Objectives

The aim of this analysis was to determine the cost-effectiveness and budget impact of introducing flucytosine as induction therapy for cryptococcal meningitis in HIV infected adults in a public sector setting in South Africa in order to inform whether flucytosine should be included on the Essential Medicines List

The objectives were to;

1. Conduct a cost-effectiveness analysis comparing the following regimens to the current standard of care 2 week course of fluconazole/amphotericin B available in the public sector
    a. short course (1 week) flucytosine/amphotericin B or
    b. 2 week course flucytosine/amphotericin B or
    c. 2 week oral flucytosine/fluconazole
2. Conduct an additional cost-effectiveness analysis comparing the oral flucytosine/fluconazole regiment to the short course (1 week) flucytosine/amphotericin B
3. Conduct a budget impact analysis on the introduction of flucytosine to the Essential Medicines List

3. Cost-effectiveness Analysis

3.1. Methods

A cost-effectiveness decision analysis model was developed based on survival estimates from the ACTA trial at 2 and 10 weeks (6). The model included 4 treatment arms:

- **2wk AmBd/Flu (SC)** - 2 week course of fluconazole/amphotericin B (current standard of care)
- **1wk AmBd/5FC** - 1 week short course flucytosine/amphotericin B
- **2wk AmBd/5FC** - 2 week course flucytosine/amphotericin B
- **Oral** - 2 week oral flucytosine/fluconazole

The pharmacoeconomic model uses mortality rates as a primary efficacy endpoint to arrive at an incremental cost-effectiveness ratio (ICER) of cost/LYG (Life Years Gained) or cost/QALY (Quality Adjusted Life Years).

The time horizon of 25 years for this model was based on the average life expectancy of an HIV-infected patient at 35 years of age who is receiving ART was based on estimates from a recent South African collaborative study with a weighted average of CD4 counts and ratio of male:female demographics (9). In a recent cost-effectiveness analysis based on utilisation and outcomes data from the ACTA trial, a life expectancy of 18 years was used based on data from Rajasingham pharmacoeconomic analysis, who used a Ugandan cohort analysis (10) (11).

The study perspective was that of a third party payer, in this instance the South African Government, and therefore only direct costs were considered.

3.2. Clinical Inputs

3.2.1. Survival rates

For the survival base-case the ACTA trial outcomes at 10 weeks were selected and then extrapolated to 1 year based on an 11.2% mortality rate at 12 months from a previous cost-effectiveness analysis using a pooled analysis of 1 year mortality after treatment for CM in a South African cohort (n=262), a Ugandan cohort (n=101) and a Thai cohort n=277) (11). Although the Vietnamese study by Day et al in 2013 (12) reported 6 month mortality outcomes, these were non-significant between the treatment arms and therefore these outcomes were not included in the model. The annual mortality rate of 0.65% pa for HIV infected individuals in South Africa from the Global Burden of Disease 2016 model was applied from years 2 onwards (13).

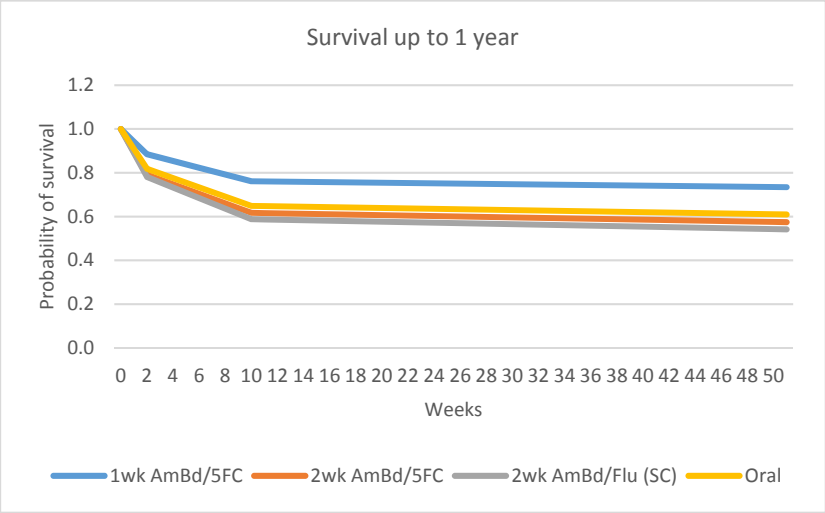


Figure 2. Survival probabilities up to 12 months of treatment

For managing relapses or recurrences, the WHO Guidelines recommend restarting the induction phase as per the initial recommendations. This model did not specifically include relapses or recurrences, however these were assumed to be in the total number of cases of CM per year and did not differ in terms of mortality rates to first infections. The Tenforde Cochrane Review only included studies of patients with a first episode of HIV-associated CM so it may not be appropriate to attribute the same efficacy of treatment to patients with recurring disease (7)

Although paradoxical cryptococcal immune reconstitution inflammatory syndrome does occur with an estimated frequency of 10-50% (3) in patients initiating ART in all the treatment regimens and this condition is associated with a high mortality, it is assumed that this is already included in the overall mortality rate attributed to CM as per the outcomes based on the clinical trial data.

3.2.2. Adverse Drug Reactions

The probability of ADRs is taken from the Cochrane review (7) and utilisation of resources from the most recently published cost-effectiveness analysis (11). In this model it is assumed that the WHO guidelines are followed to reduce the incidence of amphotericin B toxicity and this includes adequate hydration with iv fluids as well as supplementation with potassium and magnesium.

Amphotericin has widely been implicated in the development of nephrotoxicity (14, 15). The development of nephrotoxicity or anaemia is associated with increased 10-week mortality and therefore these are important ADRs to monitor and manage (16). Based on a review of the literature and discussions with the members of the Essential Medicines List Committee it was determined that for anaemia the treatment is blood transfusion and these costs were taken into consideration.

Nephrotoxicity is largely managed by pre-emptive saline, hydration and electrolyte replacement. However, if patients do develop nephrotoxicity Grade III or IV, management starts by omitting the next AmBd dose and giving additional fluids. If creatinine levels are still rising, then the patient is either moved to alternate day dosing or treatment is stopped altogether (15,16).

In neither the Bicanic nor ACTA trials were any mention made of patients who required dialysis as management of nephrotoxicity. This route of clinical management was confirmed by the Adult EML Committee and it was agreed that it is very rare that a patient requires dialysis. It is possible an extended length of stay may be required to complete the course of treatment.

Neutropenia Grade 3 and 4 was experienced in 7.5% and 3.6% of patients respectively in the ACTA trial (6). Antibiotic treatment is most commonly used for neutropenia and Chen et al included a probability of antibiotic usage based on actual utilisation from their costing analysis of the ACTA trial (10). There is very little published on the use of antibiotics as treatment of neutropenia in patients with CM so certain assumptions had to be made regarding type of antibiotic, dose, duration and probability of treatment. It was assumed that all patients who experienced neutropenia requiring IV antibiotics were still in hospital for CM treatment and therefore did not incur additional hospital costs, only those of the antibiotic treatment.

Details of the probabilities and costs of ADRs are contained in **Appendix E: Adverse Drug Reactions – Utilisation and Costs**

3.2.3. Life Years Gained and QALYs

Life expectancy was assumed to be 25 years following the first year of treatment from diagnosis of CM. This is supported by Johnson et al, 2016 in an updated estimate from the South African Thembisa model which indicates that when life expectancies are not adjusted for time on ART or baseline CD4 count, the average life expectancy for women and men aged 35 years is 26.1 and 21.1 years respectively (9) . When the model was tested for sensitivity to life expectancy this was varied from 18 years to 35 years.

An average annual mortality rate for both men and women aged 35-39 years living with HIV in South Africa was determined from the IHME data tool based on the Global, regional, and national age-sex specific mortality tables for HIV/AIDS (1980-2017) of the Global Burden of Disease study (http://ghdx.healthdata.org/gbd-results-tool) (17)

Utilities were obtained from the Merry et al cost-effectiveness study and a sensitivity analysis was conducted (18).

The cost/QALY outcome was based on the QALYs accumulated over 25 years life expectancy (Figure 3)

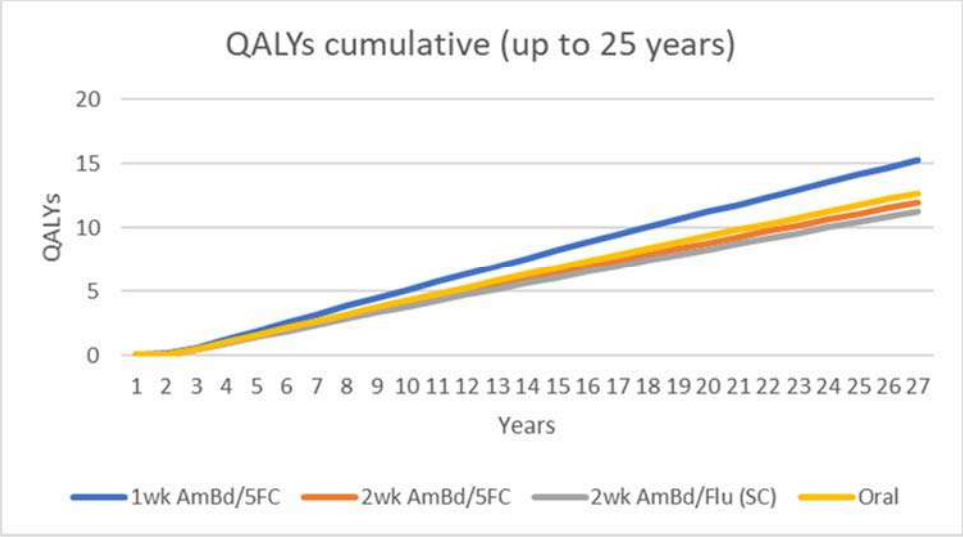


Figure 3. Accumulated QALYs per year for each treatment arm

3.3. Costs

All costs were determined for 2018. If necessary, prices or tariffs from previous years were adjusted by average annual CPI to bring them up to 2018 prices. A discount rate of 5% was used based on the South African Pharmacoeconomic Guidelines (19). All costs were presented in South African Rands (ZAR). A summary of the cost breakdown per patient per category are show in Table 1.

Total Costs Summary				
Per Patient	**1wk AmBd/5FC**	**2wk AmBd/5FC**	**2wk AmBd/Flu (SC)**	**Oral**
Medicine Costs				
Induction (week 1)	4627.37	4627.37	1508.26	3191.62
Induction (week 2)	36.26	4627.37	1508.26	3191.62
Consolidation	193.36	193.36	193.36	193.36
Maintenance	253.79	253.79	253.79	253.79
Total Medicine Costs	*5110.77*	*9701.88*	*3463.66*	*6830.39*
Hospital Costs				
Secondary	19159	19159	19159	19159
Tertiary	29850	29850	29850	29850
Other costs				
Supportive Medicines	62.46	179.79	179.79	
Laboratory Costs (Monitoring)	650.11	1 064.17	789.77	459.40
Lumbar puncture	1 414.73	1 414.73	1 414.73	1 414.73
ADR Costs				
Anaemia	344.31	849.29	711.56	275.44
Renal dysfunction				
Neutropaenia	179.17	81.08	136.05	108.93
Total ADR costs	*523.47*	*930.37*	*847.61*	*384.37*
Total Costs (per patient)	**26 920.54**	**32 449.94**	**25 854.56**	**28 247.89**

Table 1. Summary of categories of costs per patient

Medicine costs

Medicine prices were obtained from the Master Procurement Catalogue for September 2018 (20). Where public sector prices were not available, Single Exit Prices (SEP) were obtained from the Database of Medicine Prices October 2018 (21). The price of amphotericin B was obtained from the Gauteng Provincial buy-out list for November 2018. The price of flucytosine was obtained from a Section 21 quote for the Western Cape (personal comm T Leong 2019). **Appendix A. Medicine Prices**

Generally, there is no vial sharing for Amphotericin B for patients, so it was assumed that 2 vials per dose were used. This was based on an estimated patient weight of 60kg at a dose of 1mg/kg/day (communication at Adult EML Committee meeting May 2019). Although the average weight of a patient is usually assumed to be 70kg, in the ACTA trial the average weight range was 50-53kg across treatment cohorts.

The fluconazole dosing in the ACTA trial differs from that of the WHO Guidelines. The initial oral regimen used in the trial is 1200mg fluconazole for 14 days (or 7 days in the case of the short course). The WHO Guidelines recommend 800mg per day. Thereafter fluconazole was administered at 800mg per day for a further 2 weeks until ART was started and then reduced to 400mg per day (WHO Guidelines recommend continuing with 800mg) until 10 weeks where it was further reduced to the maintenance phase dose of 200mg per day.

For the 1 week short course AmBd/5FC, the WHO Guidelines recommend following up with 8 weeks of fluconazole at 800mg/day and then going onto a maintenance phase of treatment of fluconazole 200mg/day. This results in an earlier reduction in dose of fluconazole by 1 week.

In this analysis, the ACTA trial dosing was used as the base-case and a sensitivity analysis was conducted to determine the impact of using the WHO dosing guidelines instead. **Appendix B. Treatment Costs**

Pre-emptive hydration (daily saline prior to AmBd infusions) and electrolyte supplementation (KCL injections prior to AmBd infusions, 1-2 KCL tablets daily and 500mg magnesium oral twice daily if available) is recommended in the WHO guidelines (3). This is included in the base-case and a sensitivity analysis conducted to determine the impact if this was not routine standard of care. In the ACTA trial all patients received pre-emptive hydration and potassium supplementation. Details of medicine prices and treatment costs can be found in **Appendix C: Other Medicine Costs**

The infusion fees were based on the UPFS tariffs for level 2 or level 3 facilities and included a GP and facility fee as well as the cost of admin set.

Laboratory costs were obtained from the NHLS State Price List 2017. The utilisation of the costs was based on the WHO guidelines of twice weekly monitoring of potassium, magnesium and creatinine, weekly haemoglobin monitoring and full blood count for flucytosine monitoring (twice weekly for duration of treatment). **Appendix D: Laboratory Costs**

Lumbar puncture costs were determined either as a diagnostic cost (including rapid antigen assay and culture) or a therapeutic cost (to relieve raised intracranial pressure). Diagnostic costs at the time of initial presentation were the same for all arms and therefore did not make any difference in the incremental analysis however they were also used for patients who had a recurrent infection following treatment failure which would differ between treatment arms. For the budget impact analysis the initial diagnostic costs were included as well as therapeutic costs.

It was assumed that patients had one diagnostic LP and one therapeutic LP puncture regardless of which regimen they were treated with. In the ACTA trial patients received on average 3 LPs, at baseline and on days 7 and 14, however this was conducted under clinical trial conditions and the WHO guidelines do not recommend routine follow up LPs in resource limited countries (3).

Hospital costs

Base-line hospital costs were determined for a Level 2 facility with an in-patient stay of 17 days as per the ACTA trial. This took into consideration additional length of stay in a proportion of patients due to ADRs or failure to respond to treatment.

ADR costs

Anaemia: the probability of patients developing Grade IV anaemia was based on the ACTA trial and it was assumed that all patients received a transfusion. The utilisation of blood units was obtained from the Chen et al study (11). However, in the Bicanic study, it was noted that of all the patients with Grade IV anaemia in South Africa, only around 20% of those actually received a transfusion (14).

Costs of a blood transfusion were taken from the SANBS tariffs for 2018 and included the cost of whole blood, admin sets and a delivery fee.

Neutropenia: the utilisation rate of antibiotics to treat neutropenia was taken from the Chen et al study although only antibiotics that are available in South Africa on the EML were included (11).

Renal toxicity: the costs of haemodialysis were determined from the UPFS tariffs and included in the costing tables even though it was assumed there would be no uptake of dialysis and patients were managed according to current clinical practice. These costs were included in the event of a sensitivity analysis to determine the impact if renal dialysis was required. **Appendix E: Adverse Drug Reactions – Utilisation and Costs**

3.4. Results

When the proportion of patients alive in each arm is taken into consideration, the highest medicine costs were in the 2 week AmBd/5FC arm followed by the 2 week oral regimen, then the 1 week AmBd/5FC with the lowest medicines cost in the standard of care arm. However, the total cost of the 2 week SC is not much lower than the highest cost because of infusion fees at approx. R202 pd. Monitoring costs are highest in the 2 week Am/5FC arm followed by the 2 week SC. Supportive medicine costs are lowest in 1 week with no additional costs for the oral regimen.

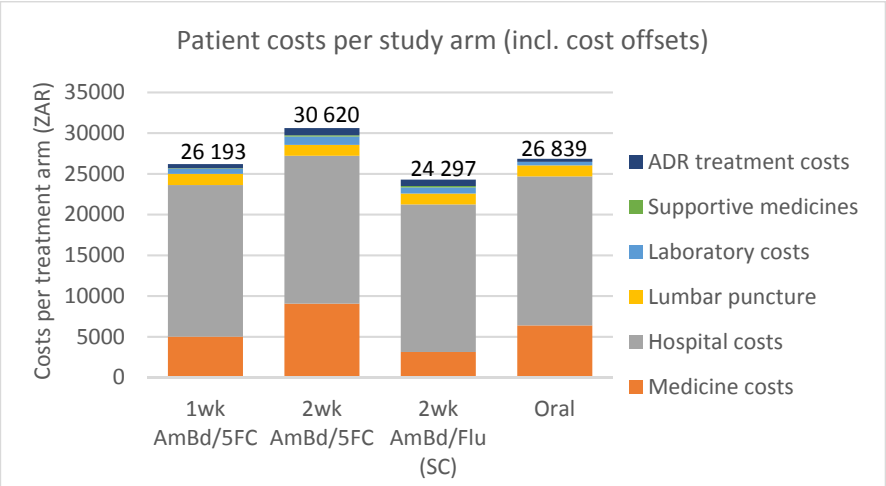


Figure 4. Costs per treatment arm per category

Appendix F. Total Costs per treatment arm

The total LYG and QALYs for each treatment arm are shown in Table 2. As expected the 1 week flucytosine arm has the highest numbers of LYGs and QALYs, followed by the oral regimen, then the 2 week flucytosine arm with the lowest in the standard of care arm.

Undiscounted				***Discounted***			
	LYG	**QALY**	**Cost**		**LYG**	**QALY**	**Cost**
1 week AmBd/5FC	17.03	16.05	26 196	1 week AmBd/5FC	16.22	15.27	26 196
2 week AmBd/5FC	13.35	12.57	30 620	2 week AmBd/5FC	12.71	11.97	30 620
2 week AmBd/Flu	12.59	11.86	24 294	2 week AmBd/Flu	11.99	11.29	24 294
Oral 5FC/Flu	14.16	13.33	26 839	Oral 5FC/Flu	13.48	12.69	26 839

Table 2. Total LYGs and QALYs per treatment arm

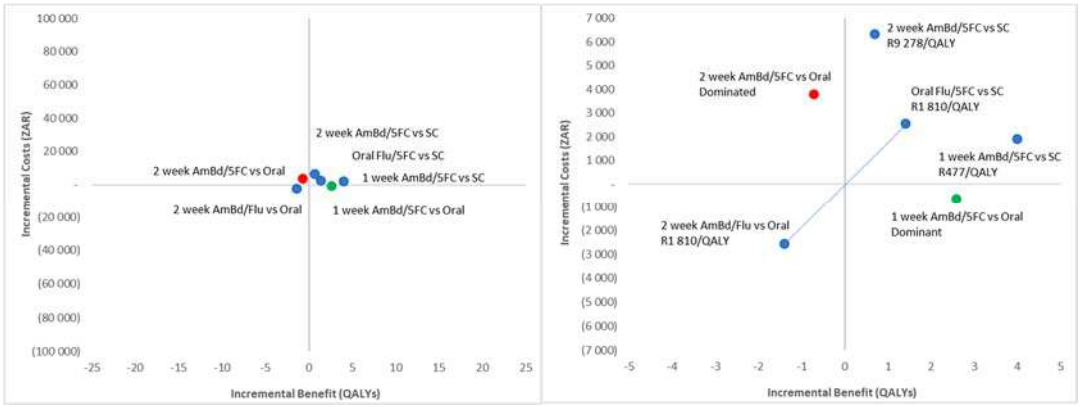
The ICERs for the different treatment arms compared to standard of care show that the 1 week flucytosine course is most cost-effective although none of the ICERs are more than R10 000/QALY which is considered to be very cost-effective. For the comparator to the oral regimen, the 1 week flucytosine course dominates with better clinical benefits (QALYs) and lower costs, whereas the 2 week flucytosine course is dominated with poorer clinical outcomes and higher costs. Compared to the oral regimen, the 2 week standard of care has poorer clinical outcomes but lower costs.

Discounted	**incr LYG**	**incr QALY**	**incr Cost**	**ICER (R/LYG)**	**ICER (R/QALY)**
vs 2 week AmBd/Flu (SC)					
1 week AmBd/5FC	4.23	3.99	1 902	450	477
2 week AmBd/5FC	0.72	0.68	6 326	8 759	9 278
Oral 5FC/Flu	1.49	1.41	2 545	1 708	1 810

Discounted	**incr LYG**	**incr QALY**	**incr Cost**	**ICER (R/LYG)**	**ICER (R/QALY)**
vs Oral regimen					
1 week AmBd/5FC	2.73	2.58	- 643	- 235	Dominant
2 week AmBd/5FC	- 0.77	- 0.72	3 781	- 4 922	Dominated
2 week AmBd/Flu (SC)	- 1.49	- 1.41	- 2 545	1 708	1 810

Table 3. Incremental costs, LYG, QALYs and ICERs for each treatment arm

When plotted on a cost-effectiveness plan, the outcomes are arranged very closely together even though some of the ICERs are in the dominant quarters. When viewed on a smaller scale the difference between the ICERs can be seen more clearly.



3.5. Sensitivity Analysis

The model is most sensitive to hospital length of stay, Infusion fees and the cost of flucytosine.

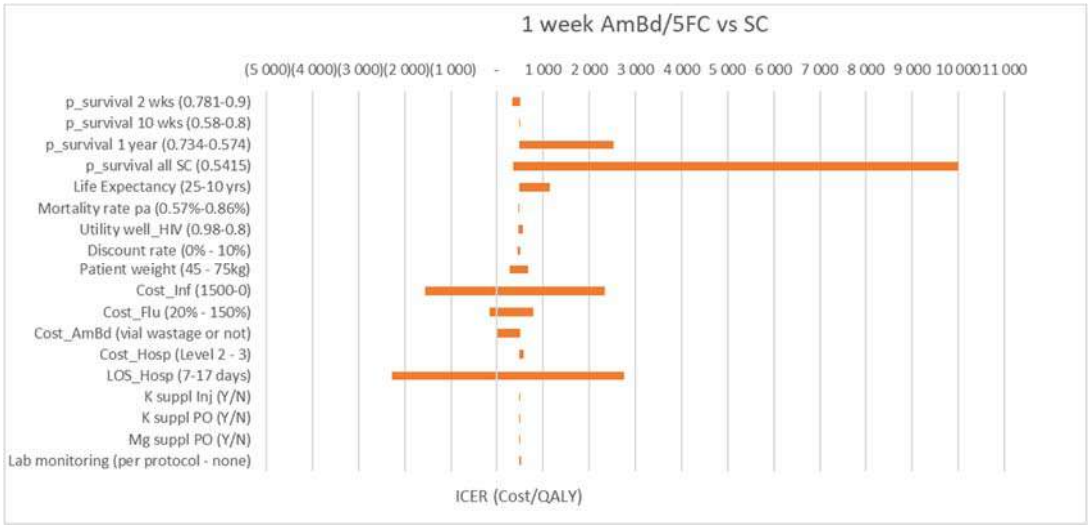


Figure 5. Tornado diagram of sensitivity analysis for 1 week course compared to standard of care

Even when the survival rate is fixed to be the same as the standard of care for each arm (ie survival probability at 2 weeks for all arms is 0.781), the ICERs do not shift much and the flucytosine regimens are still cost-effective compared to the standard of care. Interestingly as the survival rate increases for the flucytosine arms compared to SC so the cost-effectiveness decreases due to the increase in numbers of patients still alive and requiring treatment with flucytosine. It is only if the survival rate for all arms is equivalent to the standard of care at 12 months that the oral and 2 week flucytosine regimens are no longer cost effective with ICERs of R99 935/QALY and R544 326/QALY respectively.

As the life expectancy is reduced from 25 years to 18 years and then 10 years so each arm becomes less cost-effective, however only the 2 week flucytosine arm shifts to above R20 000/QALY. The model is slightly sensitive to changes in average patient weight which is to be expected as the cost of treatment increases with increasing weight.

The inclusion of costs for treatment of anaemia (blood transfusions) or neutropenia (antibiotics) does not impact substantially on the ICER outcomes, nor for the inclusion or exclusion of use of potassium or magnesium supplementation.

The model is sensitive to the price of flucytosine with the oral arm becoming cost saving at a 42% price discount and when price is discounted to 60% the 1 week flucytosine course also becomes cost saving although the 2 week flucytosine course still has an ICER of R2 260/QALY. The price at which the 1 week regimen is cost-neutral is around R1 500 per pack.

When the cost of infusion fees is increased (R500 up to R1500), the 1 week flucytosine and oral course become dominant although not at the cost of level 3 infusion fees (R233 per infusion) where there is still a small ICER for all 3 arms compared to SC. There has been some debate regarding the infusion fees and in the original 2016 Meda model an infusion fee of R800 was proposed. Although other published cost-effectiveness analyses included an infusion fee as a separate cost item, in South Africa it most likely included in the hospital daily rate. The impact of excluding the infusion fee cost was assessed and found to increase the ICERs slightly but not to more than R10 000/QALY for any arm. The impact of a higher infusion fee may be relevant in the private sector setting where infusion fees are likely to be higher and charged as a separate item on the hospital bill. In that case, the oral regimen is clearly favourable and becomes cost saving at around R500 per infusion fee.

Different levels of vial wastage for AmBd were considered with the base case of 2 vials per patient. At a weight range of 51-75kg up to 1.5 vials could be used with the other 0.5 vial shared with another patient, however this had very little impact on the model outcomes and neither did changing the price per vial.

In the sensitivity analysis the option of patients being treated at a Level 3 facility was considered. In both facilities it was assumed that patients were in the general ward and not ICU. For this analysis all patients were either in Level 2 or all in Level 3. A sensitivity analysis using the range of resource utilisation from the Chen et al costing study was conducted. If the hospital cost is increased to reflect the daily rate of a level 3 facility, the ICER increases slightly in all arms.

Due to the trial protocol in ACTA all patients were kept in hospital for 2 weeks regardless of treatment arm. The average LOS in the trial was 17 days. Other published cost-effectiveness analyses have used 15 days LOS (22). It is possible that patients who are well enough to be discharged may leave sooner if they are on the 1 week AmBd/5FC or oral regimen. This has a substantial impact on the model so that if the length of stay in hospital is reduced to 10 or 7 days for either the 1 week or oral flucytosine course, the ICERs become increasingly dominant in those arms.

Increasing or reducing the number of therapeutic lumbar punctures either in the comparator arms or standard of care does not have much impact on the ICERs. Varying the number of laboratory tests only slightly increases the ICERs if the lab monitoring is reduced.

Appendix G: Sensitivity Analysis for the Cost-effectiveness Analysis

4. Budget Impact Analysis

The budget impact analysis was based on 7 497 774 HIV infected patients in 2018 (23) with a CM prevalence of 93/100 000 based on confirmed cases of CM from the GERMS 2017 report (1). Past trends seem to suggest that cases of CM may be decreasing year on year and therefore a constant number of cases was used for 2018 to 2023. Costs of treatment were adjusted annually using a predicted CPI of 5%. It was assumed that not every patient would access flucytosine in 2018 and therefore an uptake of 60% was selected for the base case, increasing to 80% uptake by 2023.

The results of the BIA were based on absolute total costs per patient in the first year (ie assuming all patients lived the full year) as well as proportional total costs per patient in the first year (i.e. taking into consideration the probability of patients dying and no longer needing treatment). It was assumed that all the costs would be incurred in the first year and there would be no additional incremental budget impacts in the following years.

The incremental costs of both scenarios were presented as well as the budget impact if only medicine costs are considered or if all the related costs (including hospital stay, monitoring, ADRs etc) are considered.

The cost inputs were the same as those used in the cost-effectiveness analysis.

4.1. Results

Assuming the base case inputs, including the same LOS (17 days) for all treatment arms, the greatest total and incremental budget impact is with the 2 week AmBd/5FC course of treatment, followed by the oral regimen, then the 1 week course and the current standard of care having the lowest budget impact.

Total Costs	1wk AmBd/5FC	2wk AmBd/5FC	2wk AmBd/Flu (SC)	Oral
Budget Impact (2018)				
Medicine costs	21 024 705	38 008 704	13 127 540	26 832 427
Hospital costs	78 060 260	76 171 543	75 970 616	76 714 047
Lumbar puncture	5 764 090	5 624 624	5 609 787	5 664 683
Laboratory costs	2 648 768	4 230 882	3 131 652	1 839 471
Supportive medicines	262 024	714 782	712 897	-
ADR treatment costs	2 132 805	3 698 911	3 361 008	1 539 055
Total	**109 892 651**	**128 449 446**	**101 913 499**	**112 589 682**

Table 4. Total budget impact of each treatment regimen

If all patients were switched to the flucytosine regimens, the average additional cost per patient (total costs) over what is currently spent on standard of care would be R1 902 and R2 545 per patient per year for the 1 week and oral course respectively.

Total Inc. impact (2018)	Total Inc cost	Ave Inc cost per pt
vs 2wk AmBd/Flu (SC)		
1wk AmBd/5FC	7 979 152	1 902
2wk AmBd/5FC	26 535 947	6 326
Oral	10 676 184	2 545

Medicine Inc. impact (2018)	Total Inc cost	Ave Inc cost per pt
vs 2wk AmBd/Flu (SC)		
1wk AmBd/5FC	7 897 165	1 883
2wk AmBd/5FC	24 881 164	5 931
Oral	13 704 887	3 267

4.2. Sensitivity Analysis

As expected the budget impact is sensitive to patient weight with incremental costs more than doubling in the 1 week flucytosine and oral arms at 75kg compared to the basecase of 60kg.

As the price of flucytosine is reduced so the incremental budget impact decreases until at a 40% price reduction the oral regimen becomes cost saving and at a 60% price reduction both the 1 week flucytosine arm and oral regimen are cost saving. The oral regimen becomes cost saving at a higher price because it contains 2 weeks of flucytosine compared to the 1 week regimen. The 1 week course becomes cost saving at a pack price of around R1 500.

For amphotericin B, the impact of considering vial wastage or vial sharing is minimal on the budget. However, the model is sensitive to the whether an infusion fee is included or not with the incremental budget increasing for the 1 week course and the oral regimen as the cost of treatment in the 2 week courses is reduced. As the infusion fee increases so these increase and the oral and 1 week courses become cost saving.

If all patients are treated in a tertiary level facility the budget impact increases slightly, however by far the greater impact is seen when the LOS is reduced for the 1 week and oral regimens assuming that patients are able to be discharged sooner. If the LOS is reduced to 10 days or 7 days the 1 week and oral courses become increasingly cost-saving.

Appendix H: Sensitivity Analysis for Budget Impact Analysis

		Incremental Cost - Total		
		1wk AmBd/5FC vs SC	**2wk AmBd/5FC vs SC**	**Oral (5FC/Flu) vs SC**
Base case		**7 979 152**	**26 535 947**	**10 676 184**
Incidence of CM (/100 000 pts)				
	100	8 579 734	28 533 277	11 479 767
	93	7 979 152	26 535 947	10 676 184
	80	6 863 787	22 826 621	9 183 814
Patient weight (kg)	75	11 336 345	32 775 054	16 982 835
	60	7 979 152	26 535 947	10 676 184
	50	5 741 024	22 376 543	6 471 749
ADR Management				
Potassium supplementation inj	No	8 068 960	26 535 691	10 773 333
Potassium supplementation oral	No	8 090 966	26 535 628	10 797 137
Magnesium supplementation	No	8 012 150	26 535 853	10 711 879
No K or Mg supplementation	No	8 213 772	26 535 276	10 929 981
Costs				
Flucytosine (R per 100 tabs)	4 500	10 599 450	31 502 722	15 678 332
	3 756	7 979 152	26 535 947	10 676 184
	2 817	4 670 005	20 263 459	4 359 021
	1 878	1 360 858	13 990 970	-1 958 141
	751	-2 610 119	6 463 984	-9 538 735
AmphoB (SEP per vial)	45	7 979 152	26 535 947	10 676 184
	No wastage	8 065 821	26 535 461	10 860 178
Infusion fees (R per inf)	1 500	-25 962 484	26 726 524	-61 380 710
	500	186 697	26 579 701	-5 866 925
	233	7 168 528	26 540 499	8 955 256
	202	7 979 152	26 535 947	10 676 184
	No fee	13 261 287	26 506 289	21 889 968
Hospital cost (facility level per day)	Level 3	9 579 297	26 689 808	11 245 466
	Level 2	7 979 152	26 535 947	10 676 184
Length of stay	17	7 979 152		10 676 184
	10	-24 163 307		-20 911 953
	7	-37 938 647		-34 449 726
Lumbar punctures (therapeutic)	2	8 045 661	26 542 343	10 699 845
Lumbar punctures (therapeutic)	0	7 912 644	26 529 552	10 652 522
Lumbar punctures (none)	0	7 824 850	26 521 111	10 621 287
No lab monitoring	0	8 851 511	26 529 605	13 074 260
Only 1 test per patient for each lab	1	8 560 725	26 531 719	12 274 901
Full blood count	2	7 755 553	26 172 298	10 309 944

Table 5. Budget Impact sensitivity analysis

5. Conclusion and Recommendations

This updated cost-effectiveness analysis confirms that the addition of flucytosine as induction therapy in the treatment of cryptococcal meningitis in patients infected with HIV is cost-effective regardless of whether it is used as a 1 week, 2 week or oral regimen. As to be expected the 1-week flucytosine course is most cost-effective with an ICER of less than R500/QALY, followed by the oral regimen compared to the standard of care. The model is most sensitive to changes in costs rather than outcomes with the greatest impact seen where cost-savings can be achieved by reducing the price of flucytosine, reducing the infusion fee costs and reducing the hospital length of stay.

However, this analysis was based on the clinical outcomes from a rigorously controlled randomised trial (ACTA) where patients were subject to strict treatment protocols and monitoring. The outcomes in a

general clinical practice setting such as that in the public sector in South Africa may differ. Furthermore, the resource utilisation of supportive medicines, laboratory tests and monitoring as well as treatment of adverse drug reactions are also likely to differ substantially. It is recommended that if flucytosine is included on the Essential Medicines List, a study is conducted to verify these outcomes and costs.

Although the incremental budget impact of flucytosine compared to current standard of care is in the region of R8 million per annum, savings could be achieved with early discharge of patients as well as a reduction in the price of flucytosine.

It is recommended that negotiations are conducted with the manufacturer to reach a cost-neutral price (approx. 50% reduction) for the 1 week induction treatment course.

NEMLC Minutes of 11 July 2019:

Following the review of the health economics and budget impact analyses, NEMLC recommended the following:

NEMLC Recommendation: Flucytosine be considered for inclusion to the EML, pending SAHPRA registration with a reduction in price.

Rationale: Simulation confirms that flucytosine is cost-effective as induction therapy for treatment of cryptococcal meningitis amongst HIV-infected. Incremental budget impact of flucytosine compared to current standard of care is an estimated R8 million per annum, but savings could be achieved with early discharge of patients (i.e. LOS 10 days or less).

A 60% reduction in price would result in a cost-neutral budget impact (R1500.00 per 100 flucytosine tablets) for the 1 week AmBd/5FC course and cost neutrality would be achieved at a price of R2195 per pack (42% price reduction) for the oral regimen. However, this is subject to uncertainty in the model, including the impact of reduction in LOS, uptake of flucytosine and use of different regimens and so a price reduction of around 40% is likely to be reasonable.

Level of Evidence: I RCT, Costing analyses, Expert opinion

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Appendix A. Medicine Prices

Medicine	Strength	Form	Pack	Price	Cost/unit	Dose mg/kg	Dose (mg)	Units/Dose	Cost/Dose
Amphotericin B Deoxycholate (mg)	50	Inj	10	41.43	4.14	1	60	2	8.29
Fluconazole (mg)	200	Caps	28	24.17	0.86		400	2	1.73
Flucytosine (mg)	500	Oral	100	3 756.39	37.56	100	6000	12	450.77
Saline	0.9% 1l	Vacoliture	1	8.27	8.27	0	0	1	8.27
Potassium chloride inj (15% in 10ml)	(20mEq per vial)	Inj	1	1.75	1.75	1	0	1	1.75
Potassium tablets (1-2 twice daily)	600mg	Tab	100	54.47	0.54	2	0	2	1.09
Magnesium tablets (2 x 250mg twice daily)	660mg	Tab	60	19.29	0.32	3	500	1	0.32
Flucloxacillin (250mg po QID)	250mg	Caps	100	49.85	0.50		250	1	0.50
Ceftriaxone	1g vial	IV	1	5.86	5.86		1	1	5.86
Ampicillin (150-200mg/kg/day)	500mg vial	IV	1	8.94	8.94	150	9000	18	160.92
Ciprofloxacin (400mg IV tds)	400mg vial	IV	1	36.63	36.63		400	1	36.63

Appendix B. Treatment Costs

1 week AmBd/5FC								
Drug costs		**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per phase**	**Total cost (includes intial treatment phase)**
Induction phase	Amphotericin B	7	1mg/kg daily	8,29	1,00	8,29	58,00	
	Flucytosine	7	100mg/kg daily	450,77	1,00	450,77	3155,37	
	Infusions	7		202,00	1,00	202,00	1414,00	**4627,37** week 1
	Fluconazole	7	1200mg daily	1,73	3,00	5,18	36,26	**36,26** week 2
Consolidation phase	Fluconazole	56	800mg daily	1,73	2,00	3,45	193,36	**193,36**
Maintenance phase	Fluconazole	294	200mg daily	0,86	1,00	0,86	253,79	**253,79**

2 week AmBd/5FC								
Drug costs		**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per phase**	**Total cost (includes intial treatment phase)**
Induction phase	Amphotericin B	14	1mg/kg daily	8,29	1,00	8,29	116,00	
	Flucytosine	14	100mg/kg daily	450,77	1,00	450,77	6310,74	
	Infusions	14		202,00	1,00	202,00	2828,00	**9254,74**
Consolidation phase	Fluconazole	56	800mg daily	1,73	2,00	3,45	193,36	**193,36**
Maintenance phase	Fluconazole	294	200mg daily	0,86	1,00	0,86	253,79	**253,79**

2 week AmBd/Flu								
Drug costs		**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per phase**	**Total cost (includes intial treatment phase)**
Induction phase	Amphotericin B	14	1mg/kg daily	8,29	1,00	8,29	116,00	
	Fluconazole	14	1200mg daily	1,73	3,00	5,18	72,51	
	Infusions	14		202,00	1,00	202,00	2828,00	**3016,51**
Consolidation phase	Fluconazole	56	800mg daily	1,73	2,00	3,45	193,36	**193,36**
Maintenance phase	Fluconazole	294	200mg daily	0,86	1,00	0,86	253,79	**253,79**

2 week 5FC/Flu								
Drug costs		**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per phase**	**Total cost (includes intial treatment phase)**
Induction phase	Flucytosine	14	100mg/kg daily	450,77	1,00	450,77	6310,74	
	Fluconazole	14	1200mg daily	1,73	3,00	5,18	72,51	6383,2452
Consolidation phase	Fluconazole	56	800mg daily	1,73	2,00	3,45	193,36	**193,36**
Maintenance phase	Fluconazole	294	200mg daily	0,86	1,00	0,86	253,79	**253,79**

Appendix C: Other Medicine Costs

Concomitant medicines (1 week)	**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per phase**	**Total cost (includes intial treatment phase)**
Saline 0.9% 1l	7	1 daily	8.27	1.00	8.27	57.89	
Potassium chloride inj (20mEq per AmBd inf)	1	1 daily	1.75	1.00	1.75	1.75	
Potassium tablets (1-2 twice daily)	1	1-2 tabs bd	1.09	2.00	2.18	2.18	
Magnesium tablets (2 x 250mg twice daily)	1	500mg bd	0.32	2.00	0.64	0.64	**62.46**

Concomitant medicines (2 weeks)	**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per phase**	**Total cost (includes intial treatment phase)**
Saline 0.9% 1l	14	1 daily	8.27	1.00	8.27	115.78	
Potassium chloride inj (20mEq per AmBd inf)	14	1 daily	1.75	1.00	1.75	24.50	
Potassium tablets (1-2 twice daily)	14	1-2 tabs bd	1.09	2.00	2.18	30.50	
Magnesium tablets (2 x 250mg twice daily)	14	500mg bd	0.32	2.00	0.64	9.00	**179.79**

Antibiotics to treat neutropenia	**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per course**
Flucloxacillin (250mg qid po)	7	250mg qid	0.50	4.00	1.99	13.96
Ceftriaxone (1-2g IVI od)	7	1g	5.86	1.00	5.86	41.02
Ampicillin (150-200mg/kg/day)	7	150mg/kg	160.92	1.00	160.92	1126.44
Ciprofloxacin (400mg IV tds)	7	400mg tds	36.63	3.00	109.89	769.23

Appendix D: Laboratory Costs

1wk AmBd/5FC	Number of days	Cost per test	Frequency per day	Cost per course	
Serum potassium	3	28.71	1	86,13	Assumes test at day 0, 3, 7
Serum creatinine	3	28.71	1	86,13	Assumes test at day 0, 3, 7
Serum magnesium	3	28,71	1	86,13	Assumes test at day 0, 3, 7
Haemoglobin	2	58.04	1	116,08	Assumes test at day 0, 7
Full blood count	3	54.88	1	164,64	Assumes test at day 0, 3, 7
Blood draw	3	37	1	111,00	Assumes all bloods are drawn together at the same time each day
Total Cost				**650,11**	

2wk AmBd/5FC	Number of days	Cost per test	Frequency per day	Cost per course	
Serum potassium	5	28.71	1	143,55	Assumes test at day 0, 3, 7, 10, 14
Serum creatinine	5	28.71	1	143,55	Assumes test at day 0, 3, 7, 10, 14
Serum magnesium	5	28,71	1	143,55	Assumes test at day 0, 3, 7, 10, 14
Haemoglobin	3	58.04	1	174,12	Assumes test at day 0, 7, 14
Full blood count	5	54.88	1	274,4	Assumes test at day 0, 3, 7, 10, 14
Blood draw	5	37	1	185,00	Assumes all bloods are drawn
Total Cost				**1064,17**	

2wk AmBd/Flu (SC)	Number of days	Cost per test	Frequency per day	Cost per course	
Serum potassium	5	28.71	1	143,55	Assumes test at day 0, 3, 7, 10, 14
Serum creatinine	5	28.71	1	143,55	Assumes test at day 0, 3, 7, 10, 14
Serum magnesium	5	28,71	1	143,55	Assumes test at day 0, 3, 7, 10, 14
Haemoglobin	3	58.04	1	174,12	Assumes test at day 0, 7, 14
Full blood count	0	54.88	1	0	
Blood draw	5	37	1	185,00	Assumes all bloods are drawn together at the same time each day
Total Cost				**789,77**	

Oral (5FC/Flu)	Number of days	Cost per test	Frequency per day	Cost per course	
Serum potassium	0	28.71	1	0	
Serum creatinine	0	28.71	1	0	
Serum magnesium	0	28,71	1	0	
Haemoglobin	0	58.04	1	0	
Full blood count	5	54.88	1	274,40	Assumes test at day 0, 3, 7, 10, 14
Blood draw	5	37	1	185,00	Assumes all bloods are drawn together at the same time each day
Total Cost				**459,40**	

Appendix E: Adverse Drug Reactions – Utilisation and Costs

Adverse Drug Reactions - Costs									
Anaemia									
Blood Transfusion Costs	*From the SANBS State Patients Pricelist (1 April 2018 to 31 March 2019)*								
		1wk AmBd/5FC		**2wk AmBd/5FC**		**2wk AmBd/Flu (SC)**		**Oral**	
	Cost per unit	Frequency	Cost	Frequency	Cost	Frequency	Cost	Frequency	Cost
Secondary Level									
Transfusions	2 295	0.15	**344.31**	0.37	**849.29**	0.31	**711.56**	0.12	**275.44**
Renal Dysfunction									
		1wk AmBd/5FC		**2wk AmBd/5FC**		**2wk AmBd/Flu (SC)**		**Oral**	
	Cost per unit	Frequency	Cost	Frequency	Cost	Frequency	Cost	Frequency	Cost
Secondary Level									
Dialysis	1 764	0.00	-	0	-	0	-	0	-
Neutropaenia									
		1wk AmBd/5FC		**2wk AmBd/5FC**		**2wk AmBd/Flu (SC)**		**Oral**	
	Cost per course	**Frequency**	**Cost**	**Frequency**	**Cost**	**Frequency**	**Cost**	**Frequency**	**Cost**
Flucloxacillin (250mg qid po)	13.96	0.05	0.70	0.09	1.26	0.13	1.81	0.03	0.42
Ceftriaxone (1-2g IVI od)	41.02	0.58	23.79	0.66	27.07	0.60	24.61	0.06	2.46
Ampicillin (150-200mg/kg/da	1 126.44	0.11	123.91	0.04	45.06	0.07	78.85	0.06	67.59
Ciprofloxacin (400mg IV tds)	769.23	0.04	30.77	0.01	7.69	0.04	30.77	0.05	38.46
Total			**179.17**		**81.08**		**136.05**		**108.93**

Appendix F. Total Costs per treatment arm

Total Costs	**1wk AmBd/5FC**	**2wk AmBd/5FC**	**2wk AmBd/Flu (SC)**	**Oral**
Per pt costs (per arm)				
Medicine costs	5 012	9 061	3 129	6 396
Hospital costs	18 608	18 158	18 110	18 287
Lumbar puncture	1 374	1 341	1 337	1 350
Laboratory costs	631	1 009	747	438
Supportive medicines	62	170	170	-
ADR treatment costs	508	882	801	367
Total	**26 196**	**30 620**	**24 294**	**26 839**

Appendix G: Sensitivity Analysis for the Cost-effectiveness Analysis

		1wk AmBd/5FC vs SC	2wk AmBd/5FC vs SC	Oral (5FC/Flu) vs SC	Base case Reference value
Base case ICER (R/QALY)		***477***	***9 278***	***1 810***	
Clinical Outcomes	**Range**				
Survival at 2 weeks					*SC fixed at 0.781*
	0.9	498			1 wk higher than others
	0.885	477	10 299	2 139	Equivalent to 1wk AmBd/5FC
	0.818	384	9 574	1 810	Equivalent to oral base case
	0.791	346	9 278	1 676	Equivalent to 2 AmBd/5FC
	0.781	332	9 169	1 627	Equivalent to SC
Survival 2 weeks - all at SC	0.781	332	9 169	1 627	All equivalent to SC
Survival at 10 weeks					*SC fixed at 0.588*
	0.8	477			1 wk higher than others
	0.761	477	8 635	1 773	Equivalent to 1wk AmBd/5FC
	0.649	476	9 127	1 810	Equivalent to oral base case
	0.617	476	9 278	1 820	Equivalent to 2 AmBd/5FC
	0.588	476	9 420	1 830	Equivalent to SC
Survival at 1 year					*SC fixed at 0.542*
		359			1 wk higher than others
	0.7343	477	1 616	650	Equivalent to 1wk AmBd/5FC
	0.6095	1 298	4 546	1 810	Equivalent to oral base case
	0.5745	2 535	9 278	3 652	Equivalent to 2 AmBd/5FC
	0.5415	25 967	544 326	99 395	Equivalent to SC
Mortality rate pa (Yr2 onwards)					
	0.86%	488	9 512	1 855	
	0.72%	480	9 357	1 825	
	0.65%	477	9 278	1 810	Base case Reference value
	0.57%	472	9 196	1 793	
Life Expectancy	10	1 148	22 373	4 357	Assumption
	18	646	12 572	2 451	Rajasingham et al, 2012
	25	477	9 278	1 810	Chen et al, 2018
Other variables					
Discount rate	0%	454	8 829	1 722	Undiscounted
	3%	467	9 093	1 773	USA guidelines
	5%	477	9 278	1 810	SA Guidelines
	10%	503	9 776	1 906	Assumption
Patient weight (kg)	75	678	11 460	2 878	Assumption
	60	477	9 278	1 810	Base case
	50	343	7 824	1 097	Ave weight in Malloy et al, 2018
	45	276	7 097	741	Assumption
Utilities					
Well with HIV	0.98	463	9 003	1 756	Assumption
	0.95	477	9 278	1 810	Base case
	0.9	503	9 776	1 906	Assumption
	0.8	563	10 951	2 135	Assumption
Sick with CM (induction)	0.6	477	9 278	1 809	Assumption
	0.5	477	9 279	1 810	Base case
	0.4	477	9 279	1 810	Assumption
	0.3	477	9 279	1 810	Assumption
Well with CM (maintenance)	0.9	475	9 241	1 802	Assumption
	0.8	477	9 279	1 810	Base case
	0.7	479	9 316	1 817	Assumption
ADR Management					
Potassium supplementation inj	No	482	9 278	1 826	No K inj supplementation
Potassium supplementation oral	No	484	9 278	1 830	No K tab supplementation
Magnesium supplementation	No	479	9 278	1 816	No Mg supplementation
No K or Mg supplementation		491	9 278	1 853	No supplementation at all
Costs					
Flucytosine (R per 100 tabs)	4500	634	11 015	2 657	Assumption
	3 756.39	477	9 279	1 810	Current price
	2 817.29	279	7 085	739	75%
	1 878.20	81	4 892	- 332	50%
	751.28	- 156	2 260	- 1 617	20%
AmphoB (SEP per vial)	89.84				Double price
	44.92	477	9 279	1 810	Base case
	33.69				75%
	No wastage	482	9 278	1 841	No vial wastage
	8.98				20%
Infusion fees (R per inf)	1500	- 1 552	9 345	- 10 404	Assumption
	500	11	9 294	- 994	Assumption
	233	429	9 280	1 518	Level 3 facility fee
	202	477	9 278	1 810	base case
	0	793	9 268	3 710	No infusion fee
Hospital cost (facility level per day)	Level 3	573	9 332	1 906	Level 3 facility fee
	Level 2				base case
Length of stay	10	- 1 444		- 3 544	LOS 10 days
	7	- 2 268		- 5 839	LOS 7 days
Lumbar punctures (therapeutic)	2	481	9 281	1 814	2 Tx LP
Lumbar punctures (therapeutic)	0	473	9 276	1 806	No Tx LP
Lumbar punctures (none)	0	468	9 273	1 800	No LP at all
No lab monitoring	0	529	9 276	2 216	No lab monitoring
Only 1 test per patient for each lab	1	512	9 277	2 080	Only 1 test per patient for each lab
Full blood count	2	464	9 151	1 747	Full blood count

Appendix H: Sensitivity Analysis for Budget Impact Analysis

		Incremental Cost - Total			Incremental Cost - per patient		
		1wk AmBd/5FC vs SC	2wk AmBd/5FC vs SC	Oral (5FC/Flu) vs SC	1wk AmBd/5FC vs SC	2wk AmBd/5FC vs SC	Oral (5FC/Flu) vs SC
Base case		**7 979 152**	**26 535 947**	**10 676 184**	**1 902**	**6 326**	**2 545**
Incidence of CM (/100 000 pts)							
	100	8 579 734	28 533 277	11 479 767			
	93	7 979 152	26 535 947	10 676 184			
	90	7 721 760	25 679 949	10 331 791			
	80	6 863 787	22 826 621	9 183 814			
Patient weight (kg)	75	11 336 345	32 775 054	16 982 835	2 702	7 813	4 048
	60	7 979 152	26 535 947	10 676 184	1 902	6 326	2 545
	50	5 741 024	22 376 543	6 471 749	1 369	5 334	1 543
	45	4 621 960	20 296 841	4 369 532	1 102	4 838	1 042
ADR Management							
Potassium supplementation inj	Yes	7 979 152	26 535 947	10 676 184	1 902	6 326	2 545
	No	8 068 960	26 535 691	10 773 333	1 923	6 326	2 568
Potassium supplementation oral	Yes	7 979 152	26 535 947	10 676 184	1 902	6 326	2 545
	No	8 090 966	26 535 628	10 797 137	1 929	6 326	2 574
Magnesium supplementation	Yes	7 979 152	26 535 947	10 676 184	1 902	6 326	2 545
	No	8 012 150	26 535 853	10 711 879	1 910	6 326	2 554
No K or Mg supplementation	No	8 213 772	26 535 276	10 929 981	1 958	6 326	2 606
Costs							
Flucytosine (R per 100 tabs)	4500	10 599 450	31 502 722	15 678 332	2 527	7 510	3 737
	3 756,39	7 979 152	26 535 947	10 676 184	1 902	6 326	2 545
	2 817,29	4 670 005	20 263 459	4 359 021	1 113	4 830	1 039
	1 878,20	1 360 858	13 990 970	- 1 958 141	324	3 335	- 467
	751,28	- 2 610 119	6 463 984	- 9 538 735	- 622	1 541	- 2 274
AmphoB (SEP per vial)	44,92	7 979 152	26 535 947	10 676 184			
	No wastage	8 065 821	26 535 461	10 860 178	1 923	6 326	2 589
Infusion fees (R per inf)	1500	- 25 962 484	26 726 524	- 61 380 710	- 6 189	6 371	- 14 632
	500	186 697	26 579 701	- 5 866 925	45	6 336	- 1 399
	233	7 168 528	26 540 499	8 955 256	1 709	6 327	2 135
	202	7 979 152	26 535 947	10 676 184	1 902	6 326	2 545
	No fee	13 261 287	26 506 289	21 889 968	3 161	6 319	5 218
Hospital cost (facility level per day)							
	Level 3	9 579 297	26 689 808	11 245 466	2 284	6 362	2 681
	Level 2	7 979 152	26 535 947	10 676 184			
Length of stay	17	7 979 152		10 676 184	1 902	6 326	2 545
	10	- 24 163 307		- 20 911 953	- 5 760		- 20 911 953
	7	- 37 938 647		- 34 449 726	- 9 044		- 34 449 726
Lumbar punctures (therapeutic)	2	8 045 661	26 542 343	10 699 845	1 918	6 327	2 551
Lumbar punctures (therapeutic)	0	7 912 644	26 529 552	10 652 522	1 886	6 324	2 539
Lumbar punctures (none)	0	7 824 850	26 521 111	10 621 287	1 865	6 322	2 532
No lab monitoring	0	8 851 511	26 529 605	13 074 260	2 110	6 324	3 117
Only 1 test per patient for each lab	1	8 560 725	26 531 719	12 274 901	2 041	6 325	2 926
Full blood count	2	7 755 553	26 172 298	10 309 944	1 849	6 239	2 458