QATAR UNIVERSITY

COLLEGE OF PHARMACY

PHARMACOECONOMICS EVALUATION OF THE SYSTEMIC ANTIFUNGAL POSACONAZOLE FOR PROPHYLAXIS AGAINST INVASIVE FUNGAL INFECTION AMONG IMMUNOCOMPROMISED CANCER PATIENTS IN QATAR

BY

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ABSTRACT

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Title: Pharmacoeconomics Evaluation of the Systemic Antifungal Posaconazole for Prophylaxis against Invasive Fungal Infections among Immunocompromised Cancer Patients in Qatar

Supervisor of Thesis: Dr. Daoud Al-Badriyeh, PhD

The immunocompromised hematologic malignancy patients, at the National Center for Cancer Care (NCCCR) in Qatar, receive the antifungal posaconazole for prophylaxis as systemic prophylaxis against invasive fungal infections (IFIs). No economic evaluations of the prophylactic posaconazole in Qatar exist in literature, whether about the resource utilization associated with posaconazole as a stand-alone therapy, or the comparative economic impact of posaconazole against potential alternatives. The objective of this study was to evaluate the pharmacoeconomic impact of prophylactic posaconazole in hematologic malignancy patients at risk for IFIs in NCCCR, Qatar.

Methods. Decision analytic economic models to perform a cost-analysis and a cost-effectiveness analysis of posaconazole were constructed. The decision analytic models were from the hospital perspective, to follow the therapeutic pathways and consequences of systemic antifungals for prophylaxis, for a study duration of 112 days. The primary endpoint was a success with no major adverse drug reactions (ADR). Prophylaxis failure was defined by IFIs occurrence, death, and IFIs prevention but with major ADR. The cost-analysis model was based the medical records available from 2013 to 2015, at NCCCR of the Hamad Medical Corporation (HMC), but was also complemented by data extracted from literature and local expert panels. The cost-effectiveness model was based on

literature RCTs, which was adopted to the local setting by local expert panels and medical records data.

Sensitivity analyses were conducted to enhance the robustness and generalizability of the results.

Results. In the cost-analysis, 70 patients were eligible for the study inclusion. Therapy failure due to IFIs reached 43%, while death occurred in 7% of the patients, leading to successful prevention of IFIs in 50% of patients only. The primary outcome of IFI presentation without major ADR was achieved in 42.5% of patients. The average posaconazole utilization cost was QAR 109,802, with half of this consumed in failure due to IFIs. In the cost-effectiveness evaluation, similar success rate (IFI prevention without major ADR) was observed between posaconazole and fluconazole (0.76 versus 0.75, respectively), but with a significant Decremental Cost-Effectiveness Ratio (DCER) of QAR 3,922,618. The total therapy cost was higher with posaconazole (QAR 134,116 versus 80,463). The single patient pathway that influenced the outcomes of the models the most is the prevention of IFIs with having major ADR. Sensitivity analyses demonstrated the robustness of conclusions in both study models, with 96% chance for cost-savings to be in favor of fluconazole over posaconazole.

Conclusion. The current study is the first economic evaluation of posaconazole in Qatar and the region, and the first in the literature to comprehensively follow up therapies throughout their IFIs failures and ADR. Prophylactic posaconazole was associated with a considerable cost to the NCCCR setting. This was considerably higher than that associated with fluconazole against IFIs in hematological patients, while being associated with a

marginally minor improvement in outcome. This contradicts local Qatari practices in relation to only having posaconazole available for the prophylactic use in NCCCR.

DEDICATION

to

“Mama”

ACKNOWLEDGMENTS

My life during my MSc studies was not an easy one. I got married, got blessed with a child, and was also committed to a full-time job. While full of joyful moments, was mostly very stressful as well. Thanks to the many people in my life who were keen on helping me, however, challenges were overcome, and I am finally now at the point where I complete my MSc thesis successfully.

First and foremost, words of thanks cannot express how grateful I am to Allah who gave me the strength, patience, skills and opportunity to undertake my work and see it to completion.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

ANC	Absolute Neutrophil Count
AML	Acute Myeloid Leukemia
ALL	Precursor T/B-cell Lymphoblastic Leukemia/Lymphoma
ATLL	Adult T-cell Leukemia/Lymphoma
ADR	Adverse Drug Reactions
CT	Computed Tomography
CEA	Cost-Effectiveness Analyses
CBA	Cost-Benefit Analyses
CUA	Cost-Utility Analyses
CMA	Cost Minimization Analyses
CAGR	Compound Annual Growth Rate
CBC	Complete Blood Count
CRP	C-Reactive Protein
CPI	Consumer Price Index
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
DDD	Defined Daily Dose
DCER	Decremental Cost Effectiveness Ratio
FDA	Food and Drug Administration
GVHD	Graft-Versus-Host Disease
HSCT	Hematopoietic Stem Cell Transplantation
HMC	Hamad Medical Corporation
IDSA	Infectious Diseases Society of America

IV	Intravenous
IFIs	Invasive Fungal Infections
ICU	Intensive Care Unit
ID	Infectious Disease
ICER	Incremental Cost-Effectiveness Ratio
LDL-C	Low-Density Lipoprotein Cholesterol
LYG	Life Years Gained
MMM	Myelosclerosis with Myeloid Metaplasia
MDS	Myelodysplastic Syndrome
MRC	Medical Research Centre
mmHg	Millimeters of Mercury
NCCCR	National Centre for Cancer Care and Research
OTC	Over the Counter Medications
PO	Oral
P&T	Pharmacy and Therapeutic Committee
QALY	Quality-Adjusted Life Year
QAR	Qatari Riyal
RCT	Randomized Controlled Trial
USA	United States of America

CHAPTER ONE: INTRODUCTION

1.1. Clinical Overview

1.1.1. Immunocompromised Patients and Hematologic Malignancy

Patients who cannot resist infections due to a diminished or weakened immune system are defined as immunocompromised[1]. Here, being the primary identifier of low immunity, neutrophils cells play a critical role in protecting against infections. The damage to the immune system is mainly the result of disrupting the processes of chemotaxis and phagocytosis, compromising the neutrophil function, in eradicating intracellular pathogens from the body as the number of neutrophils subsides. Physicians define a case of neutropenia as an absolute neutrophil count (ANC) of 1500/microL or less. Neutropenia is considered severe if ANC is less than 500/microL, while moderate neutropenia falls between an ANC of 500 and 1000/microL[2]. Immediate pathogens (bacterial, fungal or viral) easily take advantage of such reduced immunity to attack and colonize to cause infections that are mostly of concern, especially if neutropenia is severe and lasting for a duration of above 7 days[3].

With the recognized increase in the number of immunocompromised patients, it is not surprising that the incidence of invasive fungal infections (IFIs) has been rapidly increasing over the last few decades[4]. The increase in the number of immunocompromised patients is best explained by the recent advancement in medical procedures and techniques, such as the increased exposure to intensive chemotherapy and radiation (as strategies for treating malignancies), or myelosuppressive therapies (for organ or bone marrow transplantations), which can significantly suppress immunity[5]. At the level of United States (US), as an example, the spread of cancer has increased

dramatically over the past decades to reach around 14.5 million cases in 2014, with an estimation to reach up to 19 million by 2024[6]. Another contributing factor to the emergence of susceptibility is the excessive use of broad-spectrum antibiotics that over-kill naturally colonizing bacteria, allowing for excessive growth of fungi. Also, there is overuse of corticosteroids, resulting in the elevated susceptibility to IFIs. Critical as well is the natural weakening of the immune system due to the normal aging process. Generally, with the advancements in healthcare and services, people live 40 years longer nowadays than in past decades, back in the 19th century[7,8] .

Patients with the hematologic malignancy of acute myeloid leukemia (AML), in particular, are at notably increased risk of infection, where the neutropenia associated with AML is considerably prolonged as compared to that in other cancers[9]. Apart from the disease, therapy itself, including chemotherapy and hematopoietic stem cell transplantation (HSCT), further increases the risk of severe neutropenia and, hence, increased susceptibility to the IFI as a life-threatening condition[9]. This is particularly important when taking into consideration how considerable the population of patients with the hematologic malignancy is. For example, there are approximately 20,000 new leukemia cases diagnosed every year in Europe, and about 99,000 existing patients being exposed to either chemotherapies or transplantation procedures for hematologic malignancies[10].

1.1.2. Invasive Fungal Infection

One major type of the IFI is the opportunistic infection type, which is diagnosed among populations with suppressed immune systems. Here, fungi pathogens are considered significant, causing systemic mycoses and invasive bloodstream infections[11].

In the Qatari setting, the causative fungi of most common IFIs are *Aspergillus*, *Candida*, *Fusarium*, and *Scedosporium*[12,13]. Table 1.1 summarizes the primary characteristics and consequences of these IFI-causative fungi in practices.

Table 1. 1 Clinical presentation of (and host reaction to) the most common IFI-causative fungal species[14]

Fungus	Clinical presentation	Host response	Comment(s)
Aspergillus	Allergic bronchopulmonary aspergillosis	Allergic mucous with eosinophils, Curshmann's spirals, Charcot-Leyden crystals; mucosa with suppurative and granulomatous inflammation, vasculitis, and fibrosis	Hypersensitivity reaction to fungi, most frequently *A. fumigatus*; is commonly seen in patients with cystic fibrosis or steroid-dependent asthma
	Allergic fungal rhinosinusitis	Similar to that for allergic bronchopulmonary aspergillosis	Hypersensitivity reaction to fungi that is similar to that for allergic bronchopulmonary aspergillosis
	Chronic pulmonary aspergillosis	The wall surrounding the fungus ball consists of fibrosis	Occurs in immunocompetent individuals with a variety of lung conditions (tuberculosis, emphysema, and others) in which the cavity or lesion is colonized and then a "fungus ball" or aspergilloma forms
Candida	Invasive disease	Various inflammatory responses depending on immune status, primarily suppurative inflammation with rare granulomas, invasion of blood vessels, necrotizing vasculitis	Occurs mostly as a healthcare-associated infection (patients with vascular access devices, with recent surgeries, receiving broad-spectrum antibiotics, or immunosuppressed), can involve all organs
Hyaline septated molds (*Fusarium* and *Scedosporium*)	Similar to that for *Aspergillus*	Some organisms have some peculiarities (for example, *Scedosporium* spp. are associated with pneumonia after near drowning)	

In one USA study, the prevalence of fungal infections between the late 1980s and early 2000s was investigated to demonstrate that while aspergillosis infections significantly increased by around 6%, the *Candida* infections decreased in occurrence by around 10%. An increasing rate of *Fusarium* and *Scedosporium* infections was noticed[15, 16, 17]. Here, the change in incidence of IFIs has been related to the change in the spectrum of pathogenic fungi[18, 19]. For example, aspergillosis has been spreading widely due to the fact that recent practices of managing patients with hematologic malignancies, particularly the spread of the prophylaxis against IFI, mainly targeted the *Candida* species infections. In one retrospective cohort study, in 2006, where patients with hematologic malignancies were followed from 1999 to 2003, aspergillosis was found to account for over 57% of all IFIs, while *Candida* was reported in 32% of IFIs[20].

Once a patient is infected, the IFI can be presented in highly variable clinical manifestations, related to the individual's immunity level and physiological condition[21]. With invasive candidiasis, for instance, it is characterized by a rapid onset of fever that can reach shock beside other signs of sepsis. These clinical manifestations are not specific enough where it is seldom that definite clinical signs are accurately interpreted into correct diagnoses. As a result of such doubt, several tests and procedures are needed for making a definite determination of a diagnosis. This, however, disables the early diagnosis and, ultimately, delays receiving timely optimal management[21,22]. Required types of tests can range from the conventional mycological methods (direct microscopic examination and culturing of specimens), serological techniques (galactomannan test), to the radiological evidence (X-rays and high-resolution computed tomography, CT)[21].

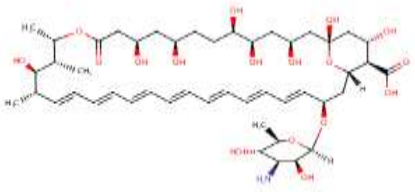
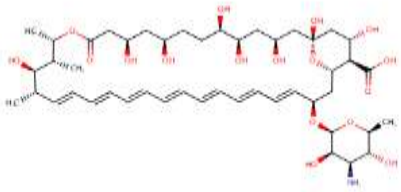
IFIs are life-threatening. Mortality rates remained unacceptable throughout the recent decades, reaching up to 90% of all proven IFIs[23, 24]. They shorten life and disturb its quality[25]. In *Candida*-related infections, the mortality rates reach over 30%, while the *Scedosporium* infections mortality is at approximately 58%. Higher mortality rates are associated with aspergillosis and the *Fusarium* infections, being 89% and 79%, respectively[15,26].

1.1.3. Antifungal Therapy

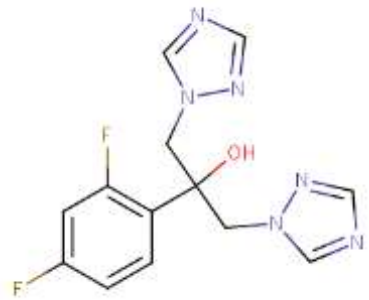
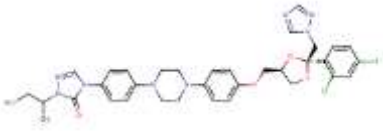
The story began more than half a century ago, i.e. in the mid-nineties, when the first azole and polyene were isolated, followed by the discovery of amphotericin B in 1960. In the late 1980s, the new generation azoles (triazoles) fluconazole and itraconazole were then introduced[27]. Ten years later, in 1990s, terbinafine (an allylamine) was discovered[28]. By that time, the antifungal's pharmaceutical market established its marked and steady growth, which was justified by the significant expansion in the number of immunocompromised patients[27]. However, the use of these diverse antifungal agents was still limited due to the insufficient spectrum of activity, drug resistance, toxicities and/or drug interactions[29]. Subsequently, pharmaceutical companies worked on producing more effective antifungal agents (or modified formulations), with improved tolerability of side effects. Amphotericin B was re-introduced in 1996 in a new liposomal formulation (liposomal Amphotericin B – LAMB),[28] a new generation of echinocandins emerged in the early 2000s[30, 31, 32], and the new triazoles voriconazole and posaconazole were later revealed in 2002 and 2006, respectively[33,34]. Very recently, in 2015, the Food and Drug Administration (FDA) had approved a new azole agent called isavuconazonium sulfate, which is a prodrug for isavuconazole[35].

Overall, there is currently a total of four classes of systemic antifungal agents used for the management of IFIs. The classes are (i) polyenes (conventional amphotericin B and its lipid formulations), (ii) azoles (fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole), (iii) echinocandins (caspofungin, micafungin, and anidulafungin), and (iv) allylamines (terbinafine)[30]. Table 1.2 describes the mechanism by which these agents work against fungi with an illustration of their chemical structure.

Table 1. 2. A brief description of systemic antifungal agents' mechanism of action, chemical structure, and the brand names available.

Antifungal class	Mechanism of action[36]	Agent	Band name [37,38]	Chemical structure
Polyenes	Depending on the concentration and the susceptibility of the fungi to this agent it could act as fungistatic or fungicidal. It acts by binding to the fungus cell membrane (specifically sterols) which leads to a disturbing the membrane permeability and leakage of intracellular components from the fungi cell and hence cell death.	Conventional amphotericin B	Fungizone Amphocin	
		LAMB	Abelcet Ambisome Amphotec	

Cont. Table 1.2. A brief description of systemic antifungal agents' mechanism of action, chemical structure, and the brand names available.

Antifungal class	Mechanism of action[36]	Agent	Band name [37, 38]	Chemical structure
Azoles	Their action is fungistatic. They inhibit the fungal synthesis of ergosterol, through inhibition of an enzyme resulting in accumulation of sterol precursors which weaken the structure and function of the fungal cell membrane.	Fluconazole	Diflucan	
		Itraconazole	Onmel Sporanox	
		Voriconazole	Vfend	

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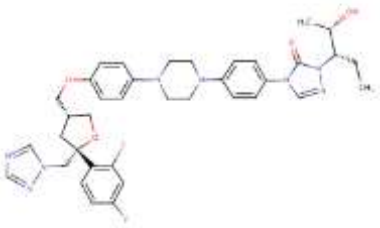
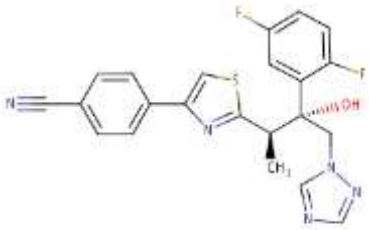
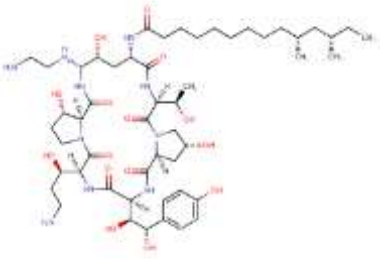
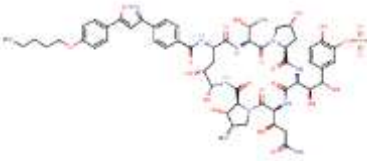
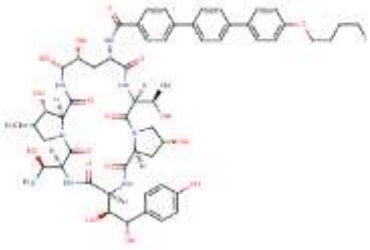
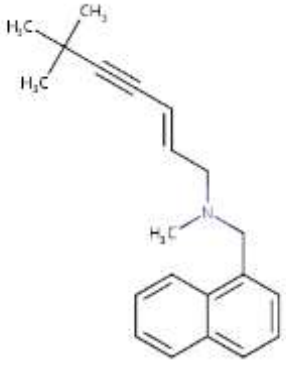
Antifungal class	Mechanism of action[36]	Agent	Band name [37, 38]	Chemical structure
Azoles	Their action is fungistatic. They inhibit the fungal synthesis of ergosterol, through inhibition of an enzyme resulting in accumulation of sterol precursors which weaken the structure and function of the fungal cell membrane.	Posaconazole	Noxafil	
		isavuconazole	Cresemba	
Echinocandins	inhibits the synthesis of 1,3 beta-D-glucan, a fundamental constituent of fungal cell walls, producing their fungicidal activity.	Caspofungin	Cancidas	

Cont. Table 1.2. A brief description of systemic antifungal agents' mechanism of action, chemical structure, and the brand names available.

Antifungal class	Mechanism of action[36]	Agent	Band name [37, 38]	Chemical structure
Echinocandins	inhibits the synthesis of 1,3 beta-D-glucan, a fundamental constituent of fungal cell walls, producing their fungicidal activity.	Micafungin	Mycamine	
		Anidulafungin	Ecalta	
Allylamines	Similar to azoles, it inhibits the biosynthesis of ergosterol. However, the agent has fungicidal action.	Terbinafine	Lamisil	

1.1.4. IFI Management Strategies and the Need for Prophylaxis

There are four strategies that are used to deal with IFIs, with the decision on each based on the patient health condition, results of clinical tests and the clinical manifestation[39]. Strategies are divided into the treatment of established fungal infections and the preventive strategy, with the latter further divided into three different approaches; prophylaxis, empiric, and preemptive therapies. For the preventative strategies, the patient will start receiving the prophylaxis once he/she is categorized as at high risk for infection. The empiric therapy is given to those who have persistent febrile (body temperature >37.5 °c) neutropenia of unknown source that is unresponsive to antibacterial therapy, while the preemptive therapy aims at treating a suspected early IFI using radiologic and/or laboratory evidence rather than fever alone. As for the treatment pathway, the candidate should correspond to specific criteria such as the European Organization for Research and Treatment of Cancer/Mycoses criteria for identifying proven and probable infections[39].

It is a logical and more practical strategy to start providing prophylaxis therapy against IFI instead of waiting for the clinical manifestation to appear and the infection to develop, specifically with patients who suffer from hematological malignancies and receiving chemotherapies or undergoing HSCT, where infections are probable. The rationale behind choosing prophylaxis is that patients with low immune systems are at high definite risk for getting IFIs, added to that the mortality rate is high once a patient has IFI, and that the chance to cure the IFI is poor, added to the consideration that early diagnosis is difficlut, as discussed earlier [26,40]. Also important to note is the substantial economic burden of the healthcare systems that are consumed into the treatment of established IFIs, where systemic antifungal agents are relatively expensive, and require prolonged

hospitalization. Here, there has been a considerable recent increase in the systemic antifungals costs, mostly the result of the emergence of newer agents that cover a broader spectrum of fungi, with improved formulations and/or enhanced safety profiles[26 27].

The prophylaxis indication first appeared in the international guidelines in the early 2000s, but that was only in relation to limited cases of immunocompromised patients with hematological malignancies. Afterwards, however, with the emergence of newer antifungal agents, the awareness towards the antifungal prophylaxis concurrently increased worldwide, more relating the prophylaxis against IFI to a wider range of cancer patients. Recommendations were mostly evident by multiple randomized clinical trials in literature[29, 41, 42].

1.1.5. Guidelines on the Antifungal Prophylaxis Use in Hematologic Malignancies

Based on the recommendations by the 2010 Infectious Diseases Society of America (IDSA) guidelines for the use of antimicrobial agents in neutropenic patients with cancer, along with the 2016 IDSA guidelines for the diagnosis and management of aspergillosis, there is an agreement that the newly diagnosed patients with hematologic malignancies, who are receiving chemotherapy for the first time or undergoing HSCT, and had or were anticipated to have neutropenia for 7 days or more, are stratified as at risk of IFI and, hence, are candidates for receiving systemic antifungal agents for prophylactic purposes[42]. The important elements for the anticipation of the IFIs are mostly related to the intensity and length of neutropenia. Based on the guidelines, a patient with an ANC of more than 700/ microL and an anticipated 5 days of neutropenia, for example, is considered at minimal risk for developing an IFI[43].

1.1.6. Available Systemic Antifungal Agents for Prophylaxis. Advantages and Disadvantages

Of all agents included under the four classes of antifungal therapy, only a few were approved for the prophylaxis indication. According to ISDA guidelines, fluconazole is the first line agent for prophylaxis when *Candida* is suspected. Fluconazole is available in oral and intravenous (IV) formulations and has tolerable side effects, with good drug-drug interaction profile and inexpensive generic cost. Drawbacks that are associated with the fluconazole administration include its narrow spectrum of activity against many *Candida* species, such as C. *guillermondii,* and *C. lusitaniae*,[44] and the lack of activity against aspergillosis. Also, breakthrough infections due to fluconazole resistance are documented with regard to *C. krusei* and *C. glabrata*[42]. The triazoles itraconazole, voriconazole, and posaconazole are available in both formulations (oral and IV) and they are active against most fungi. They, however, have higher potential than other antifungals for interactions with specific chemotherapy medications, limiting their practical benefit in real practice. Voriconazole has a hepatotoxic effect, while taking itraconazole and posaconazole cause nausea, vomiting, fever, and headache events[42]. With regards to the newest triazole 'isavuconazole', this is available in a water-soluble IV formulation, and its oral formulation has excellent bioavailability, with less drug-drug interactions than other triazoles. Nevertheless, it affects the hepatic function, added to the lack of enough supporting evidence, i.e. still in phase II trials in relevance to its prophylaxis use[45,46,47]. Echinocandins are another approved option for prophylaxis, which has a wider spectrum of activity than fluconazole, including covering aspergillosis, with enhanced safety profile. Nevertheless, these agents are highly costly and are only available in the IV form, which further adds to

the cost of administration given the need for hospitalization[42]. Both conventional and liposomal Amphotericin B are available as valid options, except that they are increasingly rarely used, due to the multiple problematic adverse reactions, e.g. nephrotoxicity, and the lack of evidence towards the prophylactic indication[42,46,48,49].

1.1.7. Status in Qatar

In a local study of the prevalence of cancer in Qatar, between 1991 and 2006, 5,000 persons were found to have diagnoses of cancer, with an annual incidence of 130 to 170 cases[50,51]. The incidence of hematologic cancers, per 100,000 population, was 4.1 for males and 5 for females[50]. As for the mortality rate, hematologic malignancies alone accounted for 32% of death of all types of cancer[52].

Focusing on IFI, records over the period 2009–2014 reported around 300 documented cases of candidiasis, with the annual mortality rate reaching a high 81.9%. Interestingly, only 11 cases of invasive aspergillosis were documented. *Fusarium* infection was also not common in Qatar, where 27 cases were reported. No reports of *Scedosporium* infections were found throughout the study period[12].

With regard to the use of prophylactic antifungals in the Qatari setting, i.e. at the National Centre for Cancer Care and Research (NCCCR) of the Hamad Medical Corporation (HMC), the main and only tertiary healthcare provider in the country, the strategy was first launched in 2006, where posaconazole was (and still is) used as the first line option, with fluconazole as an alternative when contraindications to posaconazole arise. In the NCCCR, candidates for prophylaxis therapy are those who are immunocompromised patients with hematologic malignancies and expected to have

neutropenia for >7 days, patients undergoing autologous or allogeneic HSCT, and patients receiving graft-versus-host disease therapy[53,54,55].

1.2. Economic Aspects of the Antifungal Therapy

As discussed earlier, increased incidence of IFI will consequently increase the economic burden on healthcare systems. With the emergence of newer more expensive antifungal agents, which have efficacy and safety advantages over the older cheaper ones[56], it becomes a must that the worthwhile of spending on the antifungals is evaluated against their relative outcomes, whereby spending resources on a particular preventive antifungal intervention can be characterized as a replacement of increased economic burden for reducing infections incidence. This is best described via economic evaluations, which compare the clinical outcomes and their costs among different available options[57]. Through this, decision makers ensure that the input resources consumed in a therapy achieve the maximal overall output.

1.2.1. Pharmacoeconomics

Pharmacy became recognized as a clinical discipline in the early 1960s, where sub-disciplines such as clinical pharmacy, drug information, and pharmacokinetics constituted the most on demand disciplines of pharmacy education and sciences[58]. The term 'pharmacoeconomics' however, was first used 16 years later, in a published presentation that described the need for developing research activities regarding the evolving discipline[58].

Pharmacoeconomics is defined as the description and analysis of the costs of drug therapy to healthcare systems and society. This is an important science that is increasingly penetrating into the pharmaceutical literature. It identifies, measures and compares the

costs (i.e. resources) and consequences (i.e. clinical, economic, and humanistic outcomes) of pharmaceutical services and products[58]. In other words, pharmacoeconomics, as being a branch of economics, contributes to achieving efficiency in the use of medications regarding their costs and consequences. This is important for directing the use of limited resources to yield maximum benefit to both parties; patients and healthcare systems, in addition to the society as well[59]. Additionally, a cornerstone science that has become an integral of pharmacoeconomics is decision analytic modeling, which is a systematic approach that is used to simplify the decision making, where the therapy strategy is graphically represented, based on treatments and outcomes of interest, in what is called a decision tree. This assists decision makers to define the various options available in a treatment, define all possible outcomes and consequences of each option, calculate the probability of occurrence for each outcome, and calculate the economic value of each treatment option. This will definitly enable a decision making that is better informed[60]. Figure 1.1 shows a simple example of a decision tree of therapy options and consequences[61].

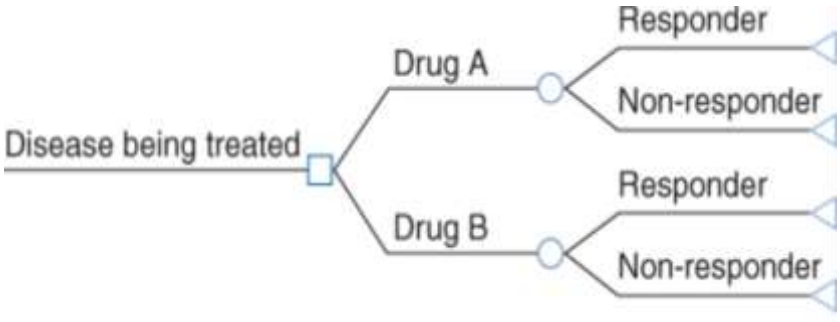


Figure 1. 1: A simplified illustration of a decision tree model of clinical pathways of available alternatives

As seen in Table 1.3, there are four types of pharmacoeconomic evaluations: (i) cost-effectiveness analyses (CEA), (ii) cost-benefit analyses (CBA), (iii) cost-utility analyses (CUA), and (iv) cost minimization analyses (CMA)[57]. Studies may utilize published clinical trials, existing medical records, decision analytic models or a combination of these to conduct the evaluation[57].

Table 1. 3. Summary of Pharmacoeconomics methodologies[62].

Method	Description	Application	Cost Unit	Outcome Unit
CMA	Finds the least expensive cost alternative	Used when benefits are the same	Monetary unit ($$$)	Assumed to be equivalent
CEA	Compares alternatives with therapeutic effects measured in physical units; computes a cost-effectiveness ratio	Compares drugs/programs that differ in clinical outcomes and use the same unit of benefit	$$$	Natural units
CBA	Measures benefit in monetary units and computes a net gain	Compares programs with different objectives or units of benefit	$$$	$$$
CUA	Measures therapeutic consequences in utility units rather than physical units; computes a cost-utility ratio	Compares drugs/programs that are life-extending with serious side effects or those producing reductions in morbidity	$$$	Quality-adjusted life years (QALYs)

While each pharmacoeconomic method having its advantages and disadvantages, CEA is the most commonly conducted in practices, for the following reasons[58]:

a. Outcome units are measured in natural units, such as low-density lipoprotein cholesterol (LDL-C), millimeters of mercury (mmHg), years of life saved, or prevention of an event. These are readily available in-patient records, which practitioners and decision makers are very familiar with.
b. Clinical outcomes are not measured in money values, making the interpretation easier to the reader and researcher.
c. Different therapeutic options with varying levels of outcomes can be compared, as long as outcomes are similar in nature. For example, one can compare the cost-effectiveness among two or more alternatives for treating diabetes using the same outcome measure, which is the blood glucose level. A comparison between alternatives that handle different health conditions and, hence, have different outcome measures (e.g. glucose level for diabetes versus cholesterol level for hypercholesterolemia) is not possible to determine with the CEA design.

On the other hand, the CEA method has its drawbacks[58].

a. Some scholars see CEA as being less comprehensive investigation compared to the CBA and CUA designs.
b. Does not explicitly assure determining the economic value of human life, unlike CBA.
c. Does not sufficiently address the humanistic dimension of outcomes, unlike the CUA.

d. Medications can only be compared against one indication at a time in the CEA. Comparing medications with multiple indications may require multiple cost-effectiveness evaluations among the same medications.

Advantages and disadvantages of the remaining methodologies are briefly discussed in Table 1.4. The pharmacoeconomic design of choice in an evaluation depends on the interest of researchers in the types of outcomes as well as the nature of the competitors involved.

Table 1. 4. The main advantages and disadvantages of CMA, CBA, and CUA

Pharmacoeconomics method	Advantages	Disadvantages
CMA	Compares costs while assuming that outcomes are equivalent	Limited application to intervention as finding a case of total equivalency is less likely to occur
CBA	Different outcomes can be compared since the outcome unit is unified (money value)	No universal agreement on one standard method for valuing medical outcomes
CUA	Multiple outcomes can be compared, incorporates mortality and morbidity into one common unit without having to estimate the monetary value of the outcomes. Utility adjustment is also applicable	The difficulty in determining an accurate utility or quality-adjusted life year (QALY) value

Discussing costs, one should take into account that the cost of a therapeutic intervention is not its acquisition cost. The actual cost, in fact, comprises the value of all and any resources spent when the intervention was applied, including these associated with consequences [59,63]. Further to costs in the pharmacoeconomic evaluations, there are four main types of costs: direct medical costs, direct nonmedical costs, non-direct costs, and intangible costs[58]. Table 1.5 provides examples of each of the cost types[58].

Table 1. 5. Examples of the four types of costs used in pharmacoeconomics evaluations

Types of cost	Example
Direct medical costs	Medications, diagnostic tests, hospitalization, and patient's counseling and education
Direct nonmedical costs	Travel costs to receive healthcare, nonmedical assistance related to condition (e.g. meals-on-wheels), and child care services for children of patients
Non-direct costs	Lost productivity for patient, lost productivity for unpaid caregiver (e.g. family member, friend)
intangible costs	Pain, suffering, fatigue, and anxiety

1.2.2. Market Value of Antifungal Agents

In the US, for example, the estimated antifungal market increased by US$1.2 billion within four years only (1999-2003). This was concurrent with the emergence of newer echinocandins and the triazole voriconazole. While the triazole posaconazole was not developed at that time, sales of azoles constituted more than half of the total market cost.

Globally, in 2012, the pharmaceutical market had a share of US$11.6 billion, consumed for systemic antifungal agents alone. In 2013, this share went even higher to reach US$11.8 billion. By 2016 the global share was US$13.1 billion. This increase is expected to grow to up to US$13.9 billion by 2018 and, after that, in 2021, the market would reach US$16.1 billion with a compound annual growth rate (CAGR) of 4.2% from 2016 to 2021[64,65].

Moreover, back in the mid-1990s, the average cost of managing a case of aspergillosis in the USA was US$62,426, while the invasive candidiasis costs up to US$44,536 per case[66,67]. The value had been steadily growing, where, the estimated cost of treating IFI in the USA was US$65,001 per a case of aspergillosis and US$81,271 per a case of candidiasis in 2012[68]. Although literature lacks information regarding the economic burden of IFI treatment in Qatar, therapeutic costs are expected to be at a similar trend to the international level.

CHAPTER TWO: LITERATURE REVIEW

2.1. Pharmacoeconomics Studies: Prophylaxis Against IFI

As emphasized in Chapter One, the incidence of IFIs has been on the rise over recent decades as it is associated with an increased risk for infections, especially among patients newly diagnosed with hematologic malignancies who are undergoing their first chemotherapy or HSCT.

Given that this type of infection is accounting for elevated rates of morbidity and mortality, with a diagnosis that is difficult to detect, the prophylactic strategy against IFI is a reasonable practice that demonstrated improvement in outcomes[69]. A meta-analysis of randomized controlled trials (RCTs) concluded that using systemic antifungal prophylaxis was associated with a significant reduction in IFI and infection-related mortality among neutropenic patients receiving chemotherapy or undergoing HSCT[70]. Another rationale for prophylaxis strategy is the substantial economic burden on the healthcare system for treating established IFI. In 2005, a study in the Netherlands estimated a mean total cost of treating invasive aspergillosis that is approximately US$32,000 per patient with hematologic malignancy[71]. As for invasive *Candida* infection, the direct cost for 15 days of treatment is around US$5,000, despite not accounting for costs of treatment failure, antifungal switch, and other medical costs[72]. In recent years, higher costs were reported, wherein 2015, as an example, a cost-analysis of the expenditure of systemic antifungal agents in Turkey among patients with hematologic malignancies reported a total cost of US$1,271,789 (US$18,039 per patient)[73].

The increase in the cost of newer available choices for effective and safe prophylactic therapy has made it increasingly difficult and complex for physicians

nowadays to make decisions on agents for first-line use[60,74]. Indeed, while multiple clinical trials have revealed an apparent mortality reduction among patients at risk due to the utilization of broad-spectrum antifungal prophylaxis[69], there is a literature controversy with following this approach due to the higher costs associated with these newer broad-spectrum agents, besides the issue of emerging drug resistance[64,75,76]. Hence, it is extremely crucial to apply pharmacoeconomics evaluations on the different prophylactic agents to aid making decisions that provide the best value for limited healthcare resources[64].

The following paragraphs chronologically provide a summary of relevant studies that were conducted among the hematologic malignancy populations, starting with a focus on studies investigating the necessity of the prophylaxis indication, mostly via triazole antifungals[41,42].

- **Economic Evaluations of Prophylaxis Versus Placebo**

In 1995, a CBA was conducted through a double-blind, controlled trial to evaluate fluconazole as a prophylaxis therapy compared to no prophylaxis in patients with hematologic malignancies undergoing extensive chemotherapy. The study revealed that the net benefit was not statistically significant, where the incidence of systemic mycoses was unaffected (8/76 with fluconazole, versus 8/75). The study, therefore, concluded that fluconazole did not reduce healthcare costs[77]. However, a different conclusion was reported one year later, when Wakerly et al. performed a cost-minimization analysis on two groups of patients; chemotherapy and HSCT recipients, to compare the cost consequences of prophylactic treatment using fluconazole alone, oral polyenes alone, a combination of both, and no prophylaxis. Authors concluded that prophylactic strategies are cheaper options than the ‘no prophylaxis’ approach.

Nevertheless, sensitivity analyses suggested that the most cost-beneficial approach depends on the underlying patient conditions as well as the data source used for drawing model probabilities[78]. The usefulness of prophylaxis was clearer in a Japan study, in 2006, when Nomura et al. compared the cost-effectiveness of fluconazole prophylaxis to the no prophylaxis option. Study data on resource use and costs were retrieved from hospital claims and Japanese reimbursement charges. The researchers confirmed that prophylaxis with fluconazole has clinical benefits along with favorable Incremental Cost-Effectiveness (ICER) Ratio of US$625/ year of survival[79].

Penack et al. were interested in evaluating the polyenes, not the triazoles, they conducted a CBA of low-dose LAMB prophylaxis versus no prophylaxis in 2007. The researchers utilized an RCT, with the economic data (i.e. medication and tests costs) obtained via German market prices and cost catalogs. This demonstrated that the use of LAMB prophylaxis in patients at high risk may result in significant cost savings compared with placebo reaching a net benefit of US$1,159 per patient[80].

In 2008, a decision analytic model was designed by de Vries et al. to assess the cost-effectiveness of itraconazole, fluconazole, versus no prophylaxis for hematology patients undergoing chemotherapy or HSCT as a preventative strategy against IFIs. Measures of failure to prevent IFI were extracted from a published meta-analysis while costs were derived from a national database. For both Netherlands and Germany, de Vries et al. concluded that itraconazole resulted in enhanced clinical outcomes with lower total costs reaching approximately US$5,300 per each IFI avoided. In fact, the probabilities that itraconazole dominated other options was 98% in both countries[81].

- **Comparative Economic Evaluations for Prophylaxis**

With the emergence of echinocandins, both Schonfeld et al. (2008)[82] from the USA and Sohn et al. (2009)[83] from Korea conducted cost-effectiveness studies of prophylactic micafungin versus fluconazole, where the time the need for prophylaxis was supported by guidelines. The latter relied on costs and life expectancy data from Korean sources, while Schonfeld et al. utilized clinical outcome data from published literature. The conclusions from both studies were similar, demonstrating micafungin as dominant for prophylaxis among cancer patients with HSCT. The difference in total hospital costs per patients was US$3,859 in the first study, where the second reported a cost savings of KW 95,511,000 (US$1 = KW1,127.31).

In 2011, Wilke performed a literature review of the pharmacoeconomics evaluations of echinocandins for treatment and prophylaxis indications[84], whereupon reviewing 17 articles the author determined that of all echinocandins, only micafungin can be a cost-effective choice for prophylaxis, but only when fluconazole resistance was indicated. This led to the conclusion that echinocandins are probably not the first-line options for standard prophylaxis cases.

Most studies were more interested in the comparative cost-effectiveness of triazoles (not polyenes and echinocandins) for prophylaxis. In between 2008 and 2010, four studies, by Stam et al.[85], Collins et al.[86], O'Sullivan et al.[87], and Greiner et al.[88], compared the cost-effectiveness of posaconazole with that for standard azoles (itraconazole and fluconazole). The different studies were based on the same published RCT, by Cornely et al.[89], in their analysis. While Collins et al. had considered cost per IFI avoidance as the outcome measure, the remaining three studies chose to expand their decision analytic models into a

Markov model, which allowed for the estimation of QALY gained[85] or life years gained (LYG)[87,88]. The final conclusions obtained from the four studies were similar despite the different settings and countries of evaluations and the use of different outcome measures as per the researcher's interest. The net result was that posaconazole is a cost-effective and cost-saving alternative compared to the standard azoles among neutropenic patients undergoing chemotherapy for treating the leukemia type of cancer.

Following on the triazoles, Al-Badriyeh et al.[90] performed the first CEA between two new triazoles, posaconazole and voriconazole, using a retrospective hospital chart review in Australia. The population of interest was AML patients in the induction stage of chemotherapy. The authors claimed that posaconazole was cost saving over voriconazole by US$13,400 per patient, due to lower rate of death with IFI and lower probability of discontinuation due to oral intolerance. The same research team then reported, by Heng et al.[91], also in Australian patients with AML, utilizing medical records, that for the purpose of patients who are undergoing their consolidation stage of chemotherapy, fluconazole was the most cost effective over posaconazole and voriconazole. Authors reported that fluconazole was 26% and 13% more cost saving over the newer azoles, posaconazole and voriconazole, respectively. That was mainly due to the higher rates of therapy success in fluconazole recipients. This was the first and only study that contradicts all previous economic studies on prophylactic posaconazole in literature, suggesting that fluconazole is better than posaconazole in some populations under especial local practices trends.

- **Cost Analysis Evaluations of the Economic Impact of Prophylactic Antifungal Use**

While not comparative, the following studies, published within 2011 to 2015, were describing the costs and financial burden of systemic antifungals and medical resources utilized for prophylaxis indication.

Imataki O et al.[92] conducted a systematic simulation analysis in 2011 describing the medical cost analysis of systemic antifungal agents in Japan. The study was of fifteen RCTs, and considered probabilities of prophylaxis failure, need for empiric therapy, breakthrough infections, and incidence of side effects as outcome consequences. The estimated costs for prophylaxis and treatment of IFI was: oral itraconazole= US$1,035, oral fluconazole= US$1,552, micafungin= US$2,245, and US$3,028 for LAMB. The studies also accounted for costs of side effects and cost of infection management in case of therapy failure.

In 2014, Heimann SM et al.[69] performed a cost analysis of the direct medical costs of posaconazole and polyene in patients with AML. The study calculated costs consumed in the general ward and intensive care unit (ICU), including costs of mechanical ventilation, diagnostic procedures, all antimicrobial agents, and staff involvement. Posaconazole cost US$22,517 per patient, while this was lower with polyene (US$24,795). The primary cost driver in favor of posaconazole was the shorter length of stay and ICU treatment.

In 2015, Gedik H[5] published a retrospective study describing the expenditures associated with using systemic antifungal medications for both treatment and prophylaxis purposes among patients with hematologic malignancies in Turkey. The antifungal agent that cost most was LAMB, given for the treatment purpose, with an average cost per month of US$29,322 and a total cost per year of US$366,537; followed by caspofungin

(US$28,410 per month and US$355,125 annually). Posaconazole and fluconazole were used in the study for primary and secondary prophylaxes, respectively. Posaconazole costs US$337,757 per year, and the annual total cost of voriconazole was US$177,230 for the IV formulation and US$34,951 when orally administered.

Also, in 2015, Ceesay et al.[93] summarized the economic burden of systemic antifungal use among patients with different hematologic malignancies. The study included patients from King's College Hospital in London through a cohort design considering the perspective of the hospital for cost analysis. It was declared by the authors that the variation in total costs of IFI is associated with factors such as primary diagnosis, core hematologic treatment, and IFI status (i. e. proven, possible, no evidence). Considering prophylaxis costs only, AML patients cost over US$5,000 per patient while myeloma patients cost the least (US$850 per patient). Prophylaxis in patients who received allogeneic HSCT cost US$5812, and this was US$1147 in the autologous patients. As for patients with proven IFI after prophylaxis, the prophylactic strategy cost was US$4,535 compared to US$2,755 spent for patients with no IFI developing.

- **Core Message of Literature Studies**

As seen above, treatment options that are eligible to use in prophylaxis were economically evaluated in different types of hematologic malignancies. In earlier studies, the evaluations were mostly of prophylaxis versus none. Afterwards, the need for prophylaxis was deemed definite in literature, and studies more focused on how newer prophylactic antifungals agents (i.e. micafungin, posaconazole) economically compare to older agents[71].

To recap, economic evaluations of systemic antifungal agents for prophylaxis in immunocompromised patients with different hematological malignancies demonstrated favorable potential. However, it is difficult to specify a single prophylactic agent as superior. The generalizability of economic evidence is not clear due to much variability in several factors of consequence in the economic evaluation. As one main of such factors, patients with hematological cancer can be categorized according to the main treatment received; (i) chemotherapy and (ii) HSCT, whereby the underlying disease and its therapy have an influence on the immunity level, which consequenty influence the occurrences of IFI[71]. Other important factors that limited the generalizability relate to the (i) type of pharmacoeconomic evaluation used (i.e. cost analysis, cost-effectiveness, cost-benefit), (ii) time horizon to follow patients, (iii) study perspective (i.e. hospital or payer), (iv) outcome measure and its definitions, and (v) cost data[71].

2.2. Study Rationale and Significance

As indicated in Chapter One, posaconazole was and still the only first-line prophylactic antifungal used in NCCCR in Qatar. No economic data or a local evidence on the use of systematic antifungals in Qatar was ever generated at any level. There is, therefore, a need for a Qatari-based research that aims at analyzing the cost of the currently used prophylactic antifungal in use at the NCCCR in Qatar, i.e. posaconazole, among newly diagnosed hematologic malignancy patients, including as compared to fluconazole, a potential alternative antifungal that is widely recommended for first-line prophylactic use in AML settings[91,94,95].

There is no information on the economics of using systemic antifungals in cancer patients, not only in Qatar, but regionally, including as prophylaxis. This includes any

reports of resource utilization about the antifungals in general. Evaluating the impact of posaconazole on resource consumption is most important for better understanding its impact on hospital budgets for decision makers and practitioners to consider, beyond the acquisition costs only. This includes understanding the economic impact of the clinicians' handling practices of side effects, or their handling strategies of discontinuations. Such information can certainly be useful for decision makers and clinicians alike when considering and revising their protocols and practices in Qatar.

Evaluating the comparative value of posaconazole will also be significant as, internationally, there are conflicting reports on the economic usefulness of posaconazole against other commonly used systemic antifungals in practice, e.g. fluconazole85[,91,96,97]. Especially that posaconazole and fluconazole are the most widely used antifungals among immunocompromised hematologic malignancy patients. The value of the comparative evaluation of posaconazole from the local perspective cannot be underestimated, which is due to, as already discussed earlier, how locally specific and not generalizable the pharmacoeconomics studies are. For example, while, as per most international practices, alternative prophylactic antifungals are administered to patients in cases of discontinuations due to side effects, the practice in Qatar is that the prophylactic administration of an antifungal is stopped until the side effects resolve, before the initial antifungal is re-administered.

In all economic litearture of posaconazole, cost-effectiveness studies were conducted to justify the use of an expendive drug over cheaper older ones[85,91.96.97]. The case of the Qatari practice is different, however; whereby, posaconazole, due to general evidence of supoeriority, is the first and only prophylaic antifungal that NCCCR ever had

and used in hematology patients. Here, the future research question would be about how much an alternative that is associated with slightly less effectiveness, but much reduced cost, would produce in cost saving over posaconazole in the NCCCR. The only prophylactic antifungal agent that demonstrated to be non-inferior to posaconazole is fluconazole. To figure out how much cost saving the NCCCR setting would achieve by replacing posaconazole with fluconazole is a most important component of working to comprehensively, comparatively understand the value of posaconazole.

While the economic evaluations of systemic antifungal agents are exponentially increasing in literature nowadays to support answering questions on best choices of therapy from the clinical and economic point of views[60], there is no information on how this science is utilized and/or its strengths and weaknesses with regards to systemic antifungal agents that are used among patients at risk of IFI. Indeed, the quality of methodologies utilized to conduct economic evaluations within this context has not been evaluated yet, including for the guiding of further future economic evaluations in the field of focus[98]. Here, systematic reviews are one of the common valuable types of journal publications. They are a vital requirement to ensure evidence-based medicine statements. In the context of pharmacoeconomics research, however, it is doubtful that such statements are as reliable and robust as those made in the context of clinical research[99,100]. As discussed earlier, the economic evaluations are difficult to generalize due to high variability in setting practices, methods used, input data, and affordability. Hence, within the context of economic evaluations of systemic antifungal agents used as a preventative strategy against IFI, a systematic review of the literature to answer questions about characteristics and quality of research of systemic antifungal agents in patients with hematological malignancies,

including the strength and limitation of methodological aspects used, will be valuable. Identifying literature methodological characteristics and trends will work to identify methodological gaps and practical recommendations for the researchers to consider in planning and organizing their future research in settings. In addition, decision makers would have a better understanding of the quality of generated evidence as they would be able to contrast it against the current strengths and weaknesses of methods in the literature.

2.3. Study Objectives

Mainly, this research looks at generating information that would direct the efficient delivery and management of posaconazole for prophylaxis against IFI in hematologic malignancy patients undergoing chemotherapy or HSCT in the local Qatari setting. It will be significant to conduct an economic analysis in the local Qatari setting where resources are scarce and/or infectious disease (ID) departments are busy and hazardous, such as in the ID department at the NCCCR. The more the cases of successful prophylaxis against IFI, the fewer occasions for getting invasive infections, which results in a reduced need for exposing the patient to further expensive systemic antifungals for treating such infections that is of high mortality rates. In addition, since the current clinical practices in Qatar can be different from in other settings, it will be inappropriate to assume that using other similar studies in literature is valid for guiding the Qatar settings when it comes to impact on cost and, therefore, local economic evaluations of posaconazole are indeed needed.

The research in the thesis was therefore undertaken via two phases:

Phase 1: Pharmacoeconomics Evaluations of Posaconazole

A comprehensive economic assessment of the utilization of posaconazole for prophylaxis against IFI among immunocompromised patients with hematological malignancies, who are receiving chemotherapy or undergoing HSCT at the NCCCR in Qatar. This was conducted through the following two evaluations;

- Evaluation 1: Cost-analysis of the overall resource utilization associated with the prophylactic use of posaconazole.
- Evaluation 2: Cost-effectiveness analysis of the comparative economic value of posaconazole against fluconazole.

Phase 2: Systematic Review of Methodological Trends and Gaps, and the Reporting Quality of Comparative Economic Evaluations on the Use of Systemic Antifungal Agents Used for Prophylaxis Against IFI

Adding to the conclusions made via phase 1 of the thesis, recommendations for relevant future research are made based on a comprehensive systematic review that was conducted to summarize the quality of the methodological aspects, including strength and weaknesses, of the comparative economic evaluations on the use of systemic antifungal agents used for prophylaxis against IFI in immunocompromised patients with hematologic malignancy, who are undergoing chemotherapy or HSCT.

CHAPTER THREE: MATERIALS AND METHODS

3.1. Phase 1: Pharmacoeconomics Evaluations of Posaconazole

As per the study objectives of phase 1, methods of the study relate to two different evaluations that will be discussed separately.

3.1.1. Evaluation 1: Cost-Analysis of the Overall Resource Utilization Associated with the Prophylactic Use of Posaconazole

This is to perform a cost analysis simulation model of using the systemic antifungal agent posaconazole as indicated for the prophylaxis against IFIs among patients with hematological malignancies in the NCCCR ,in Qatar.

3.1.1.1. Model Structure

An economic model was constructed to follow posaconazole's use and potential consequences of interest as prophylaxis in patients with hematologic malignancies, as illustrated in Figure 3.1.

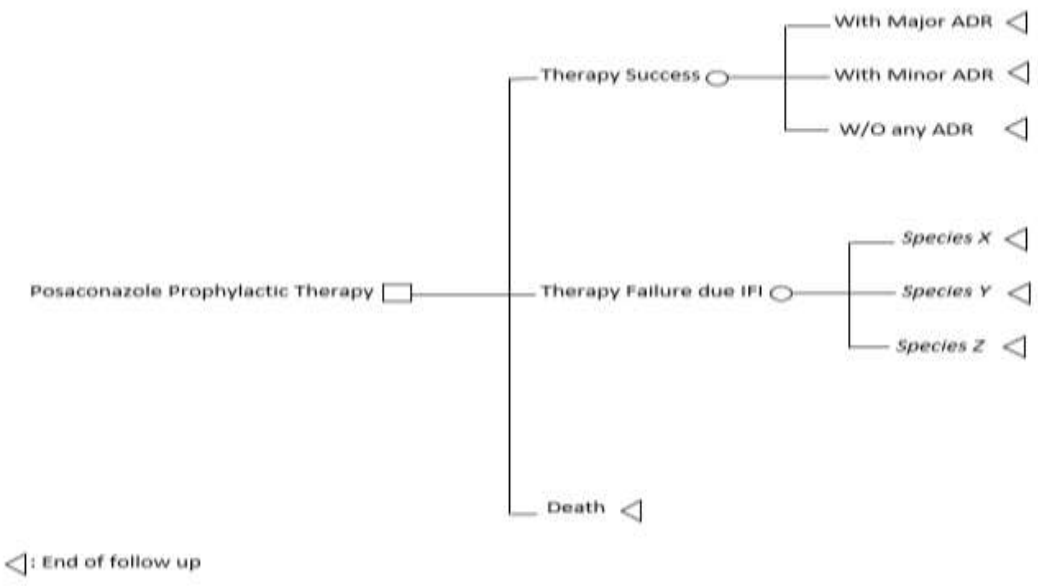


Figure 3. 1: Economic model of posaconazole use as prophylaxis in hematologic malignancies

The model included three possible outcome pathways on whether the prophylactic therapy was successful, and, if not, for what reason. Therapy success was defined as survival with the absence of proven/possible/probable IFIs within 112 days (4 months) of receiving the first does of prophylaxis while patients are under their chemotherapy cycle or undergoing a HSCT. The duration of follow up is consistent with the relevant literature evaluations of systemic antifungal agents for prophylaxis purpose, whereby relevant drug outcomes are considered to be those who are reported by 3 to 4 months of starting the prophylaxis therapy. IFI is anticipated to appear as soon as few weeks only among the chemotherapy and HSCT immunocompromised patients[86,101,102].

A successful therapy can be associated with major adverse drug reactions (ADR), minor ADR, or no ADR. Major ADR are ADR that lead to therapy discontinuation, while minor ADR do not. Failure of therapy was due to termination of prophylaxis because of

proven/possible/probable IFIs or because of death during the follow up duration. In case of IFIs and taking in consideration that type of the causative fungi, patients are switched to another licensed systemic antifungal agent for the treatment purpose. All alternative therapies were assumed to be successful.

3.1.1.2. Ethical Approval

The required NCCCR ethics approval was obtained via the ethics committee of Medical research Centre (MRC) in HMC, Qatar. (See approval letter in Appendix 1). Due to its retrospective nature, the current research was exempted by Qatar University from full ethics reviews (Appendix 2).

3.1.1.3. Patient Population

Inclusion Criteria:

1. Patients admitted to the hospital between 1st January 2013 and 31st December 2015
2. Patients with hematologic malignancy and received chemotherapy or HSCT in Qatar
3. Patients who received systemic posaconazole prophylactic therapy against IFI, with a standard dosing of 200 mg suspension, three times a day
4. Patients who did not receive any systemic antifungal agents within the 7 days prior to commencing the prophylactic therapy
5. Patients with no current or previous history of IFI

Exclusion Criteria:

1. Patients who are 15 years old or below
2. Patients who received a hematology treatment in overseas
3. Patients with previous history of IFI

4. Patients who were exposed to systemic antifungal agents within 7 days of receiving their antifungal prophylactic agent
5. Patients with a non-malignancy hematologic disease and a solid organ cancer

3.1.1.4. Study Perspective

The economic model was constructed to adopt the hospital perspective of NCCCR in Qatar, where only resources with direct medical costs were considered, including diagnostic and monitoring tests, prophylactic medical therapy, medications for managing ADR and IFIs, hospitalization, and duration of therapy. Only the resources in relevance to the prophylactic use of posaconazole and its consequences were considered. Direct medical costs associated with the patients' underlying diseases were not incuded. Due to the retrospective nature of data sources and perspective of the study, intangible and direct non-medical costs were also not included in the study.

3.1.1.5. Model Resource and Clinical Inputs and the Data Collection

The simulation model inputs were mainly derived from the electronic medical health records of the NCCCR, since the inception of the Cerner® a medical database at the hospital. A data collection form, seen Appendix 3, was utilized to extract relevant data of interest from the records. Data collected through medical records related to probabilities of success, failure and death, patients' demographics, the underlying diagnosis, other diseases, antifungal prophylaxis, duration of therapy, laboratory and microbiological tests, concurrent medications, and mortality status. For a patient, medical records data were collected throughout 112 days duration from prophylaxis onset.

ADR reporting in medical records is not comprehensive and mostly inaccurate. Probabilities of ADR, therefore, were obtained from the published clinical trial by Ullmann

et al[103]. This is a large published clinical trial that, like in the current study, evaluated posaconazole as prophylaxis in hematological malignancy.

Due to the limited patient sample size and an anticipated missing data in relation to the identification and management of IFIs, an NCCCR-based independent expert panel was created to provide information on the frequently identified IFI causative fungi in NCCCR and the strategies used to manage them along with ADR. The panel comprised a specialist senior clinical pharmacist and three hematology and infectious diseases specialist clinicians, who also had personal clinical experiences with the systematic fungal therapy in NCCCR. The expert panel provided data via meetings, where answers to questions were discussed until consensus. In preparation for meetings, all questions and required information were circulated to panel members. A list of questions to the expert panel can be seen in Appendix 4.

The expert panel was also asked to discuss the structure of the economic model and validate it.

3.1.1.6. Cost Calculation

All costs accounted for the study were calculated in Qatari Riyal (QAR) for the financial year 2016/17, and no discounting was performed due to the short-term duration of follow up.

The cost of initial prophylaxis was the cost of a complete course of posaconazole until success or death, or until switching to alternative therapies due to major ADR or occurrence of infection that require tailored treatment. The cost of alternative therapy was the cost of a complete course of the alternative agent. This is based on the assumption that if patients switched therapy after prophylactic failure, the subsequent alternative therapy

was successful. With a similar trend, the cost of managing minor ADR was also the cost of a complete course of treatment for the drug event. The overall cost of a patient is the initial cost and any alternative therapies added to the cost of resources consumed for monitoring and screening tests throughout the duration therapy.

Medication costs used were the wholesale drug prices as derived from the MyCare® pricing system, which is the local pricing database at the NCCCR. Doses for all medications were rounded to the nearest vial size. As per the routine clinical practice at HMC in Qatar, patients were not allowed to share the same posaconazole bottle. Cost of diagnostic and monitoring testing and the hospitalization stay associated with patients with hematologic malignancies was obtained from the department of finance, NCCCR. Patients receiving prophylaxis were treated as outpatients throughout the study period. Only when the patient had a failure of therapy due to IFI, hospitalization costs were accounted for.

All resource costs were inflated to 2016/17 values as per the 2017 Qatari Consumer Price Index (CPI).

3.1.1.7. Sensitivity Analysis

To assess the robustness of the study conclusion, study outcomes were evaluated via sensitivity analyses against variations in the values of key variables, related to deterministic and probabilistic inputs. Sensitivity analyses were performed using one-way, scenario and multivariate analyses.

One-way sensitivity analysis was conducted on hospitalization costs, the occurrence of major ADR, and the accountability for the cost of diagnostic tests, which may not necessarily relate the antifungal use in patients. The scenario analysis evaluated the impact of the hypothetical scenario of having patients sharing their posaconazole

bottles in therapy. Based on the Monte Carlo analysis, as described below, the probability cost of therapy was also generated in consequence to ±20% undertainty in drug prices.

Monte Carlo uncertainty and probabilistic analysis via @Risk-5.7® (Palisade Corporation, NY, USA) was also performed, to generate probability measures of cost oucomes and to rank variables as per their influence on final study outcomes. Monte Carlo is a method that allows for multiple model simulations to run, each time sampling inputs from pre-defined uncertainty ranges of input values. Here, with 10,000 iterations and a triangular type of input distribution used, a ±5% uncertainty range was assigned to the probability data obtained via the expert panel, i.e. probabilities of causative fungi accurance, while all other model probabilities varied by a ±3% uncertainty range.

3.1.2. Evaluation 2: Cost-Effectiveness Analysis of the Comparative Economic Value of Posaconazole Against Fluconazole

This is to perform a cost-effectiveness analysis model of the use of the systemic posaconazole compared to fluconazole in the prophylaxis against IFI among cancer patients with hematological malignancies in NCCCR in Qatar.

3.1.2.1. Model Structure

A decision analytic model was constructed to capture downstream consequences of prophylactic posaconazole versus fluconazole in patients with hematologic malignancies as illustrated in Figure 3.2.

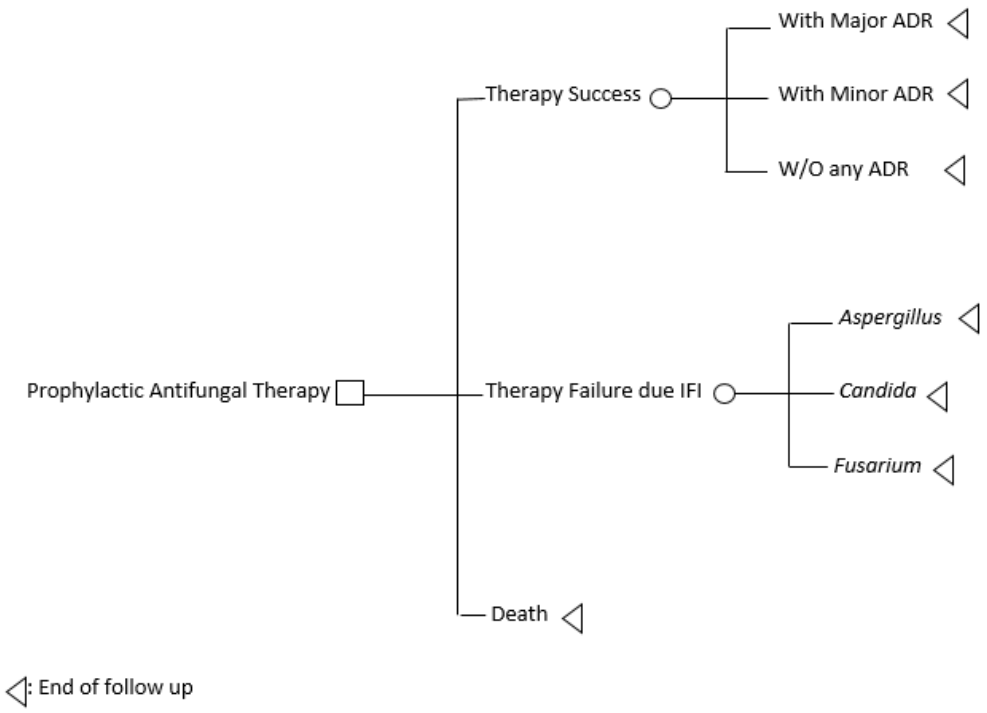


Figure 3. 2. Decision analytic model of prophylactic antifungal therapy in hematologic malignancies

For posaconazole and fluconazole, identical model pathways were followed. A successful prophylaxis is that not associated with proven/possible/probable IFIs or death during the patient follow up in the Ullmann et al. trial[103], i.e. 112 days of receiving the first dose of prophylaxis while on undergoing chemotherapy or HSCT. Prophylaxis can be successful and associated with major ADR, minor ADR, or no ADR. ADR that lead to therapy discontinuation are considered major, and those that do not are minor.

Prophylaxis failures if proven/possible/probable IFIs or death occurs during follow up. As per the Ullmann et al[103]. trial, an identified IFI is the result of *Aspergillus*, *Candida*,

or *Fusarium* fungi. As a consequence to an IFI, a patient was assumed to switch to another licensed systemic targeted antifungal therapy.

3.1.2.2 Ethical Approval

As discussed under 3.1.1.2 the required ethics approval was obtained as appropriate via the MRC of HMC. As was also discussed, the research was exempted by Qatar University from the full ethics committee review.

3.1.2.3. Study Perspective

The economic model adopted the hospital perspective of NCCCR. Only direct medical costs were considered, including costs of diagnostic and monitoring tests, prophylaxis therapies, medications for managing ADR and IFIs, hospitalization, and duration of therapy. Only the resources in relevance to the prophylactic use of posaconazole and fluconazole were considered. Intangible and non-medical costs were not included in the study.

3.1.2.4. Model Input

Input model data that were primarily derived from the Ullmann et al[103]. trial included propabilities of the different health states and the duration of therapy with each, *Vide Infra* in Chapter 4 of the thesis.

Based on the trial, patients on posaconazole suspension received 200 mg three times a day, and fluconazole was administered as capsules of 400 mg once daily throughout the treatment duration, which is all identical to the administration of these in the Qatari setting.

To adopt the economic model to the local Qatari setting, an independent expert panel was arranged from the perspective of NCCCR, comprising a specialized senior clinical pharmacist and three consultant clincians with clinical expertise in systemic fungal

therapy and specialist knowledge in hematology and infectious diseases. The panel provided required data about the patient management in Qatar, which were not available from the literature, *Vide infra* in Chapter 4. Data included screening and monitoring tests conducted in relevance to the IFIs, in addition to strategies of managing the different ADR and IFIs, which included what the major ADR and IFIs in the local setting are. Before the meetings, members of the panel were provided with a list of questions of interest, added to a copy of the trial manuscript by Ullmann et al[103]. During the meeting, time and opportunities to discuss were given to members until consensus was achieved.

The expert panel was also asked to discuss and validate the decision tree of the study model.

3.1.2.5. Cost Calculation

Costs were calculated in QAR for the financial year 2016/17, with no cost discounting performed.

The cost of initial prophylaxis was the cost of a complete course of posaconazole or fluconazole until success, death, or until switching to alternative therapies due to major ADR or IFIs. The cost of an intervention due to the ADR or IFIs is the cost of a complete course of the intervention. Here, it is assumed that when patients are given interventions due to ADR or IFIs, the intervention is successful. The cost of each treatment outcome was the cost of initial and interventional therapies, added to the cost of resources consumed. Regardless of the outcome, patients were analyzed according to the group that they were initially assigned to.

Medication costs used were the wholesale drug prices as derived from the MyCare® pricing system, which is the local pricing database at the NCCCR. Doses for all

medications were rounded to the nearest vial size. As per the routine clinical practice at HMC in Qatar, patients were not allowed to share the same posaconazole bottle. Cost of diagnostic and monitoring testing and the hospitalization stay associated with patients with hematologic malignancies was obtained from the department of finance, NCCCR. Patients receiving prophylaxis were treated as outpatients throughout the study period. Only when the patient had a failure of therapy due to IFI, hospitalization costs were accounted for.

All resource costs were inflated to 2016/17 values as per the 2017 Qatari CPI.

3.1.2.6. Sensitivity Analysis

To assess the robustness of results, sensitivity analyses were performed via one-way, scenario and multivariate analyses. Costs have a potential impact on the study outcome and, hence, variation in costs was investigated via the one-way sensitivity analyses. This included costs of antifungal agents (±20%) and cost of hospitalization (±100%) added to the duration of hospitalization. Investigating the overall cost without accounting for costs of diagnostics tests, and only accounting for the regular monitoring tests, was conducted, given the lack of relevance to the fungal therapy. Key deterministic and probabilistic data provided by the expert panel are associated with uncertainty and were also assessed. Scenario analysis was also performed by evaluating the case of changing the practice to the sharing of posaconazole bottles between patients.

Probabilistic sensitivity analyses using Monte Carlo simulation was performed via @Risk-5.7® (Palisade Corporation, NY, USA) to test against uncertainty. As previously discussed, Monte Carlo is a method that enables multiple model simulations, using pre-defined uncertainty ranges of input values. A triangular type of distribution was performed with an uncertainty range of 0-100% associated with the probability of prophylaxis failure

due to possible infection, to account for potential high variability in infection epidemiology among different settings. An uncertainty of ±5% was assigned to all other outcome probabilities in the model. The uncertainty analysis was based on 10,000 model simulation, with the corresponding costs calculated, and a probabilistic distribution of cost outcomes obtained. The study variables that influence the overall cost outcomes the most were also determined.

3.2. Phase 2: Systematic Review of Methodological Trends and Gaps, and the Reporting Quality of Comparative Economic Evaluations on the Use of Systemic Antifungal Agents Used for Prophylaxis Against IFI

This is a systematic review of all pharmacoeconomics publications on the use of systemic antifungal agents for prophylaxis against IFI among immunocompromised cancer patients in the English-language medical literature until Jan 2018. The study was to review the characteristics, methodological trends and gaps, and the reporting quality of literature research. This will enable the consolidation of conclusions made in Phase 1 of this thesis with recommendations to enhance future research on the topic of antifungal prophylaxis.

3.2.1. Literature Review

The electronic databases Pubmed database, Embase database, Economic evaluation database, Econlit database, Cochrane Library, and Medline database were utilized to search relevant literature. The search strategy included three main domains; the therapy, disease, and research design. Search indices included the MeSH terms "Antifungal Agents"[Mesh], "Pre-Exposure Prophylaxis"[Mesh], "Mycoses"[Mesh], Fungal"[Mesh], "Immunocompromised Host"[Mesh], "Neoplasms"[Mesh], "Cost-Benefit Analysis"[Mesh], "Economics"[Mesh], "Costs and Cost Analysis"[Mesh]. Keyword terms

included prophylaxi, Lung diseases, systemic, invasive. The search strategy via PubMed is in Appendix 5, which was adapted for other databases.

3.2.2. Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Literature publications were included until January 2018. No considerations were made of whether articles are freely available
2. Therapy based comparative studies. No considerations were made of whether studies are retrospective or prospective
3. Studies of systemic antifungal agents for the prophylaxis indication
4. Studies of undelying immunocompromised cancer patients at risk of IFI
5. Pharmacoeconomics studies

Exclusion Criteria:

1. Non-English language
2. Non-human studies
3. Non-comparative research, e.g. letters, general reviews, editorials
4. Studies on topical antifungal agents and/or non-invasive fungal infections
5. Non-economic based studies

Data Collection and Handling

Screening for initial eligibility via the search terms was by assessing the title and abstract first. Articles that were found via the database search were further screened for eligibility by manual analysis of study abstracts. Then, for final inclusion in the study, a follow up manual screening by reviewing the full text of the initially eligible articles was conducted. This process, in addition to data extraction, was separately performed for

conformance by each of investigators. Disagreements were further discussed by the research team as led by a third investigator. Before formal data extraction, and for validation purposes, a random sample of three included articles was independently reviewed by each of the study investigators before discussed to ensure consistency and agreement among all.

Extracted data from included full texts related to study characteristics and methodological features, incuding general paper information (authors, year of publication, publishing journal, method of economic evaluation, drugs compared, country, population of underlying disease, participants age, sample size); clinical effectiveness component (study setting, clinical measure definition, source of effectiveness data, time horizon of follow up, clinical outcome results); economic effectiveness component (perspective, study setting, date of analysis and date of economic data, time adjustment type, source of economic data, modeling type and pathways used, type of costs considered, measure of benefit used; and study results (sensitivity analysis outcome, statistical analysis used, main economic findings, authors conclusions).

A template of the developed data extraction form is supplemented in Appendix 6. All investigators have training in pharmacoeconomics research. Descriptive statistics and tabulations were used to present results. The PRISMA checklist (Appendix 7) was followed for completing the systematic review.

3.2.3. Quality Assessment

A reporting quality assessment was of the pharmacoeconomics studies was performed by using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Appendix 8)[104]. While there are other available checklists for the

economic evaluations, the objective of the quality checklist was not to investigate bias for evidence generation but to guide the content description of articles, where CHEERS is considered most comprehensive and appropriate. The quality assessment was independently conducted by the different individual investigators, as described above.

CHAPTER FOUR: RESULTS

4.1. Phase 1: Pharmacoeconomics Evaluations of Posaconazole

As per the study objectives, results of this phase of the study relate to two different evaluations that will be described separately.

4.1.1. Evaluation 1: Cost-Analysis of the Overall Resource Utilization Associated with the Prophylactic use of Posaconazole

4.1.1.1. Eligible Patients and Underlying Malignancies

A total of 70 eligible patients, admitted to the NCCCR between January 2013 and December 2015, and who received systemic posaconazole for the prophylaxis against IFI, were included into this retrospective analysis. Table 4.1 provides a brief breakdown of numbers of included patients as per the type of diagnosis of hematological malignancies.

Table 4. 1. Types of hematological malignancies in patients included in the analysis

Hematological malignancies	n (%)
Acute myeloid leukemia (AML)	45 (64.29)
Precursor T/B-cell lymphoblastic leukemia/lymphoma (ALL)	22 (31.43)
Adult T-cell leukemia/lymphoma (ATLL)	1 (1.43)
Myelosclerosis with myeloid metaplasia (MMM)	1 (1.43)
Myelodysplastic syndrome (MDS)	1 (1.43)
Total	70 (100)

4.1.1.2. Clinical Outcomes

Out of 70 patients, who received systemic posaconazole for prophylaxis against IFI in the retrospective analysis, 30 (42.86%) had failed their therapy due to IFI. The majority of those patients were diagnosed with AML (n=22) while the rest had ALL (n=7) and ATLL (n=1) patients. Only 5 patients had died before completing the follow-up 112 days (4 patients with AML and 1 with ALL), which is a crude mortality rate of 7.14%. The mean age of included patients was 39.97 ± 15.15 (ranging from 16 to 70), with the majority (n=58, 82.86%) of the study patient population being males. The mean number of days of receiving posaconazole among patients, where therapy was successful (no IFI or death within 112 days), was 63.1 days. The patients who failed therapy due to developing IFIs had a mean posaconazole duration of 56.3 days, and those who failed therapy due to death had a mean therapy duration of 25.4 days. In Table 4.2, probability estimates of success, failure due to IFI, IFI-causative fungi, ADR with success, and death are provided. Death medical reports did not clarify or investigate the reason of death; therefore, no information on IFI-specific mortality is available.

Table 4.2. Model input probabilities of ADR and IFI-causative fungi

Study clinical outcome	Probability with posaconazole	Resource
Therapy success	0.50	NCCCR medical records
With major ADR	0.13	Ullmann et al.[103]
With minor ADR	0.15	
Without ADR	0.72	
Therapy failure due to IFI	0.43	NCCCR medical records
Aspergillus	0.30	NCCCR expert panel
Candida	0.60	
Fusarium	0.03	
Mucormycetes	0.03	
Tricosporon	0.03	
Death	0.07	NCCCR medical records

Patients received routine screening procedures and monitoring tests during prophylaxis among all hematological malignancy patients in NCCCR during the study duration (Table 4.3).

Table 4. 3.Utilization of screening procedures and monitoring tests in patients

Screening tests (imaging)	No. of tests conducted	Test frequency	Screening tests (pathology)	No. of tests conducted	Test frequency
Chest X-ray	652	Weekly	Respiratory culture	46	Weekly
Other X-ray	51	As needed	Parasite stool	15	Biweekly
CT scan[1]	143	Weekly	Acid-fast bacilli	38	Biweekly
Ultrasound	40	Weekly	C. Diff toxin[4]	55	As needed
MRI[2]	37	Weekly	C. Coli antigen[5]	22	As needed
Nuclear Medicine	30	As needed	Galactomannan test	324	As needed
ECG[3]	64	Weekly	PCR virology[6]	65	As needed
Screening tests (Pathology)			Monitoring tests		
Urine culture	219	Weekly	ALT/AST[7]	3,454	Twice weekly
Stool culture	48	Weekly	Creatinine	5,178	Weekly
Blood culture	771	Weekly	CBC[8]	5,302	Weekly

[1] CT: Computed Tomography
[2] MRI: Magnetic Resonance Imaging
[3] ECG: Electrocardiogram
[4] C. Diff: Clostridium Difficile
[5] C. Coli: Campylobacter Coli
[6] PCR: Polymerase Chain Reaction
[7] ALT/AST: Alanine Transaminase/Aspartate Transaminase
[8] CBC: Complete Blood Count

Based on the expert panel, the management of minor ADR, as deemed relevant to posaconazole, were as in Table 4.4. Also, as per the expert panel, the alternative antifungal therapies given after the discontinuation due to major ADR or the failure of prophylaxis are as in Tables 4.5 and 4.6.

Table 4. 4. Management of minor ADR during posaconazole administration

Type of ADR	Management medication	Details (dose, frequency, duration)
Headache	Paracetamol	1000 mg every 6 hours for 10 days as needed
Nausea and vomiting	Metoclopramide	10 mg twice daily for 2 weeks as needed
Diarrhea	Metronidazole	500 mg every 8 hours for 10 days

Table 4. 5. Antifungal alternative medication in case of discontinuation due to major ADR

Cause of therapy discontinuation[a]	Management medication	Details (dose, frequency, duration)
Sever liver and biliary disorder	LAMB	5 mg/kg/day for 12 weeks

[a] Patients stop prophylaxis in this case and start the alternative therapy for treatment purpose once evidence of infection appears

Table 4. 6. Antifungal alternative medications to therapy failure due to the occurrence of IFI

Causative pathogen	Alternative treatment	Details (dose, frequency, duration)
Aspergillus	Voriconazole	Loading dose 6 mg/kg twice daily for day 1, followed by maintenance IV dose 4 mg/kg twice daily for 2 weeks, then oral 200 mg twice daily for 10 weeks
Candida	Caspofungin	Loading dose 70 mg once daily for day 1 followed by 50 mg once daily for 6 weeks
Fusarium	LAMB + Voriconazole	Voriconazole: Loading dose 6 mg/kg twice daily for day 1, followed by maintenance IV dose 4 mg/kg twice daily for 2 weeks, then oral 200 mg twice daily for 10 weeks + LAMB: 5 mg/kg/day for 12 weeks
Mucormycetes	LAMB+ surgical debridement	5 mg/kg/day for 6 weeks
Tricpsporon	Voriconazole	Loading dose 6 mg/kg twice daily for day 1, followed by maintenance IV dose 4 mg/kg twice daily for 2 weeks, then oral 200 mg twice daily for 10 weeks

4.1.1.3. Economic Outcomes

The cost inputs of resources included in the model are summarized in Table 4.7. Based on the study model, as illustrated in Chapter 3, the average overall cost of posaconazole was QAR 109,802 per patient. The cost of the success of therapy was QAR 52,029 per patient, the total cost due to IFI-based failures was QAR 54,948 per patient, and the cost associated with the death pathway was QAR 2,824 per patient. Table 4.8 summarizes the calculation of the overall cost of posaconazole therapy.

Table 4. 7. Resource costs

Item	Unit	Unit cost (QR)
Posaconazole	105 mL oral suspension	3295.56
Voriconazole	200 mg IV vial	364.18
	200 mg oral tablet	148.89
Caspofungin	50 mg IV vial	1203.96
	70 mg IV vial	1573.14
LAMB	50 mg IV vial w/microfilter	655.47
Paracetamol	500 mg oral tablet	0.03
Metronidazole	500 mg oral tablet	0.07
Metoclopramide	10 mg oral tablet	0.05
Chest X-ray	1 test	36
CT scan	1 test	486
Ultrasound scan	1 test	84
MRI scan	1 test	876
Nuclear medicine	1 test	1,000
ECG	1 test	600
Sputum culture	≥1 tests (1 culture)	92
Urine culture	1 test (1 culture)	92
Stool culture	≥ 1 tests (1 culture)	92
Blood culture	1 test (1 culture)	92
Respiratory culture	1 test	92
Parasite stool	1 test	92

Acid-fast bacilli	1 test	92
Clostridium Difficle toxin	1 test	200
Campylobacter Coli antigen	1 test	200
Skin biopsy	1 test	123
PCR virology	1 test	200
Surgical debridement	1 procedure	1,000
Galactomannan (ELISA)	1 test	66
Co-agulation test	1 test	42
Fibrinogen	1 test	28
C-reactive protein	1 test	24
Complete blood count	1 test	30
Renal function test	1 test	90
Liver function test	1 test	30
Hospitalization	Inpatient per day	100

All costs are based on pricing system of NCCCR

Table 4. 8. Cost consequences of utilizing posaconazole at NCCCR as per the study model

Antifungal agent	Outcome Event	Cost of pathway x probability (QAR[a])	Arm cost (QAR)	Average Cost (QAR, 95% CI[c])
Posaconazole	Success with major ADR[b]	29,705	52,029	109,801 (109,750 - 109,852)
	Success with minor ADR	3,922		
	Success without ADR	18,402		
	Failure due to Aspergillus	13,293	54,948	
	Failure due to Candida	29,311		
	Failure due to Fusarium	7,153		
	Failure due to Mycormycosis	3,715		
	Failure due to Tricosporon	1,477		
	Death	2,824	2,824	

[a] QAR: Qatari Riyal
[b] ADR: Adverse Drug Reaction
[c] CI: Confidence Interval, Based on 10,000 iterations of multivariate Monte Carlo simulations

The costs as per the different patient management components are illustrated in Figure 4.1, where it is shown that the main cost driver was success with the major ADR pathway (30% of total expenditure), followed by the average cost of monitoring tests (19%), and *Candida*-based failure pathways (17.5%), and then the acquisition cost of posaconazole (15%). Prices and estimated monthly costs antifungal agents are shown in Table 4.9.

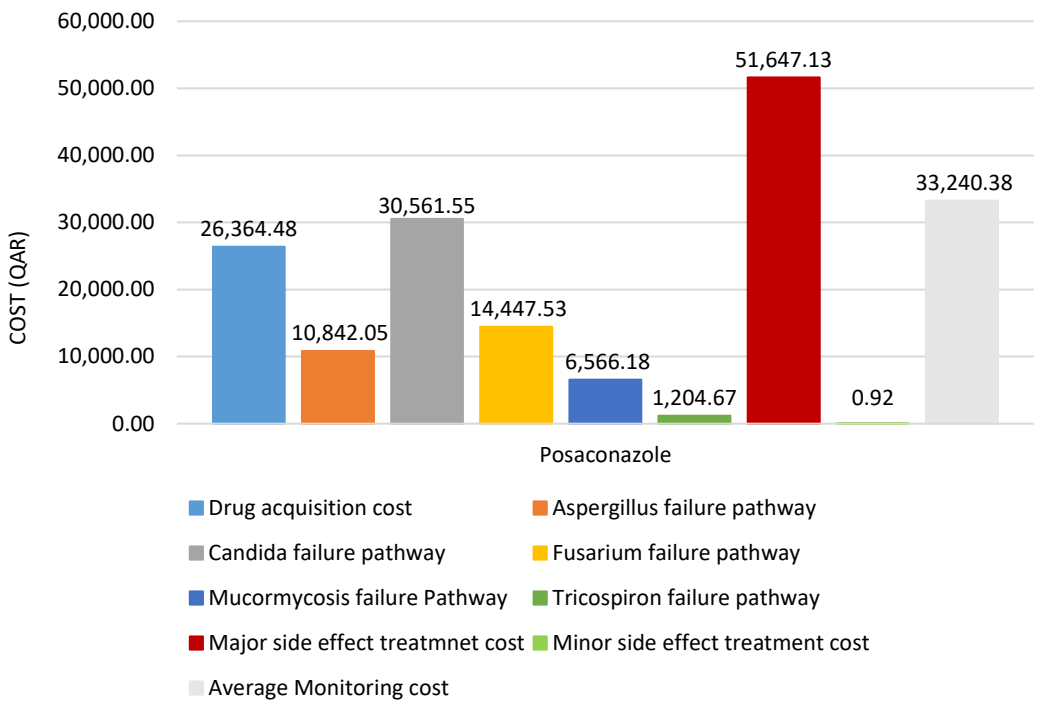


Figure 4. 1. Cost of management breakdown of patients on posaconazole

Table 4. 9. Systemic antifungal agents utilized in the model with their costs

Antifungal agent	DDD (mg)[a]	Mean DDD per month (mg)	Mean cost per month (QAR)
Posaconazole	600	18,000	16,47
Voriconazole (IV)[b]	568	17,040	31,028
Voriconazole (PO)[c]	400	12,000	8,933
Caspofungin	50	1,500	36,119
LAMB	355	10,650	139,615

[a] DDD: defined daily dose (based on patient's average weight at NCCCR), [b] IV: intravenous, [c] PO: oral

As illustrated in Figure 4.2, while the death outcome was associated with the lowest monitoring cost (QAR 19,774), the monitoring in cases of *Aspergillus*, *Fusarium*, and *Tricosporon* infections, and as anticipated, necessitated higher consumption of resources and was, hence, associated with higher cost (QAR 37,590).

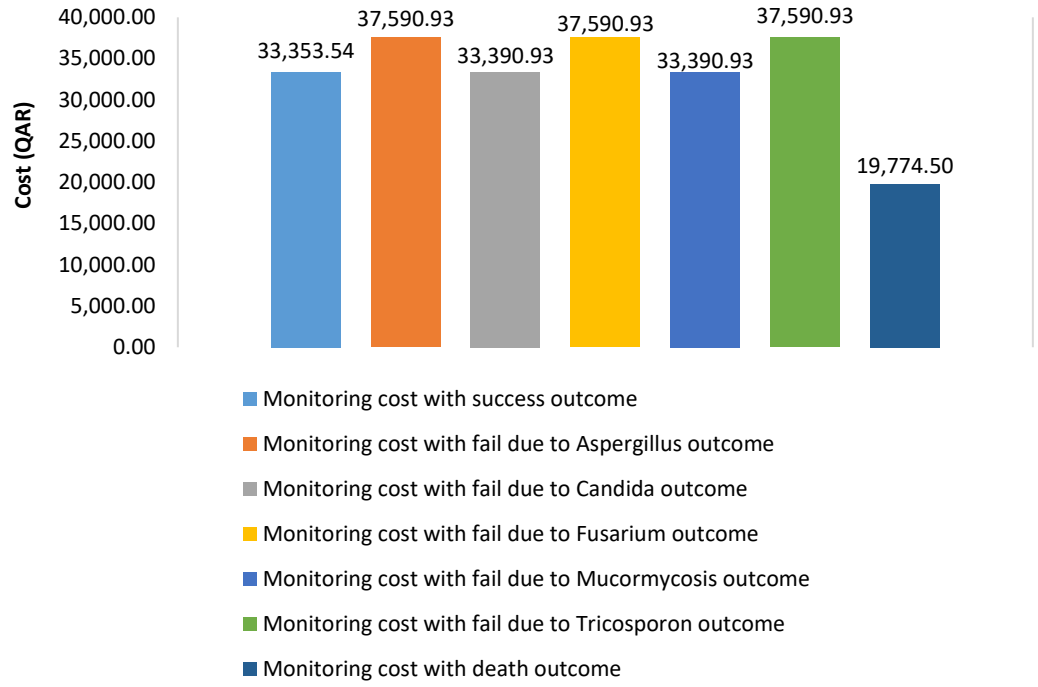


Figure 4. 2. Cost of monitoring based on the outcome

According to the data collected from NCCCR records, the cost of all tests and procedures that were conducted for all included patients throughout the whole following up period (112 days) reached QAR 1,082,066. Table 4.10 provides the cost contribution of each test in the overall cost.

Table 4.10. Breakdown of cost contribution of each monitoring and diagnostic tests in the overall cost

Test /procedure	Cost (QAR)	Contribution (%)
X-rays	25,308	2.3
CT-scan	69,498	6.4
Ultrasound	3,360	0.3
MRI	32,412	3
Nuclear medicine	30,000	2.8
ECG	38,400	3.5
Urine culture	20,148	1.9
Stool culture	4,416	0.4
Blood culture	70,932	6.6
Respiratory culture	4,232	0.4
Parasite stool	1,380	0.1
Acid fast-bacilli	3,496	0.3
Clostridium Difficile toxin	11,000	1
Campylobacter Coli antigen	4,400	0.4
Galactomannan test	21,384	2
PCR virology	13,000	1.2
ALT/AST	103,620	9.6
Creatinine	466,020	43.1
CBC	159,060	14.7
Total costs	1,082,066	100

4.1.1.4. Sensitivity Analysis

One-way Sensitivity Analysis

Table 4.11 Shows the uncertainty range of input variables used in one-way sensitivity analyses.

Table 4.11. **Uncertainty range for variables in sensitivity analysis**

Variable	Uncertainty range		
	Low	Base case	High
Posaconazole cost/bottle	QR2,636.45	QR3,295.56	QR3,964.67
Voriconazole cost/vial (IV)	QR291.34	QR364.18	QR437.02
Voriconazole cost/tablet (PO)	QR119.11	QR148.89	QR178.67
Caspofungin cost/vial (50 mg)	QR963.18	QR1,203.97	QR1,444.76
Caspofungin cost/vial (70 mg)	QR1,258.51	QR1,573.14	QR1,887.77
LAMB cost/vial	QR522.38	QR655.47	QR788.56
Hospitalization cost/day	QR0	QR100	QR200
Accounting for the costs of diagnostic tests	No	Yes	-
Accounting for major ADR occurrence	No	Yes	-

Not including major ADR into the analysis, only limiting ADR to minor, led to a reduction of QAR 26,370 in the cost per patient (QAR 109,802 vs. 83,432). Eliminating the cost of hospitalization just reduced the total cost of therapy by 2.7% (QAR 109,802 vs. 106,796), and the cost of the major ADR and failure due to IFIs pathways by QAR 546 and QAR 2,460, respectively. Not accounting for costs of diagnostic procedures produced 14.6% reduction in the total posaconazole cost to QAR 93,816 per patient. The outcome of ±20% variation in drug prices is as illustrated in Table 4.12. Figures 4.3 - 4.8 illustrate the probability cost-of-therapy curves with variations in drug prices. The cost-of-therapy curve demonstrate the probability of different potential cost values to take place. It is a reflection of the distribution between varied input values within an uncertainty range and the resulting outcome to each.

Table 4.12. Sensitivity to variability in drug prices

Antifungal Medication	Min price (QAR)[a]	Base case price (QAR)	Max price (QAR)	Min total cost (QAR)	Mean total cost (QAR)	Max total cost (QAR)
Posaconazole	2,636	3,295	3,954	108,122	113,486	118,849
Voriconazole (IV)[b]	292	364	437	113,006	113,457	113,900
Voriconazole (PO)[c]	119	149	178	112,806	113,455	114,098
Caspofungin 70 mg	1260	1573	1884	113,376	113,456	113,536
Caspofungin 50 mg	965	1,203	1,442	110,938	113,451	115,967
LAMB	535	666	796	107,279	113,463	119,650

[a] QAR: Qatari Riyal [b] IV: intravenous [c] PO: oral

Figure 4.3. Cost-of-therapy probability curve with posaconazole price change

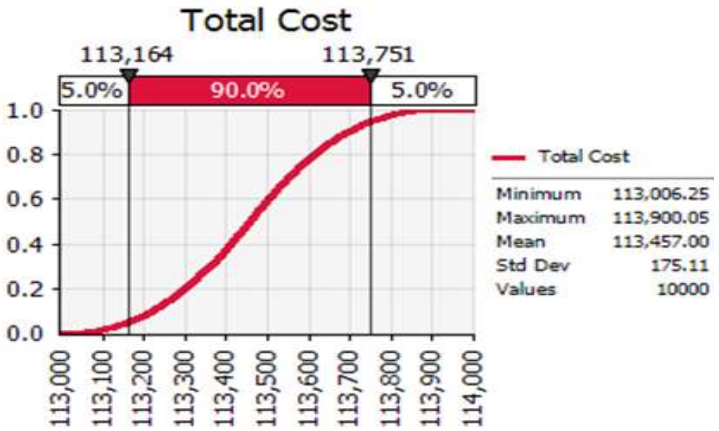


Figure 4.4. Cost-of-therapy probability curve with voriconazole (IV) price change

Figure 4.5. Cost-of-therapy probability curve with voriconazole (PO) price change

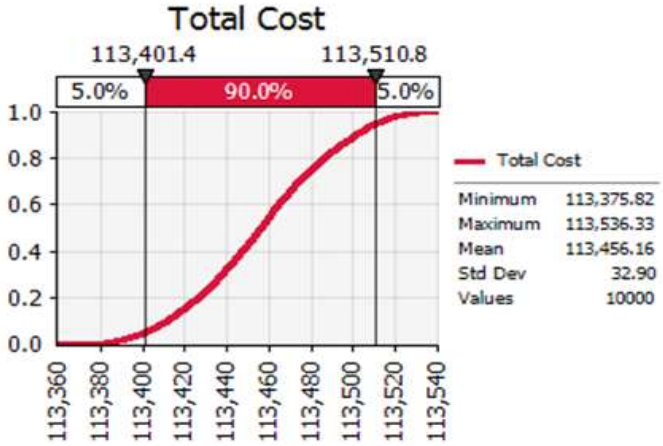


Figure 4.6. Cost-of-therapy probability curve with caspofungin (70 mg vial) price change

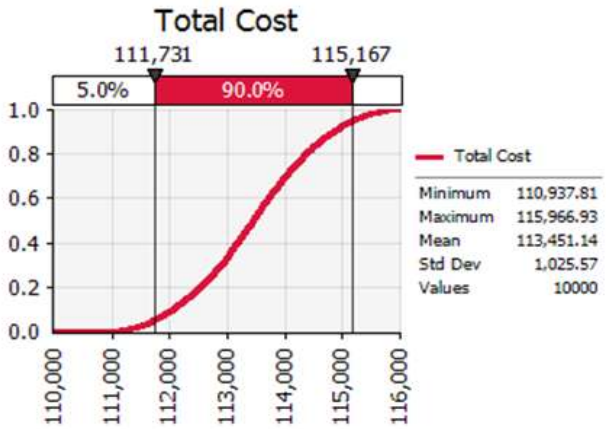


Figure 4.7. Cost-of-therapy probability curve with caspofungin (50 mg vial) price changes

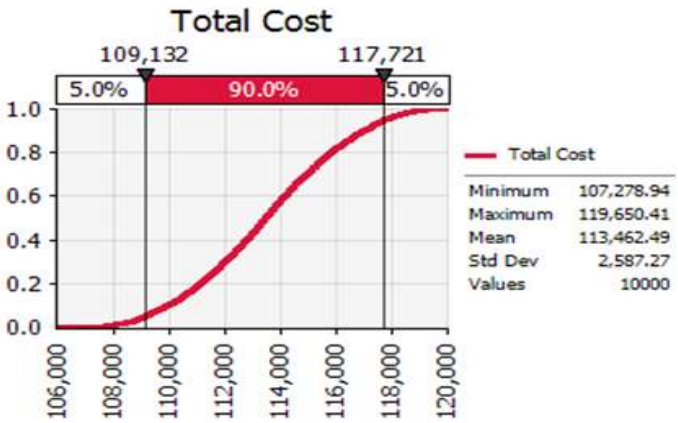


Figure 4.8. Cost-of-therapy probability curve with LAMB price changes

Multivariate Probabilistic Sensitivity Analysis

Table 4.13. Input variables and uncertainty distributions used in multivariate analysis

Input variables	Uncertainty distribution
	posaconazole
Success	Triangular distribution, 0.485,0.5,0.515
With major ADR	Triangular distribution, 0.1261,0.13,0.1339
With minor ADR	Triangular distribution, 0.1482,0.15282,0.1574
Without any ADR	Triangular distribution, (0.6957,0.71717,0.7387
Therapy failure	Triangular distribution, 0.416,0.42857142,0.441
Due to *Aspergillus*	Triangular distribution, 0.285,0.3,0.315
Due to *Candida*	Triangular distribution, 0.57,0.6,0.63
Due to *Fusarium*	Triangular distribution, 0.03166,0.03333,0.03499
Due to Muocormycosis	Triangular distribution, 0.03166,0.03333,0.03499
Due to Tricosporon	Triangular distribution, 0.03166,0.03333,0.03499
Death	Triangular distribution, 0.0679,0.0714285,0.0721

Figure 4.9 shows the probability cost-of-therapy curve with posaconazole in the multivariate analysis. In the tornado analysis shown in Figure 4.10, the model pathways are ranked as per their influence on the study outcome; whereby the success has the highest impact on the therapy cost, and failure due *Fusarium* infection has the least impact on the outcome.

Figure 4.9. Cost-of-therapy probability curve with posaconazole in multivariate analysis

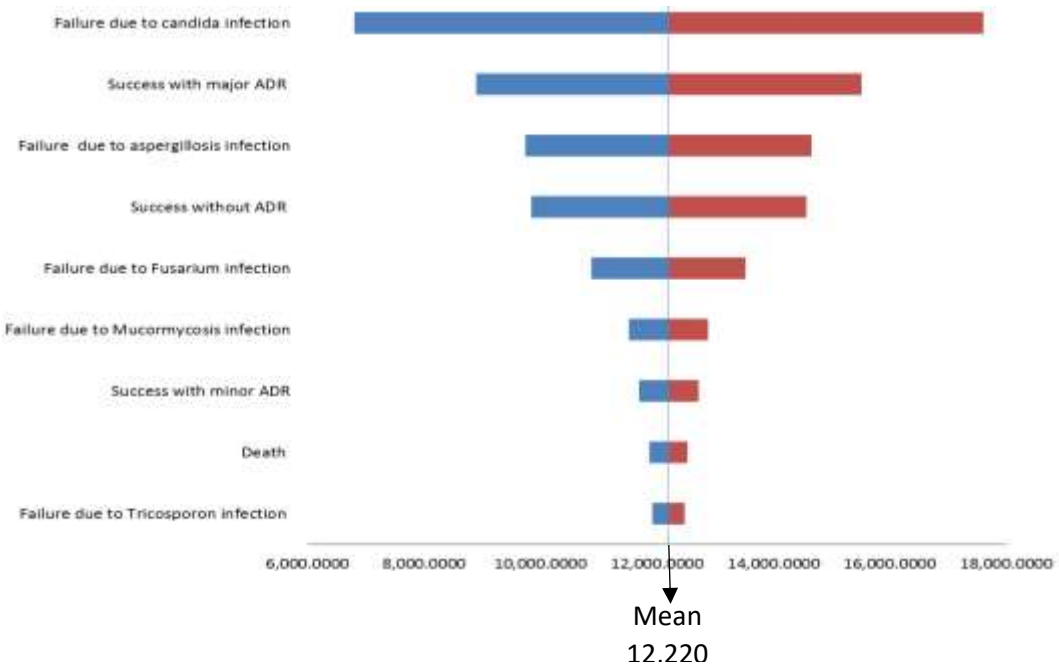


Figure 4. 10. Tornado diagram showing the influence of model outcomes on the average posaconazole overall cost

Scenario Sensitivity Analysis

The analysis of the scenario of sharing the posaconazole bottle among different patients led to a minor reduction in the total average cost of posaconazole, by only QAR 908 per patient.

4.1.2. Evaluation 2: Cost-Effectiveness Analysis of the Comparative Economic Value of Posaconazole Against Fluconazole

4.1.2.1. Study Model and Patients

As indicated in Chapter 3, the current study's economic model, with the structure of which also described in Chapter 3, is based on the multicenter, double-blind and double-dummy, multinational clinical trial by Ullmann et al[103], which was adopted to the local setting via an expert panel and the medical records. Included patients in the trial were above 12 years old and weighed over 34 kg, who had undergone HSCT and had either acute GVHD or chronic GVHD. Patients were excluded if they had a history of proven or probable fungal infections, or if IFI was suspected at baseline, had hepatic dysfunction that is clinically significant as indicated by elevated levels of alanine aminotransferase or aspartate aminotransferase (10 times higher than the normal upper limit), had renal dysfunction, or had taken medications known to interact with azoles.

The study assigned 301 eligible patients to receive posaconazole and 299 patients to receive fluconazole for the prophylaxis against IFI. Patient baseline characteristics and demographic data were similar and comparable between both arms[103].

4.1.2.2. Data Provided by Expert panel

On the basis of the median and range durations provided by Ullmann *et al.*[103], the duration of therapy was estimated to be 80 days with posaconazole and 77 days with

fluconazole. For both prophylactic options, patient monitoring comprised a daily complete blood count (CBC) and renal function tests, while liver function tests were collected twice weekly. As for diagnostic tests, chest X-ray, galactomannan by ELISA, fibrinogen test and C-reactive protein (CRP) were performed on a weekly basis. All patients received a CT scan at least once upon physician request. Blood, urine, sputum, and stool microbiological cultures were performed at least once a week. The 40 patients with major ADR, reported in 107 patients on posaconazole with ADR, had severe hepatotoxicity that necessitates therapy discontinuation. As for the fluconazole arm, severe hepatotoxicity occurred in 29 patients, and the remaining 86 patients (out of 115 patients with ADR) had minor ADR. Out of all 43 IFIs that were detected in the study, aspergillosis occurred in 7 patients receiving posaconazole and 21 patients in the fluconazole arm. *Candida* and *Fusarium* infections occurred in the remaining 15 patients (4 patients with each study drug were infected with *Candida*, while 5 in the posaconazole arm got *Fusarium* infection versus 2 in the fluconazole arm). Medications recommended by the expert panel for the management of minor ADR, which were irrelevant to the study drugs, are clarified in Table 4.14. As per the expert panel, patients with major ADR in NCCCR would have their prophylactic therapy withhold to avoid further harm and will be starting an antifungal treatment once signs of IFI appear, with the choice of therapy being LAMB. This, together with the alternative antifungal therapies to the failure of prophylaxis, are as in Tables 4.15 and 4.16.

Table 4.14. Management medications of minor ADR due to posaconazole and fluconazole

Type of ADR[a]	Management medication	Details (dose, frequency, duration)
Headache	Paracetamol	1000 mg every 6 hours for 10 days as needed
Nausea and vomiting	Metoclopramide	10 mg twice daily for 2 weeks as needed
Diarrhea	Metronidazole	500 mg every 8 hours for 10 days

[a] Minor liver and biliary disorders receive no interventions as per NCCCR practices, where the patient will only be under observation

Table 4. 15. Antifungal discontinuation alternatives due to major ADR, regardless of study drug

Cause of therapy discontinuation[a]	Management medication	Details (dose, frequency, duration)
Severe liver and biliary disorder	LAMB	5 mg/kg/day for 12 weeks

[a] As per expert panel, other major ADR in the trial were not reported in NCCCR and hence will not be of study interest

Table 4. 16. Antifungal alternatives to therapy failure due to IFIs

Causative pathogen [a]	Alternative medication[b]	Details (dose, frequency, duration)
Aspergillus	Voriconazole	Loading dose 6 mg/kg twice daily for day 1, followed by maintenance IV dose 4 mg/kg twice daily for 2 weeks, then oral 200 mg twice daily for 10 weeks
Candida	Caspofungin	Loading dose 70 mg once daily for day 1 followed by 50 mg once daily for 6 weeks
Fusarium	LAMB + Voriconazole	Voriconazole: Loading dose 6 mg/kg twice daily for day 1, followed by maintenance IV dose 4 mg/kg twice daily for 2 weeks, then oral 200 mg twice daily for 10 weeks + LAMB: 5 mg/kg/day for 12 weeks

[a] Minor liver and biliary disorders had no intervention as per NCCCR practice as the patient will be under supervision

[b] The alternative medication is the same for both arms (posaconazole and fluconazole)

4.1.2.3. Model Outcome Probabilities

For each of the posaconazole and fluconazole therapies, outcome probabilities and the duration of therapy in the different patient states were calculated as follow:

- Posaconazole Arm
    - In 301 patients in the posaconazole arm of the Ullmann et al. study the number of deaths in the exposure period = 22, and the number of patients who got IFIs = 16; hence, number of patients in the success arm is: 301 - 22 - 16 = 263, and the probabilities of occurrence of each outcome and consequences are as follow:
        - Therapy success: 263/301 = 0.87.
        - Therapy failure due to IFI: 16/301 = 0.05.
        - Therapy failure due to death: 22/301 = 0.07.
        - Major ADR events: 40/301 = 0.133. 40 major ADR were reported with posaconazole in the trial.
        - Minor ADR, headache: 3/301 = 0.01.
        - Minor ADR, diarrhea: 8/301 = 0.03.
        - Minor ADR, nausea and vomiting: 35/301 = 0.12.
        - Total minor ADR: 46/301 = 15.3.
        - No any ADR events: 1 - (0.133 + 0.153) = 0.714, which adds to 215 patients.
        - Probabilities of causative pathogen: *Aspergillus* = 7/16 = 0.44, *Candida* = 4/16 = 0.25, *Fusarium* = 5/16 = 0.31.
        - If the mean number of days of therapy until failure due to IFI event = 102, percentage of patients who had IFIs = 5.3%, the mean number of days of therapy for all outcomes (success, failure, and death) = 80, and percentage

of patients who had therapy success or death = 100% - 5.3% = 94.7%, then the mean number of days of therapy with patients who had therapy success or death (i.e. X) is: (102 * 0.053) + (X * 0.947) = 80, and so X = 78.8 days of therapy.

- Fluconazole Arm
  - In 299 patients in the fluconazole arm of the Ullmann et al. study the number of deaths in the exposure period =24 and the number of patients who got IFIs = 27; hence, the number of patients in the success arm is: 299 – 24 - 27 = 248, and the probabilities of occurrence of each outcome and consequences are as follow:
    - Therapy success: 248/299 = 0.83.
    - Therapy failure due to IFI: 27/299 = 0.09.
    - Therapy failure due to death: 24/299 = 0.08.
    - Major ADR events: 29/299 =0.0969. 29 major ADR were reported with fluconazole in the trial.
    - Minor ADR, headache: 8/299 = 0.3.
    - Minor ADR, diarrhea: 12/299 = 0.4.
    - Minor ADR, nausea and vomiting: 43/299 = 0.14.
    - Total minor ADR: 63/299 = 0.211.
    - No any ADR events: 1 - 0.0969 + 0.2107 = 0.692, which is 207 patients.
    - Probabilities of causative pathogen: *Aspergillus* = 21/27 = 0.778, *Candida* = 4/27 =0.148, *Fusarium* = 2/27 = 0.074.
    - If the mean number of days of therapy until failure due to IFIs = 88, percentage of patients who had IFI = 9%, mean number of days of therapy

for all outcomes (success, failure, and death) = 77, and percentage of patients who had therapy success or death = 100% - 9% = 91%, then the mean number of days of therapy with patie nts who had therapy success or death (i.e. X) is: (88 * 0.09) + (X * 0.91) = 77, and so X = 75.9 days of therapy.

The clinical outcomes and their probabilities are summarized in Table 4.17.

Table 4. 17. Outcomes and probabilities of posaconazole and fluconazole[103] used in the model

Study clinical outcome	Probability with posaconazole, % (n=301)	Probability with fluconazole, % (n=299)
Therapy success[a]	87.4 (263)	83.0 (248)
With major ADR	13.3 (40)	9.70 (29)
With minor ADR	15.3 (46)	21.1 (63)
Without ADR	71.4 (215)	69.2 (207)
Therapy failure due to IFI	5.30 (16)	9.00 (27)
Aspergillus	44 .0 (7)	77.8 (21)
Candida	25.0 (4)	14.8 (4)
Fusarium	31.0 (5)	7.40 (2)
Death	7.30 (22)	8.00 (24)

[a] All ADR are only considered in the success arm

4.1.2.4. Economic Outcomes

Table 4.18. Summarizes all cost inputs used in the current model.

Table 4.18. Recourse costs

Item	Unit	Unit cost (QR)
Posaconazole	105 mL oral suspension	3295.56
Fluconazole	50 mg oral capsule	6.83
Voriconazole	200 mg IV vial	364.18
	200 mg oral tablet	148.89
Caspofungin	50 mg IV vial	1203.97
	70 mg IV vial	1573.14
LAMB	50 mg IV vial w/microfilter	655.47
Paracetamol	500 mg oral tablet	0.03
Metronidazole	500 mg oral tablet	0.07
Metoclopramide	10 mg oral tablet	0.05
Chest X-ray	1 test	36
CT scan	1 test	486
Ultrasound scan	1 test	84
MRI scan	1 test	876
Sputum culture	≥1 tests (1 culture)	92
Urine culture	1 test (1 culture)	92
Stool culture	≥ 1 tests (1 culture)	92
Blood culture	1 test (1 culture)	92

Skin biopsy	1 test	123
Galactomannan (ELISA)	1 test	66
Co-agulation test	1 test	42
Fibrinogen	1 test	28
CRP	1 test	24
Complete blood count	1 test	30
Renal function test	1 test	90
Liver function test	1 test	30
Hospitalization	Inpatient per day	100

All costs are based on pricing system of NCCCR

Based on success definition of the current project (success with no major ADR), posaconazole and fluconazole were of similar effectiveness to prevent IFIs (0.76 vs. 0.75). As reported by Ullmann et al, posaconazole was associated with a slightly lower rate of IFIs than fluconazole (0.05 vs. 0.09, odds ratio, 0.56; 95% CI, 0.30–1.07; p = 0.07). Prophylaxis with fluconazole was associated with a rate of success with minor ADR of 0.17 compared to 0.13 with the posaconazole prophylaxis. On the other hand, for success rate with major ADR, the rate was lower in the fluconazole recipients than those taking posaconazole (0.08 vs. 0.11). While failure due to *Fusarium* infection was of a slightly lower rate with fluconazole than with posaconazole (0.01 vs. 0.02), the rate of the *Aspergillus* infection was higher in the fluconazole arm (0.07 vs. 0.02). The overall therapy cost of each of posaconazole and fluconazole is as in Table 4.19.

The estimated total average costs (including managing side effects, drug discontinuation, monitoring, and treatment in case of prophylaxis failure) were QAR 80,463 per patient in the fluconazole arm and QAR 134,116 per patient in the posaconazole arm, with a mean difference of QAR 53,653 in favor of fluconazole. Posaconazole was also associated with a higher overall cost of success (QAR 114,145 versus QAR 66,243), and a higher total cost of managing IFIs (QAR 14,221 versus QAR 11,018), respectively. The cost of treating major ADR was QAR 17,877 higher with posaconazole.

Table 4. 19. Clinical outcomes, probabilities and costs of consequences as per the study model

Alternative	Outcome Event	Probability	Cost (QAR)	Average Cost (QAR, 95% CI[a])
Posaconazole	Success with major ADR	0.11	54,339	134,116 (133,915-134,317)
	Success with minor ADR	0.13	10,506	
	Success without ADR	0.63	49,300	
	Failure due to aspergillosis infection	0.02	3,321	
	Failure due to candida infection	0.01	2,028	
	Failure due to Fusarium infection	0.02	8,872	
	Death	0.07	5,750	
Fluconazole	Success with major ADR	0.08	36,462	80,463 (80,342-80,584)
	Success with minor ADR	0.17	6,973	
	Success without ADR	0.57	22,808	
	Failure due to aspergillosis infection	0.07	6,432	
	Failure due to candida infection	0.01	1,356	
	Failure due to Fusarium infection	0.01	3,230	
	Death	0.08	3,202	

For the purpose of the cost-effectiveness analysis, the 'success' outcome of interest in the simulation model was the success with no major ADR within 112 days of receiving the prophylactic therapy. Hence, the probability of therapy success with posaconazole is: 0.13 + 0.63 = 0.76, while this is: 0.174 + 0.571 = 0.75 with fluconazole. Taking this and the higher cost of posaconazole in consideration, a Decremental Cost-Effectiveness Ratio (DCER) of fluconazole over posaconazole for each lost case of success was calculated as follows:

$$DCER = \frac{Cost\ of\ posaconazole - Cost\ of\ fluconazole}{Effect\ of\ posaconazole - Effect\ of\ fluconazole} = \frac{134{,}116.25 - 80{,}463.38}{0.76 - 0.75} = \text{QAR}$$

3,922,618 to be saved with fluconazole for each lost case of success

Figure 4.11 illustrates the cost components and their proportional contribution to the total costs of fluconazole and posaconazole therapies.

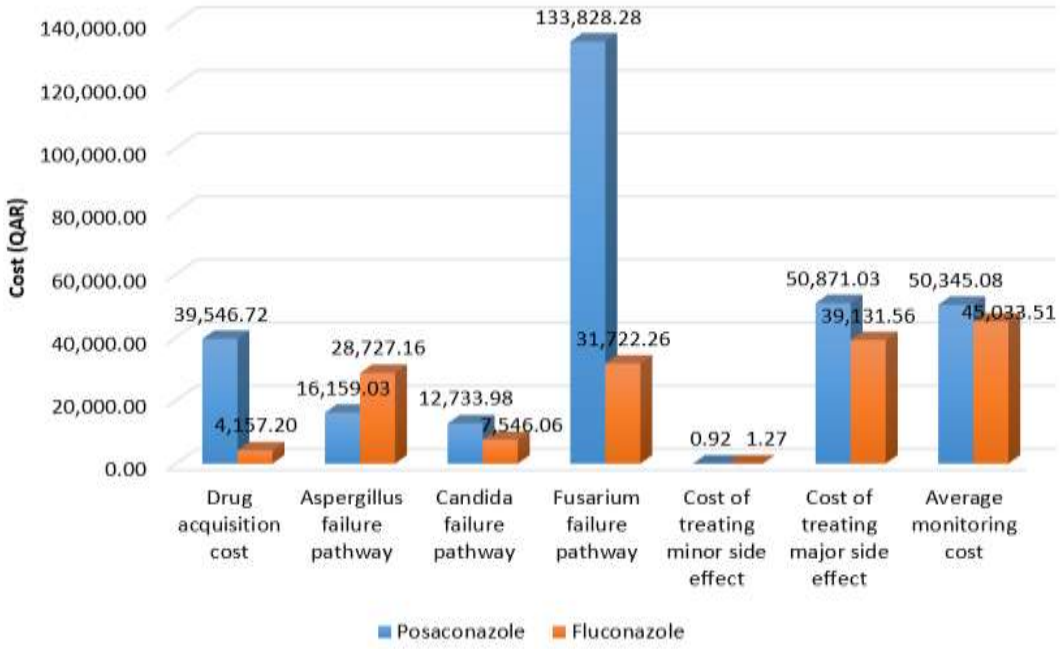


Figure 4.11 Breakdown of cost components for both antifungal alternatives

As for hospitalization and its cost, patients at the NCCCR receive prophylaxis therapy through visiting the outpatient clinic, where no need for hospitalization is indicated. Cost of hospitalization was only considered in two situations; when patients get IFI and, hence, require treatment therapy and/or when a major liver and biliary ADR occurs, seeing that patients would discontinue the prophylaxis therapy and will need to be under close monitoring. Interestingly, the cost of hospitalization with posaconazole was slightly lower than that associated with fluconazole (QAR 8,442 versus QAR 8,610, per patient).

4.1.2.5. Sensitivity Analysis

One-way Sensitivity Analysis

Key variables, the ranges over which they were varied, and their outcomes are as in Table 4.20. Important is that the study outcomes were not sensitive to any uncertainty that was associated with any of the model's key inputs.

Table 4.20. Variation range for variables used in one-way sensitivity analyses with their cost-effectiveness outcome

Variable	Variation range			Average posaconazole cost (QAR)	Average fluconazole cost (QAR)	DCER of lost success (QAR)[a]
	Low	Base case	High			
Posaconazole cost/bottle	QR2,636.45	QR3,295.56	QR3,964.67	142,810 vs. 126,782	91,239	3,770,438 vs. 2,598,548
Fluconazole cost/tablet	QR43.76	QR54.70	QR65.46	134,796	92,297 vs. 90,182	3,107,174 vs. 3,261,812
Voriconazole cost/vial	QR291.34	QR364.18187	QR437.02	135,091 vs. 133,823	91,807 vs. 90,176	3,164,480 vs. 3,191,130
Voriconazole cost/tablet	QR119.11	QR148.89377	QR178.67			
Caspofungin cost/vial (50 mg)	QR963.18	QR1,203.96581	QR1,444.76	134,253 vs. 133,983	90,880vs. 90,608	3,171,051 vs. 3,171,184
Caspofungin cost/vial (70mg)	QR1,258.51	QR1,573.13721	QR1,887.77			
LAMB cost/vial	QR522.38	QR655.47	QR788.56	144,463 vs. 123,773	97,866 vs. 83,622	3,406,780 vs. 2,935,454
Hospitalization cost/day	QR0	QR100	QR200	136,141 vs. 133,451	92,638 vs. 89,840	3,180,528 vs. 3,188,456
Duration of therapy in posaconazole	-	78.8 days for success and death pathway 102 days for failure pathway	53 days for success and death pathway 62 days for failure pathway[a]	121,665	91,239	2,224,490

[a] The estimated durations are based on the actual average duration of prophylaxis identified in e-medical records at NCCCR

Cont. Table 4.20. Variation range for variables used in one-way sensitivity analyses with their cost-effectiveness outcome

Variable	Variation range			Average posaconazole cost (QAR)	Average fluconazole cost (QAR)	DCER of lost success (QAR)[a]
	Low	Base case	High			
Duration of therapy in fluconazole	-	75.9 days for success and death pathway 88 days for failure pathway	53 days for success and death pathway 62 days for failure pathway	134,796	77,569	4,183,922
Fusarium probability in posaconazole arm	0.25 (-20%)	0.31	-	132,285	80,463	3,788,735
Fusarium probability in fluconazole arm	0.06 (-20%)	0.07		134,116	79,675	3,980,239
Major ADR in posaconazole arm	0.05 (-60%)	0.13		101,513	80,463	1,538,935
Major ADR in fluconazole arm		0.10	0.2 (+100%)	134,116	116,926	1,256,807
Counting for the costs of diagnostic tests	No	Yes	-	117,336	72,813	3,255,144

[a] The estimated durations are based on the actual average duration of prophylaxis identified in e-medical records at NCCCR

Multivariate Probabilistic Sensitivity Analysis

The input variables and their uncertainty distributions are shown in Table 4.21. Importantly, out of 10,000 simulations, the multivariate probabilistic sensitivity analysis of the economic model calculated that only in <5% of cases the DCER with posaconazole would be reduced to less than QAR 1,200,000 per success. The model outcome was robust in 95.6% of cases, with 4.4% chance for posaconazole to become dominant over fluconazole; higher rate of success without major ADR and lower overall cost.

Table 4. 21. Input variables and uncertainty distributions used in Monte Carlo simulation

	Uncertainty distribution	
Input variables	posaconazole	fluconazole
Success		
With major ADR	Triangular distribution, 0.1067,0.11,0.1133	Triangular distribution, 0.0776,0.08,0.0824
With minor ADR	Triangular distribution, 0.1261,0.13,0.1339	Triangular distribution, 0.1649,0.17,0.1751
Without any ADR	Triangular distribution, 0.6111,0.63,0.6489	Triangular distribution, 0.5548,0.572,0.589
Therapy failure		
Due to *Aspergillus*	Triangular distribution, 0.0194,0.02,0.0226	Triangular distribution, 0.0679,0.07,0.0721
Due to *Candida*	Triangular distribution, 0.0097,0.01,0.0103	Triangular distribution, 0.0097,0.01,0.0103
Due to *Fusarium*	Triangular distribution, 0.0194,0.02,0.0206	Triangular distribution, 0.0097,0.01,0.0103
Death	Triangular distribution, 0.0679,0.07,0.0721	Triangular distribution, 0.0776,0.08,0.0824

The tornado diagram in Figure 4.12 shows the rank of different study outcomes as per their influence on the study outcome, with the top influencing outcome being the success without ADR, and the least outcome of impact being the failure due to *Candida* infections.

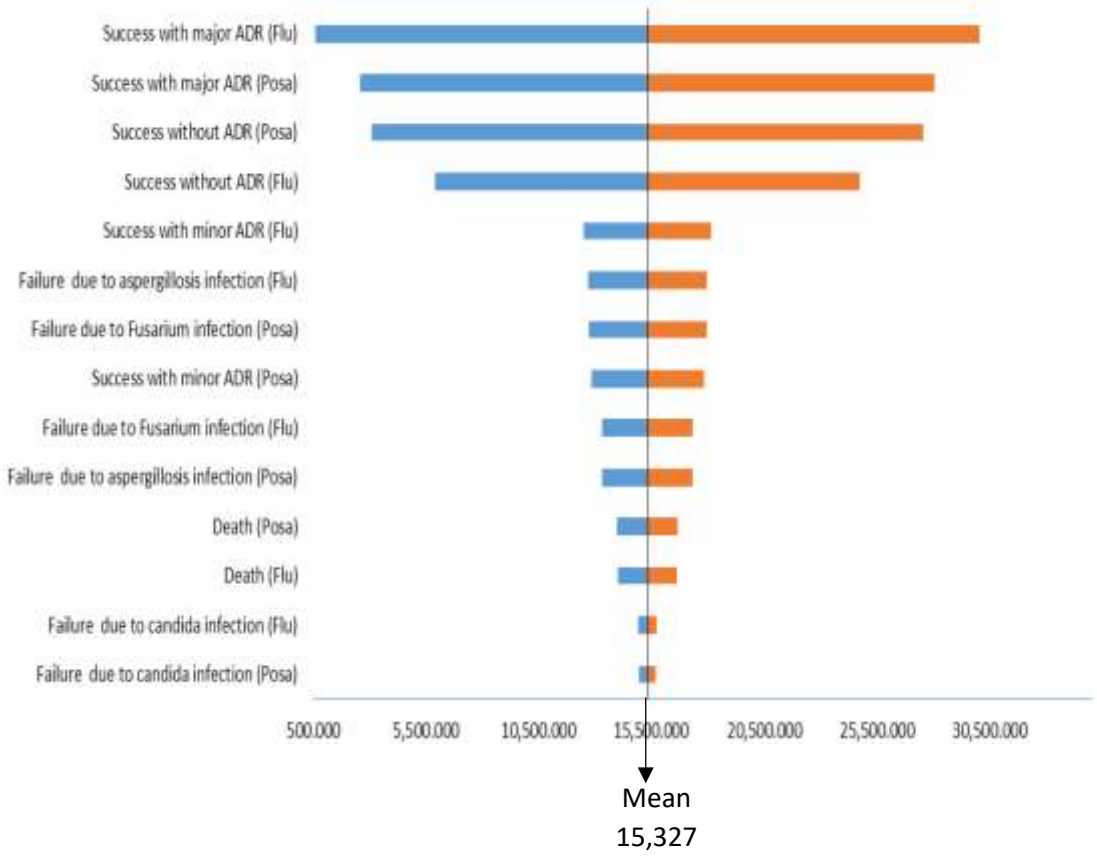


Figure 4. 12. Tornado diagram of all variables with their extent of influence on cost using the Monte Carlo simulation

Scenario Sensitivity Analysis

The model was insensitive to the scenario of sharing the posaconazole bottles among patients, unlike the practice in NCCCR, Qatar. The DCER of fluconazole changed to QAR 2,996,157 saved per lost case of success.

4.2. Phase 2: Systematic Review of Methodological Trends and Gaps, and the Reporting Quality of Comparative Economic Evaluations on the Use of Systemic Antifungal Agents Used for Prophylaxis Against IFI

4.2.1. Inclusion and Study Description

Out of 841 articles attained from the systematic search of the literature, only 19 articles were eligible for inclusion in the study analysis (Figure 4.13). Table 4.22 provides a brief description of the included studies. The years the studies were conducted between 2008 and 2013, except for one that was published earlier in 1997. Seven studies were conducted in the United States (USA)[82,86,87,102105,106,107], whereas the remaining studies reported data from Australia[90,91] , Canada[108], Spain[109,110,111], The Netherland[81,85], Korea[83], Greece[112], France[113], Germany[111], and Switzerland[88], with 1 to 2 studies in each.

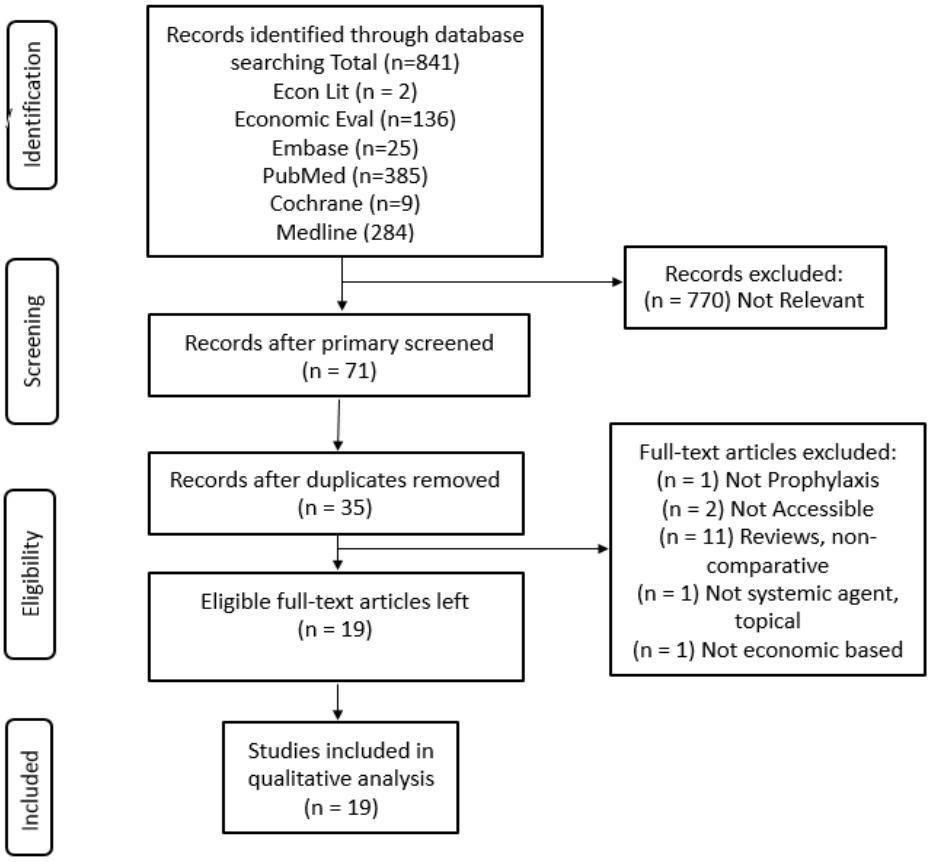


Figure 4. 13. Flowchart of literature search and inclusion

Table 4. 22.Characteristics and main results of included economic articles

Record No.	Last author, year	Country	Economic analysis method	Perspective, time horizon	Source of clinical data	Intervention	Comparator	Sensitivity analysis	Main economic finding
Neutropenia patients with AML[a],MDS[b]									
1	de Vries, 2006[81]	Germany & Netherland	Cost-effectiveness	Hospital, less than 1 year	Rinaldi[114] & Kanda[137]	Itraconazole	Fluconazole or placebo	One-way	Itraconazole dominated fluconazole /placebo
2	Stam, 2008[85]	Netherland	Cost-effectiveness	Hospital,100 days	Cornely[89]	Posaconazole	fluconazole or itraconazole	One way and Scenario	Posaconazole dominated fluconazole /itraconazole
3	Collins, 2008[86]	USA	Cost-effectiveness	Hospital,100 days	Cornely[89]	Posaconazole	fluconazole or itraconazole	One-way	Posaconazole dominated fluconazole /itraconazole
4	Dranitsaris, 2011[108]	Canada	Cost-effectiveness	Hospital, until no IFI or IFI happen with death or survival	Cornely[89]	Posaconazole	fluconazole or itraconazole	One-way	Posaconazole dominated fluconazole /itraconazole
5	Papadopoulos, 2013[105]	USA	Cost-effectiveness	Payer,100 days	Cornely[89]	Posaconazole	fluconazole or itraconazole	One-way & Multivariate	Posaconazole dominated fluconazole /itraconazole

[a] AML: Acute Myeloid Leukaemia [b] MDS: Myelodysplastic Syndrome

Cont. Table 4.22. Characteristics and main results of included economic articles

Record No.	Last author, year	Country	Economic analysis method	Perspective, time horizon	Source of clinical data	Intervention	Comparator	Sensitivity analysis	Main economic finding
6	Athanasakis, 2013[132]	Greece	Cost-effectiveness	Third party payer,100 days	Cornely[89]	Posaconazole	fluconazole or itraconazole	Multiple way	Requires ICER
7	Grau, 2012[109]	Spain	Cost-effectiveness	Hospital, until death of IFI (markov)	Cornely[89] & Kantarjian[115]	Posaconazole	fluconazole or itraconazole	One-way & multivariate	Posaconazole dominated fluconazole /itraconazole
8	Michallet, 2011[113]	France	Cost-effectiveness	Hospital, until death of IFI or other cause of death (markov)	Cornely[89]	Posaconazole	fluconazole or itraconazole	One-way & multivariate	Posaconazole dominated fluconazole /itraconazole
9	Greiner, 2010[88]	Switzerland	Cost-effectiveness	Hospital ,100 days	Wingard[121] & Kantarjian[115]	Posaconazole	fluconazole or itraconazole	One-way	Posaconazole dominated fluconazole/itraconazole among neutropenic patients only
10	O'Sullivan, 2009[87]	USA	Cost-effectiveness	Payer,100 days	Cornely[89]	Posaconazole	fluconazole or itraconazole	One-way, & scenario	Posaconazole dominated fluconazole /itraconazole

[a] AML: Acute Myeloid Leukaemia
[b] MDS: Myelodysplastic Syndrome
[c] HSCT: Haematopoietic Stem Cell Transplant
[d] AIDS: Acquired Immune Deficiency Syndrome

Cont. Table 4.22. Characteristics and main results of included economic articles

Record No.	Last author, year	Country	Economic analysis method	Perspective, time horizon	Source of clinical data	Intervention	Comparator	Sensitivity analysis	Main economic finding
11	O'Sullivan, 2012[102]	USA	Cost-effectiveness	Payer,112 days	Ullmann[103]	Posaconazole	Fluconazole	One-way	Posaconazole is in the range of accepted criteria for cost-effectiveness
12	Schonfeld, 2008[82]	USA	Cost-effectiveness	Hospital,4 weeks	Burik[116]	Micafungin	Fluconazole	One-way	Micafungin dominated fluconazole
13	Sohn, 2009[83]	Korea	Cost-effectiveness	Payer, one year	Park[117], Moeremans[118], Burik[116], Min[119] & Briggs[120]	Micafungin	Fluconazole	One-way	Micafungin dominated fluconazole
14	Mauskopf, 2013[106]	USA	Cost-effectiveness	Hospital, one year	Wingard[121]	Voriconazole	Fluconazole	One-way	Voriconazole is not dominant

[a] AML: Acute Myeloid Leukaemia
[b] MDS: Myelodysplastic Syndrome
[c] HSCT: Haematopoietic Stem Cell Transplant
[d] AIDS: Acquired Immune Deficiency Syndrome

Cont. Table 4.22. Characteristics and main results of included economic articles

Record No.	Last author, year	Country	Economic analysis method	Perspective, time horizon	Source of clinical data	Intervention	Comparator	Sensitivity analysis	Main economic finding
HSCT									
15	Sánchez-Ortega, 2013[101]	Spain	Cost-effectiveness	Hospital,100 days	Sanchez-Ortega[101]	Posaconazole	Itraconazole	One-way	Requires ICER
16	de la Ca´mara, 2009[111]	Spain	Cost-effectiveness	Hospital,112 days	Ullmann[103]	Posaconazole	Fluconazole	One-way & multivariate	Requires ICER
AML									
17	Heng, 2013[91]	Australia	Cost-effectiveness	Hospital, not applicable	Chart review	Fluconazole	Posaconazole or Voriconazole	One-way, multivariate & scenario	Requires ICER
18	Al-Badriyeh, 2010[90]	Australia	Cost-effectiveness	Hospital, until therapeutic success or death	Chart review	Voriconazole	Posaconazole	One-way & scenario	Posaconazole dominated voriconazole
AIDS									
19	Scharfstein, 1997[107]	USA	Cost-effectiveness	Third party payer, Until no more than 0.1% of the original cohort is still alive (Markov)	Powderly [122]	Fluconazole	Placebo	One-way & two-way	Requires ICER

[a] AML: Acute Myeloid Leukaemia
[b] MDS: Myelodysplastic Syndrome
[c] HSCT: Haematopoietic Stem Cell Transplant
[d] AIDS: Acquired Immune Deficiency Syndrome

4.2.2. Study Population

Of the 19 included studies, around three quarter of them (n=14) were conducted among neutropenic patients suffering from AML and MDS, two studies focused on AML patients only, two focused on HSCT, and one included AIDS patients (Table 4.22). Age of patients was >13 years old in ten studies, and the age in the remaining (n=9) was in the range of 30-55 years old.

4.2.3. Study Comparators

Comparators among studies were posaconazole, fluconazole, itraconazole, micafungin, voriconazole, and placebo. Posaconazole was the most frequently involved drug in evaluations, where it was evaluated 23 times; versus itraconazole in 9 studies, fluconazole in 11 studies, voriconazole in 2, and once against placebo. Besides 11 evaluations against posaconazole, fluconazole was evaluated against itraconazole and micafungin twice each, and against voriconazole and placebo once each. Study drugs and comparators are as in Table 4.22 and Figure 4.14.

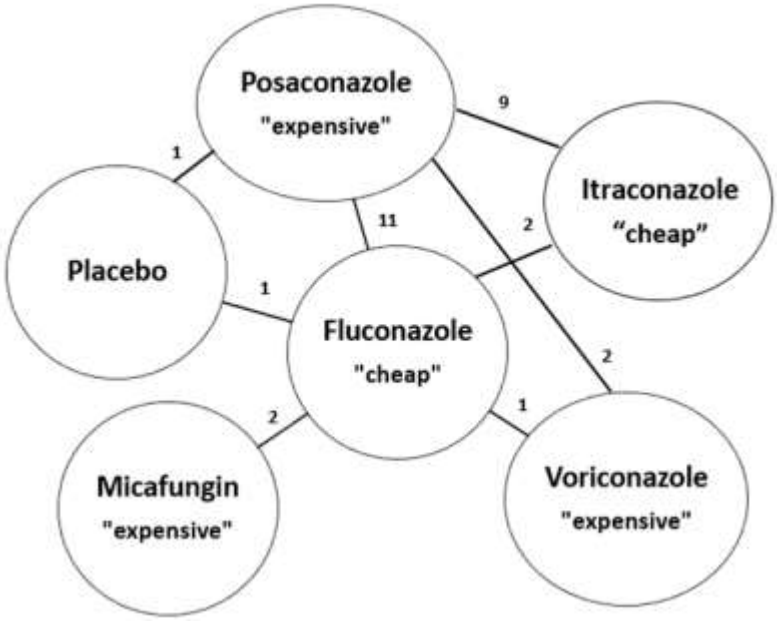


Figure 4. 14. Study comparisons

4.2.4. Method of Economic Evaluation

With regards to the design of the pharmacoeconomic evaluations, all 19 articles utilized cost-effectiveness methodology and, except in two of them, they included decision analytic modeling[82,110]. Table 4.23 shows a CEA grid that summarizes how cost and outcomes compare among studies, with a state of dominance in 12 studies, mostly in favor of posaconazole, requiring no ICERs to be calculated. As for the remaining 7 articles, only five required ICER measurement due to an alternative having both higher effect and cost[107,110,111,112] or lower effect and cost[91]. As summarized in Table 4.24, 12 studies incorporated cost per life year gained as an economic measure, 7 used the cost per IFI

avoided outcome, 2 used the cost per QALY outcome, and 6 included the cost saving per patient measure.

Table 4.23. CEA grid summary of study outcomes

Cost/Effect	Higher Effect	Same Effect	Lower Effect
Higher Cost	4[a]		
Same Cost			
Lower Cost	12 (9 for posaconazole)	2[b]	1[c]

[a] Scharfstein et al, 1997107, Athanasakis et al, 2013112, Sánchez-Ortega et al, 2013110, and de la Ca´mara et al, 2009111
[b] O'Sullivan et al, 2012[102] and Mauskopf et al, 2013106
[c] Heng et al, 2013[91]

Table 4.24. Outcome measures of economic evaluations

Type of outcome measure	Cost per life year gained	Cost per IFI avoided	QALY	Cost saving per patient.
Last author[a]	Papadopoulos, 2013 O'Sullivan, 2009 O'Sullivan, 2012 Mauskopf, 2013 Scharfstein, 1997 Dranitsaris, 2011 Grau, 2012 Sánchez-Ortega, 2013 de la Ca´mara, 2009 Stam, 2008 Athanasakis, 2013 Greiner, 2010	O'Sullivan, 2009 O'Sullivan, 2012 Mauskopf, 2013 Sánchez-Ortega, 2013 de Vries, 2006 Athanasakis, 2013 Greiner, 2010	Scharfstein, 1997 Stam, 2008	Collins, 2008 Schonfeld, 2008 Heng, 2013 Al-Badriyeh, 2010 Sohn, 2009 Michallet, 2011

[a] Different outcome measures can be reported under the same author as some economic evaluations included more than one outcome measure

4.2.5. Clinical Inputs and Definitions

Outcomes of interest were extensively variable among the different decision models. Figure 4.15 illustrates all the different clinical measures that were used in studies, noting that a study can include several comparative models. A summative decision tree that includes all decision analytic trees in the studies' models is shown in Appendix 9.

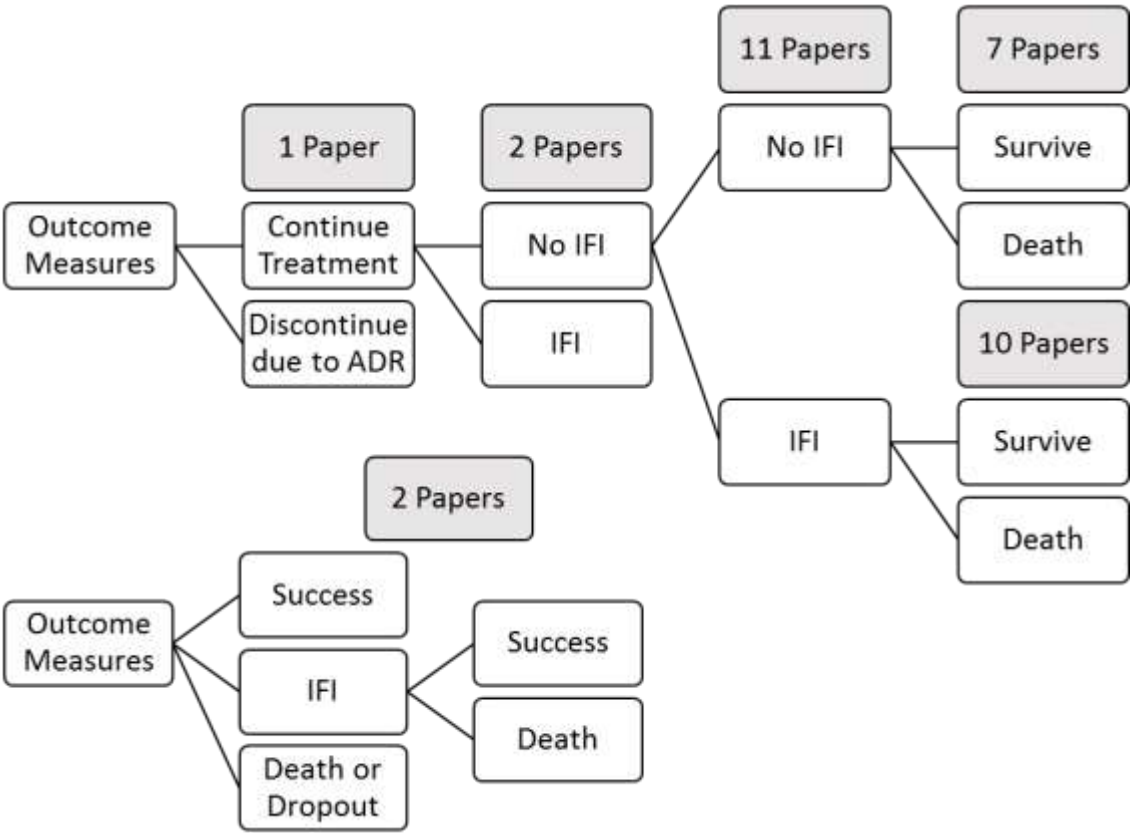


Figure 4.15. Different clinical outcome pathways used in study models

Important is that the way different researchers defined similar outcome measures in studies were different. For example, success was defined by Sohn et al[83]. as the absence of proven, probable, or suspected systemic fungal infection through the end of prophylactic therapy and the entire analysis period, while Al-Badriyeh et al[90]. defined it as the absence of initial antifungal discontinuation for the duration of the induction stage. Another example is the definition of IFI. Mauskopf et al106. defined this as having proven, probable, or presumptive IFI at 180 days post-therapy, whereas Grau et al109. followed the criteria of the European Organization for the Research and Treatment of Cancer and the Mycoses Study Group for defining patients with IFIs[123]. Appendix 10 includes further details on types of outcome measures used and their definitions.

4.2.6. Source of Clinical Data

Of the 19 articles, 16 extracted clinical data from published RCTs, where more than half of the studies (n=9) utilized the same RCT, by Cornely et al[89]. Details on the resources of clinical inputs in models are clarified in Appendix 10**.** The remaining three studies relied on data extracted from chart reviews[90,91] or meta-analysis[81] studies.

4.2.7. Study Perspective

Except for 4 articles that were based on the payer perpective[83,87,102,105] and two articles that were based on the third party payer107,112, studies (n=13) adopted the hospital perspective, including medications, ICU stay, and hospital stay costs. However, the types of costs used were mostly inappropriate. While only direct medical costs were considered in all studies, six studies reported social perspectives of analysis.

4.2.8. Modeling and Time Adjustment

89.5% of studies (n=17) included decision analysis modeling, including 9 Markov models for simulating the future use of medications. In the latter, discounting of cost was conducted, with the discount rate used being 3% in most studies, except in two articles that used discount rates of 1.5%[129] and 5%105. One study, De Vries et al[81]. did not use neither discounting nor inflation, which they justified by a less than 1 year follow up where no cost adjustment is required. On the other hand, the study by O'Sullivan et al.[102] utilized, as appropriate, both discounting and inflation. In the 10 studies that adjusted costs due to inflation, the consumer price index was appropriately used as relevant to the year of study.

4.2.9. Sensitivity Analysis

Sensitivity analysis was performed in all included articles. The majority of articles (n=11), however, used only one-way sensitivity analysis as the easiest to perform and understand, while the remaining combined the one-way analysis with two-way analysis107, multivariate109,111,113, or alternative scenario analyses[102,90,91,129].

4.2.10. Statistical Analysis

Only 3 of all the included studies had some statistical analysis performed. The Kaplan–Meier analysis was applied by O'sullivan et al.[102], the bootstrap resampling was conducted by Mauskopf et al.106, and the bootstrap procedure with a bias-corrected percentile method was performed by Sánchez-Ortega et al110.

4.2.11. Quality Assessment of the Studies

The CHEERS checklist was used to assess the reporting quality of the pharmacoeconomics evaluation articles included. Table 4.25 provides a summary of the quality assessment in all 19 articles.

Table 4.25. Quality assessment of included papers of pharmacoeconomics evaluations based on CHEERS checklist

Section/Item	Last author, date									
	de Vries, 2006	Stam, 2008	Collins, 2008	Dranitsaris, 2011	Papadopoulos, 2013	Athanasakis, 2013	Grau, 2012	Michallet, 2011	Greiner, 2010	O'Sullivan, 2009
Title/Abstract/Introduction										
Title	PA	PA	A	A	PA	A	A	PA	A	A
Abstract	A	PA	A	PA	PA	A	A	PA	PA	PA
Background/objectives	PA	A	A	A	PA	A	A	A	A	PA
Methods										
Target population/subgroups	A	A	PA	A	A	A	A	A	A	A
Setting/location	A	A	A	A	PA	A	A	A	A	A
Study perspective	A	A	A	A	A	A	A	A	A	A
Comparators	A	A	A	PA	NA	NA	A	PA	NA	A
Time horizon	PA	A	A	PA	A	A	PA	PA	A	A
Discount Rate	NA	A	NA	NA	A	A	A	A	A	A
Choice of health outcome	A	A	A	A	A	A	A	A	A	A
Measurement of effectiveness	A	A	A	A	A	A	A	A	A	A
Estimating resources and costs	A	A	A	PA	A	A	A	A	A	A
Currency, price date, conversion	A	A	A	A	A	PA	A	A	NA	A
Choice of model	PA	PA	PA	PA	PA	PA	PA	PA	PA	PA

A: Adequate (information was explicitly presented in the text)
PA: Partially adequate (information was NOT explicitly presented, but was suggested)
NA: Not adequate (no information about the matter was available in the text)

Cont. Table 4.25. Quality assessment of included papers of pharmacoeconomics evaluations based on CHEERS checklist

Section/Item	Last author, date									
	de Vries, 2006	Stam, 2008	Collins, 2008	Dranitsaris, 2011	Papadopoulos, 2013	Athanasakis, 2013	Grau, 2012	Michallet, 2011	Greiner, 2010	O'Sullivan, 2009
Title/Abstract/Introduction										
Assumptions	A	A	A	A	A	A	A	NA	A	A
Analytical model	PA	PA	PA	PA	PA	PA	PA	PA	PA	PA
Results										
Study parameters	A	A	NA	A	A	A	A	A	A	A
Incremental costs and outcomes	A	A	A	A	A	A	A	A	A	A
Characterizing uncertainty	PA	A	A	PA	PA	PA	PA	PA	PA	A
Characterizing heterogeneity	PA	A	A	PA	PA	PA	PA	PA	PA	A
Discussion/others										
Study findings, limitation, generalizability, current knowledge	PA	A	A	A	A	PA	PA	A	A	PA
Source of funding	A	A	NA	A	A	A	A	A	A	A
Conflict of interest	A	NA	A	NA	NA	A	A	A	A	NA

A: Adequate (information was explicitly presented in the text)
PA: Partially adequate (information was NOT explicitly presented, but was suggested)
NA: Not adequate (no information about the matter was available in the text)

Cont. Table 4.25. Quality assessment of included papers of pharmacoeconomics evaluations based on CHEERS checklist

Section/Item	Last author, date O'Sullivan, 2012	Schonfeld, 2008	Sohn, 2009	Mauskopf, 2013	Sánchez-Ortega, 2013	de la Ca´mara, 2009	Heng, 2013	Al-Badriyeh, 2010	Scharfstein, 1997
Title/Abstract/Introduction									
Title	A	PA	A	A	A	A	A	A	PA
Abstract	PA	A	A	PA	A	PA	PA	PA	PA
Background/objectives	A	A	A	PA	A	A	PA	PA	A
Methods									
Target population/subgroups	A	A	A	A	A	A	A	A	PA
Setting/location	A	A	A	A	A	A	A	A	A
Study perspective	A	A	A	A	A	A	A	A	A
Comparators	A	A	A	PA	A	A	A	PA	A
Time horizon	A	A	A	A	A	A	NA	PA	A
Discount rate	A	NA	NA	NA	NA	A	NA	NA	NA
choice of health outcome	A	A	A	A	A	A	A	A	A
Measurement of effectiveness	A	A	A	A	A	A	A	A	A
Estimating resources and costs	A	A	A	A	A	A	A	A	A
Currency, price date, conversion	A	A	A	A	PA	A	A	A	A

A: Adequate (information was explicitly presented in the text)
PA: Partially adequate (information was NOT explicitly presented, but was suggested)
NA: Not adequate (no information about the matter was available in the text)

Cont. Table 4.25. Quality assessment of included papers of pharmacoeconomics evaluations based on CHEERS checklist

Section/Item	Last author, date O'Sullivan, 2012	Schonfeld, 2008	Sohn, 2009	Mauskopf, 2013	Sánchez-Ortega, 2013	de la Ca´mara, 2009	Heng, 2013	Al-Badriyeh, 2010	Scharfstein, 1997
Choice of model	PA	NA	PA	PA	NA	PA	PA	PA	NA
Assumptions	A	A	A	A	NA	A	NA	A	A
Analytical model	PA	PA	PA	PA	PA	PA	PA	PA	PA
Results									
Study parameters	A	PA	A	PA	PA	PA	PA	A	A
Incremental costs and outcomes	A	A	A	A	A	A	A	A	A
Characterizing uncertainty	PA	PA	PA	A	PA	PA	A	A	PA
Characterizing heterogeneity	PA	PA	PA	A	PA	PA	A	A	PA
Discussion/others									
Study findings, limitation, generalizability, current knowledge	PA	A	PA	PA	PA	PA	PA	PA	PA
Source of funding	A	A	A	NA	A	A	A	PA	PA
Conflict of interest	NA	NA	NA	NA	A	A	A	NA	NA

A: Adequate (information was explicitly presented in the text)
PA: Partially adequate (information was NOT explicitly presented, but was suggested)
NA: Not adequate (no information about the matter was available in the text)

CHAPTER FIVE: DISCUSSION

5.1. Phase 1: Pharmacoeconomics Evaluations of Posaconazole

The current study was conducted as per the clinical practice of NCCCR, a public provider that is regulated, as part of HMC, by the Supreme Council of Health in Qatar. The selection of the drug formulary at the hospital is determined by the local Pharmacy and Therapeutic (P&T) Committee. Traditionally, and due to the perception of wealth, with Qatar having the highest income per capita in the world, the P&T committee of HMC mostly makes its decision based the safety and efficacy of drugs, with no much focus on cost-cutting measures. In recent years, however, due to increasing populations and pressure on unlimited healthcare budget, there has been an increasing interest in the economic considerations of therapies. The need for efficient therapies that cut costs to healthcare systems is particularly important in relation to medications such as systemic antifungals, where a global increase in the market value of antifungals is anticipated to increase to reach US$ 16.1 billion by 2021[124].

This is the first pharmacoeconomics evaluation in Qatar that evaluates the posaconazole utilization cost for prophylaxis against IFIs among hematologic malignancy patients undergoing chemotherapy or HSCT in NCCCR. The study consists of two evaluations, where Evaluation-I aims at determining the overall expenditure of using posaconazole at NCCCR, and Evaluation-II provides a cost-effectiveness analysis comparing posaconazole to fluconazole.

In Evaluation-I**,** all eligible patients (n=70) from NCCCR were included in the analysis and followed up from the day of starting prophylaxis therapy until 112 days (4 months) from the onset. A study population of 70 patients is consistent with other relevant

cost-analyses of medications in literature. A study was conducted in Germany by Rieger et al. enrolled 36 IFI patients vs. 72 control patients[125], while Gedik et al. from Turkey included 126 patients receiving one of the three antifungals (voriconazole, LAMB, or caspofungin)[126]. All relevant directly utilized resources, including antifungal medications for prophylaxis and treatment, side effects management medications, hospitalization, and monitoring and diagnosing tests were considered in the study. The study was from the hospital perspective where only direct medical costs were accounted for. Direct nonmedical costs were difficult to include for the lack of reporting and documentation in the hospital records.

As expected, patients with AML, being the most common hematological malignancy worldwide, constituted the majority of the included population (over 60%) followed by ALL patients (31.4%). Eventually, 73% of patients who failed prophylaxis therapy (n=30) due to getting IFIs were AML patients and 80% of patients who died before 112 days (n=5) were also the ones diagnosed with AML. AML constituted the majority of many other similar studies as being the most common type of hematological cancer. In the Ullmman et al. study, for example, more than 67% of included patients had AML[127]. Another study conducted by Sánchez-Ortega had all 100% of the study population as AML patients[128], while in the Stam et al. study, over 70% of included patients had AML[129].

The current thesis results are showing that effectiveness of posaconazole in preventing infection is relatively low (50% prophylaxis success without IFI or death in 112 days). This seems lesser than the effectiveness of posaconazole in other settings. A study by Conely et al., for example, conducted in Germany, showed that the rate of IFI among posaconazole patients reached only 2%, with 16% death during the study[89]. However, the

mean number of days of receiving prophylaxis in this study was much higher than that reported in similar other settings. For example, patients in NCCCR spent an average of 63 days of prophylaxis, while this was reported in Australia to be 19 days in AML patients receiving posaconazole[90]. The mean number of days of prophylaxis for patients who died before 112 days was 25 days in the current study, which is considerably shorter than the identified average duration of 63 days of prophylaxis. It seems that patients who died had much worse health status due to either being in advanced stage of malignancy or suffering from severe chemotherapy-related side effects. It is very difficult to ascertain the reason behind death in such a complex population, given that patients are receiving multiple medications for different indications, adding to the fact that the current documentation in Cerner® database in NCCCR does not report the reason behind death, whether death is because of specific type of fungal/bacterial/viral infection, major side effect intolerance, underlying disease, or cancer itself.

With regards to the monitoring tests and diagnostic procedures that are performed for every single patient throughout the follow-up period, the study reveals that the hospital conducted more than 650 chest X-ray tests, 37 MRIs, 143 CT scans, 30 nuclear medicine tests, and 40 ultrasound tests for imaging. As for pathology tests, more than 1,600 tests were performed including 324 galactomannan tests, 771 blood culture tests, and 219 urine culture tests. Almost 14,000 tests were done for the monitoring of the patient organ status, including about CBC, ALT/AST, and creatinine levels. This is added to a cumulative cost of QAR 1,082,066, with measuring creatinine levels contributing to 43.1% of the cost. This is expected as patients with hematological malignancies are exposed to many factors that threaten their renal function, including the disease itself, chemotherapy,

immunocompromising medications, antimicrobial medications, etc. This was not consistent with other cost analysis studies as reported by Heimann et al., where diagnostic tests constituted only 3% of overall posaconazole cost[69]. Generally, only few papers reported costs of some diagnostic tests separately from the overall antifungal cost while none had accounted for costs spent on monitoring for safety aspects. Nevertheless, it seems that the clinical practice in the NCCCR is missing an important parameter to monitor the safety and efficacy of the prophylaxis therapy, which is the monitoring of the posaconazole blood levels. The current model, therefore, did not account for the cost of the drug therapeutic monitoring (DTM) of posaconazole. Consistently, other cost analysis studies did not account for the cost of DTM[110,125,126,109], although that the serum trough concentration measure of the posaconazole suspension is highly recommended by the IDSA due to the drug's considerable variations (both interindividual and intraindividual) in bioavailability and drug-drug interaction[130]. About costs spent on monitoring of patients (for both safety and efficacy), negligible differences were observed among different possible patient outcomes.

According to the decision analytic model in the study, NCCCR spent around QAR 110,000 per patient when used posaconazole for prophylaxis. This high cost is only associated with posaconazole utilization in hematological malignancy patients and does not include costs of chemotherapy or any non-posaconazole related costs. Important is that half of this cost (QAR 55,000) is spent on managing the overall IFIs with prophylaxis failure, which raises a concern about how efficient the use of posaconazole for prophylaxis in NCCCR is. This is an important finding, especially as this is the first cost-analysis in literature to follow up the antifungals use to include the cost associated with potential

alternative therapies to IFIs failures. Other cost analyses of prophylaxis did not account for measuring costs of treating IFIs after prophylaxis failure and only reported the overall cost of prophylactic therapy[69,109]. Furthermore, the highest contributing patient pathway to overall cost, of all pathways, was the treatment and management of major hepatic ADR, at around 30% of the QAR 110,000. This was the result of only 13% of the patients in the success arm needing to stop their prophylaxis at some point in NCCCR for not tolerating the hepatic adverse effect of the drug, with these eventually exposed to higher risk for infection and, hence, an economic burden for the treatment of resulting probable/proven IFIs. This is another important finding in this study, especially as this is the first literature cost-analysis to follow up patients for the cost of consequences of ADR-specific discontinuations. In confirmation of the results, upon performing sensitivity analysis, only one variable revealed a major reduction in overall posaconazole expenditure (by 24%), which is eliminating major ADR costs by distributing its probability of occurrence to the minor and no ADR pathways. This only emphasizes the need for practices to consider the risk for major ADR in patients receiving posaconazole, and not just merely give posaconazole universally to all patients as is the case in NCCCR, Qatar.

LAMB acquisition cost, as an alternative therapy, reached around QAR 140,000 per month for either treating infections of seriously strong pathogens (*Fusarium* and *Muocormyctes*) or replacing posaconazole in case of hepatic disorders. However, *Mucormycosis* and *Fusarium* are rare fetal fungal infections, which have less than 3% probability (based on the expert panel) to occur in NCCCR patients, and, hence, their cost contribution in the overall model cost was less than 3.4% and 6.5%, respectively. Grau et al. also used only LAMB for IFI treatment if prophylaxis failed, where treatment costs

reached only QAR 47,171 (EUR 1 = QAR 4.49), indicating higher costs being spent in Qatari settings[109]. Gedik et al. performed cost analysis study on treatment of IFI using caspofungin, voriconazole, and LAMB, where the combined expenditure of antifungals was reported to be QAR 65,662 per patient, a total expenditure of QAR 4,629,312 (USD 1 = QAR 3.64)[126].

Given the limited availability of data of interest for the purpose of a comprehensive decision analytic model in this study, gaps in data were populated from literature as well as an expert panel. While the literature data was of an RCT that is of identical population and posaconazole use to those in the current study, and that the expert panel was made of relevant experts who provided ideal locally-specific and relevant data, the fact remains that such data are associated with uncertainty, which is a limitation in this study. Nevertheless, it is for this reason that a comprehensive multivariate Monte Carlo analysis was conducted, where the expert panel and RCT data were assigned ranges of uncertainty in the economic model of the study. With a narrow range of cost-outcome variation, however, between QAR 109,000 and 118,000, the uncertainty analysis demonstrated that the study outcome was robust and not sensitive to uncertainties. Other input uncertainties related to that the diagnostic tests may not necessarily relate to the antifungal use, and that the analytic model had assumed that the single posaconazole vial is not shared among different patients. Both of these concerns were evaluated, however; whereby, the model was re-run when accounting for not considering costs of tests for IFI diagnosis and for sharing the same posaconazole bottles between patients. Both scenarios did not significantly change the overall cost (93,815.9 and 108,894, respectively).

After looking at the absolute value of the cost of posaconazole use in the Qatari setting, it is only logical to also look at the relative value of posaconazole as compared to other prophylactic antifungals that are potentially beneficial. Hence, the Evaluation-II in the first phase of this thesis was to conduct a cost-effectiveness analysis that compares posaconazole to an alternative. Fluconazole was the other alternative as it showed effectiveness throughout several years in the same population among overseas settings[86,91,102,111,129]. As indicated earlier in the thesis, posaconazole is the only antifungal in consideration for prophylaxis in NCCCR. No other alternatives are considered, including fluconazole. Head-to-head comparative data of posaconazole versus fluconazole were, therefore, obtained from a major published RCT of 600 immunocompromised patients using either posaconazole or fluconazole, with a study population and a posaconazole administration standards that are identical to those in the NCCCR practice. The main findings in the RCT declared that posaconazole had similar efficacy to fluconazole in preventing IFI since the difference was not statistically or clinically significant. The effectiveness in the RCT was defined by survival without IFIs before the end of the 112 days follow up. For the purpose of the current evaluation, however, as consistent with the local practices and as validated by the expert panel of the study, the success of interest was defined as survival for 112 days of receiving the first dose of prophylaxis without getting IFI and without having major ADR. The results from the current evaluation decision model were also that the rate of success between the two study drugs is minor. The study revealed a slightly higher effect of interest for posaconazole (0.76 vs. 0.75), but with much higher cost. Therefore, a DCEA was performed revealing that QAR 3,922,618 is to be saved with fluconazole over posaconazole per additional lost case of success with no major ADR.

While there is no defined threshold budget in Qatar, one can look at the international threshold budget provided by the World Health Organization (WHO) to be between QAR 365,000 to 547,500 (USD = QAR 3.65)[131]. The DCER is, therefore, considered high and supports the use of fluconazole over posaconazole in Qatar. There are no relevant DCER that is reported in literature, but looking at the ICER, a study in the USA revealed a much lower ICER of QAR 310,492 per IFI avoided and QAR 55,692 per life-year saved that the ratio in the current study (USD 1= QAR 3.64)[102]. Similar results were shown by Ca´mara et al. as well with ICER of QAR 91,224 per life year gained (EUR 1 = QAR 4.49)[111]. The ratio went even lower in Greece with QAR 29,089 per IFI avoided for posaconazole versus fluconazole/itraconazole (EUR 1 = QAR 4.49)[132]. However, one should consider the different outcome of interest from one study to another beside differences in overall costs of antifungal agent among different countries. This is very important and emphasizes the fact that outcomes of pharmacoeconomics evaluations are not readily generalizable to other settings, and that consistently reporting posaconazole as cost-effective against fluconazole in other settings, does not necessarily make posaconazole a cost-effective option in the Qatari setting, based on the Qatari practices of managing IFIs and major ADR.

Looking at the breakdown of cost contributions based on the failure pathways where alternatives are given, one can see that the costs of alternative pathways were consistently higher with posaconazole as compared to fluconazole, except for the costs spent on treating aspergillosis infection in cases of failure due to IFIs (QAR 16,159 vs. 28,727). This is explained by the fact that higher rate of prophylaxis failure due to aspergillosis infection among patients was reported with fluconazole, requiring further

hospitalization and management. This further emphasizes how important the local relevance is in the pharmacoeconomics evaluations; whereby, in a setting where *Candida* infections are more prevalent than *Aspergillus* infections, the relative cost of posaconazole will only further increase. Fluconazole is more effective against *Candida* than it is effective against *Aspergillus* infections[91].

Also emphasized in the current study is how important it is for decision-makers to consider the cost of alternatives besides the initial medication costs. This is as the former can overtake the latter in value. For example, in the posaconazole pathway where patients failed therapy due to *Fusarium* infection, the alternative therapies given (combination of voriconazole and LAMB) where way more costly than the initial posaconazole therapy (QAR 133,828 vs. 31,722). Similarly, as another example, following up on major ADR, LAMB was associated with a higher cost than the initial cost (QAR 50,871 vs. 39,131). As discussed in Evaluation-I, it is a strength that the current evaluation followed up consequences beyond the IFIs and ADR-specific outcomes, to also include alternative therapies given. No other relevant studies performed this in the literature.

As discussed in Evaluation-I above, despite an occurrence rate of 8-11% only, the cost of success with major ADR contributed highly to the overall cost of antifungals (40-45% with both study groups). Not accounting for major ADR, however, and unlike in the non-comparative cost analysis in Evaluation-I, did not affect the study outcome. This was anticipated given that the overall costs of both medications were similarly influenced by the respective value of major ADR.

Also, as was discussed in Evaluation-I, the therapeutic drug monitoring of posaconazole is part of the standard patient management in overseas settings, but this was

not part of patient management in the current economic modeling of posaconazole use, which was due not being part of the standard practice in NCCCR. This, however, does not influence the study outcome as excluding it underestimates the cost of posaconazole as compared to fluconazole. This is when posaconazole is already associated with a higher cost as compared to fluconazole.

As discussed earlier, while an expert panel was necessary to fill some gaps in data, it provided data that are inherently associated with uncertainty. Similar to insensitivity to major ADR, however, the study outcome was insensitive to the uncertainty in all key input variables investigated in the one-way and scenario analyses.

Important is that, based on the Monte Carlo analysis, this study conclusion persisted in 96% of cases, with only in about 4% of cases, posaconazole dominated fluconazole. Also, DCER of fluconazole was over QAR 1,200,000 saved in 95% of cases.

The decision analytic model in Evaluation-II of Phase-I was based on a published RCT. While this comes with the advantage of relying on a well-established methodology, with high internal validity due to randomization, blinding, and controlling of confounding factors[133], the use of published RCTs comes with important limitations to the economic evaluation. First is the limited generalizability of results to the local setting due to the controlled nature of RCTs concerning the patient's criteria and the medication regimens[134]. Second, the specific duration that is pre-defined by the RCT might limit knowledge on important consequences and outcomes that could influence the overall cost of therapy. Mortality, requesting higher doses, switching to alternatives, and withdrawal due to intolerance are some examples of possible consequences and outcomes that might be missed in published RCTs. Nevertheless, for the purpose of the current evaluation, the

patient's characteristics and the drug administration in the RCT by Ullmann et al. are all identical to those in the local NCCCR setting. Also, the duration of follow up (4 months) is realistic, consistent with other studies as discussed earlier, and is appropriate to follow in this evaluation. Important is that the data was adopted to the local setting via a locally-based expert panel. Even in the sensitivity analysis, which was conducted to increase the robustness and generalizability of studies, local hospitalization data from the NCCCR medical records were incorporated, as already discussed in Chapter 3.

As noted above, a strength in both of Evaluation-I and Evaluation-II in Phase-I of this thesis is a decision analytic model that is more comprehensive than other models reported in the literature. The model represents all the possible consequences of using antifungal prophylaxis and, hence, an overall cost of prophylaxis that is more accurately measured. None of the previous studies accounted for the cost of treating the specific major and minor ADR with prophylactic antifungals. The only study that considered the cost of alternatives to side effects with prophylactic antifungals was that by Heng SC et al[91]. In this, however, all patients universally received LAMB in all cases on side effects, including the minor ones, such as nausea, vomiting, diarrhea, which could be easily treated with the much lesser costly over the counter medications (OTC).

Despite outcome robustness in the current evaluations, outcomes can only be fully proven via a follow up future research that evaluates, whether prospectively or retrospectively, the comparative clinical and economic impacts of posaconazole and fluconazole for prophylaxis against IFIs in immunocompromised patients with hematological malignancies, and undergoing chemotherapy or HSCT, at local Qatari NCCCR setting. This, however, is obviously very difficult currently as fluconazole is not

available as a prophylactic option in the NCCCR. Locally-specific posaconazole studies, like the current ones, are therefore considered important for the quality assessment of local practices. It seems that fluconazole is equally effective to posaconazole, including based on local interests and practices, with a considerable anticipated amount of cost-savings. Adding fluconazole to the arsenal of available systemic antifungals for the prophylaxis against IFIs in cancer patients can only be beneficial and will enable the availability of local fluconazole data that can be then utilized into locally-based and relevant head-to-head evaluations between the prophylactic posaconazole and fluconazole in the NCCCR setting.

5.2. Phase 2: Systematic Review of Methodological Trends and Gaps, and the Reporting Quality of Comparative Economic Evaluations on the Use of Systemic Antifungal Agents Used for Prophylaxis Against IFI

Phase-2 of this thesis was a comprehensive thematic systematic review that focused on the literature designs and methods used in the pharmacoeconomics evaluations of systemic antifungal agents for prophylaxis indication against IFI among immunocompromised patients. The reason this comes as the last component of this thesis is that, as discussed earlier, this systematic review is not to review the literature to identify gaps in knowledge. Gaps that research in the current thesis will look to partially or entirely fix. Based on the research in Phase-1 and other relevant literature, this systematic review is meant to identify methodological limitations, hence, make recommendations for future research in the field.

This systematic review is the first to identify the characteristics, trends and reporting quality of published research in economic evaluations about the use of systemic antifungals. The current systematic review is the first to give recommendations for future

pharmacoeconomics studies to consider, within the context of antifungal agents for the immunocompromised population, by comprehensively identifying methodological gaps in the current literature. A review by Pechlivanoglou et al. focused on cost-benefit and cost-effectiveness of all studies of antifungals for prophylaxis[71]. While a review by Wilke focused on echinocandins only regardless of the purpose of use, whether it is for treatment or prophylaxis[84], a review by Lyseng-Williamson only focused on posaconazole for prophylaxis among any immunocompromised condition including cancer[135]. These reviews were looking to summarize recommendation about practices and did not look at trends and gaps of methodological aspects.

This review analyzed 19 publications of economic evaluations of systemic antifungals. While studies answered the questions that they were performed to answer, there was a wide range of methodological trends and gaps that existed in these studies. It seems that studies did not adhere well to current standards for conducting and reporting economic evaluations, such as those by the Panel of cost-effectiveness in health and medicine[136] or by the British Medical Journal's guidelines for economic submissions. This mostly resulted in different ranges of ICERs, limiting the robustness of the body of evidence and the guidance to decision-makers in other settings. This mostly led to that different conclusions were made for the same medication in various studies for the same use; whereby it is hard for decision-makers to come up with aggregate evidence in favor or against any antifungal option.

Perspective. The utilization of health care and patient resources, including work productivity, are expected to be largely affected in cancer populations. Only 4 studies, however, identified the social perspective as of interest in their evaluations. The majority

of studies were from hospital and payer perspectives, which are common perspective, mostly due to convenience, and typically includes the direct medical type of costs. What is Important is that those studies with the social perspective only included the direct medical costs, with no non-medical or productivity costs involved. This is an inappropriate interpretation of what the social aspect entails in studies.

Modeling. All 19 studies included decision analytic modeling, which is appropriate as modeling is essential for better understanding the different effects and costs of an intervention. However, the validity of a model and its results rely on the evidence and assumptions it is based on. About the evidence, all included studies were non-experimental in design, where studies extracted data from secondary sources. In fact, the majority of modeling studies relied on the same sources of data, which were few published RCTs[89,103,110,137]. This is a limitation as prospective RCTs would have generated more robust and convincing evidence for the local setting. Even if RCTs are not feasible due to limitations in resources, the incorporation of locally-based data from local medical records and expert panels would have provided more relevant results.

Markov modeling. Markov models are ideal for pharmacoeconomics evaluations in a recurrent condition such as fungal infections in cancer papers, where the Markov model has an advantage over decision analytic models in incorporating longer time horizons. It extends the results of clinical trials and extrapolates intermediate endpoints into final outcomes. It seems, however, that authors in studies were not consistently interested in the long-term horizon follow up durations as about 9 of the included 19 studies included Markov modeling. What is believed to have contributed to this limited use of Markov design is the existing gaps in the local clinical and quality of life data and evidence to use

in populating the longer horizon multi-state model. In relevance to Markov modeling, discounting is required to adjust future values of variables to their current values. Except in one study by de Vries et al.[81], this was conducted in studies, with the discount rate varying from 1.5%[129] and 5%[105], but with no justification given to any.

Reporting of cost. It is important that the cost components and measuring approaches are clearly reported in studies. This is to enable the reproducibility and applicability of results. While all included 19 studies identified costs considered, studies did not provide details of how these were calculated. For example, none of the studies indicated whether costs used are hospital charges or costs. Hospital charge is not an ideal estimation of cost as this is decided on to compensate for the cost of other services and facilities provided by the hospital setting. Using charges instead of costs produces less accurate conclusions.

QALY. QALY is crucial in most chronic diseases, and of particular importance in cancer patients, where QALY is a widely preferred summary multidimensional value of outcomes in pharmacoeconomics. It incorporates trade-offs between quality of life and quantity of life in a common metric.

Outcomes. Despite the importance of health states, such as success, failure and death, in decision making, QALY is also essential to consider in cases of chronic patient management and follow up, incorporating trade-offs between quality of life and quantity of life in a common metric. While several studies did indeed develop Markov models to follow up the longer horizon of outcomes, only one study identified and measured the QALY as the outcome of interest in a study[129]. Outcomes are increasingly multi-

dimensional, and only focusing on health status outcomes, instead of both QALYs and specific health states, is a shortcoming that requires attention.

Adverse drug reactions. Drug-related adverse events have a significant influence on the direct cost and cost-effectiveness and, hence, are anticipated to be of primary consideration when differentiating between medications. While only one study included the analysis of adverse event costs[91], however, the study did not model discontinuations due to adverse events. The extent of the discontinuation and its cost are not clear in studies, which was also not included in sensitivity analyses conducted. To consider the side effects that are associated with discontinuations as equivalent to those that are not is inappropriate when guiding decision making.

Sensitivity analyses. Sensitivity analysis is a crucial component in economic evaluations, to investigate the robustness of outcomes made and also increase their generalizability. While all studies included sensitivity analyses, however, these did not justify input changes made. Importantly, sensitivity analyses were limited in variability. Only the one-way analysis was conducted, and none of the studies utilized a combination of methods that additionally includes the multivariate and scenario analyses. In the absence of correlation, the one-way analysis underestimates uncertainty, even if interpreted correctly[138].

Quality of reporting. The quality of reporting varied in relation to different aspects of the studies. Partially adequate reporting of aspects such as the analytical model, characterizing uncertainty and characterizing heterogeneity, study findings, and limitations and generalizability, was in 63% to 100% of studies. Only 16% of studies did not report adequate information about the study competitors and choice of model, and 5% of the

studies did not mention the study time horizon. Aspects such as the setting and location, perspective, selection of health outcome, estimating resources and costs, and incremental costs and outcomes, were adequately reported in 100% of the studies. 52% of studies did not sufficiently report enough information on discount rate choice and conflict of interest in studies.

Study comparators. Most of the comparisons in studies were made of expensive medications versus cheaper older ones and, also, more than 90% of these included the azole class, e.g. posaconazole. These studies, and unlike in the current thesis, have therefore mostly reported a state of dominance in favor of the newer medications, in 14 out of the 19 articles. More economic evaluations should be aiming to compare among the newer, more expensive medications, such as those of the echinocandins versus azoles[81,87]. There is also a lack of 'head-to-head' trials among new antifungal agents for prophylaxis that include more recent agents, such as micafungin. Without head-to-head studies of micafungin versus posaconazole, as an example, it is difficult to build economic evaluations that provide robust comparative data of the agents.

Definition of health states. Different types of outcome measures were considered among the various studies. For example, while some studies looked at the absence of IFIs as the primary outcome, others looked at survival after prophylaxis when made their conclusions[81,82,88,102]. Even when studies targeted the same outcome measure, the definition of the measure differed. For example, while "successful therapy" was defined as the absence of IFI during prophylaxis in studies, it was determined as the absence of discontinuation of prophylaxis during induction therapy in others[82,83,91]. This, however, is

anticipated to a degree seeing that the choice for outcome measure and its definition are primarily driven by the local interests of decision makers in practices.

Suggestions for Future Research

Based on the current systematic review, several recommendations for improving future evidence can be made.

- Reporting of study details should be enhanced in published reports. Important features can include modeling assumptions, costing components and methods, discount rate, and sensitivity analysis. There are several quality assessment checklists that authors can use to enhance reporting of essential aspects of economic studies. These include the CHEERS reporting checklist[139].
- Research evaluations should enhance their adherence to good practices when designing new studies, including about methodological concerns regarding modeling, the source of data, sensitivity analysis, cost versus perspective, outcome measures, and side effects. This can be via using existing good practice guidelines, such as the health economic evaluation (HEE) quality appraisal instrument and those posed by the international society of pharmacoeconomics and outcome research (ISPOR)[139,140,141].
- Journal reviewers and editors should push for more reliable and justified measures for assessing and defining study outcomes, to improve uniformity among studies and enable a cumulative evidence generation.
- Economic evaluations should incorporate more of head-to-head comparisons between the newer most expensive antifungal agents. If not as a primary source of comparative economic data, the evaluations can be clinical at least, which can be built on via simulation models to generate economic outcomes in different settings.

- Future research can benefit from studies that better consider the non-medical costs of therapies. This achieves consistency among costs examined and reported, and helps compile a better understanding of the social impact of being on medications. To enhance the availability of data for such a purpose, future research in local settings should better document and audit social effects of long-term therapies, including the association between intermediate and final outcomes of interest.
- Quality of life considerations in cost-effectiveness evaluations of long-term antifungal prophylaxis needs to increase in literature. QALY can be more considered when assessing therapies, instead of focusing on clinical health states only.
- All economic evaluations conducted in studies compared the different comparators against the prophylactic indication only. Different antifungals, however, can also have different levels of effectiveness against other indications of interest at the same practice setting. Recent methods such as the multi-criteria decision modeling should be used, therefore, to enable a more efficient selection of antifungals; whereby, these will be compared based on their overall performance against multiple criteria and indications at the same time in the same setting.

Study Limitations

There are several limitations in the current review. The literature search was restricted to the English language, which may exclude relevant studies in other less common languages such as Chinese, French, and German. However, authors do not have the ability or the resources to translate the non-English literature. Moreover, despite the comprehensive search via several important search engines in this review, additional search

terms and/or combinations among them are possible and can lead to identifying additional studies that were missed in the current review.

CHAPTER SIX: CONCLUSION

Posaconazole is the first and only systemic antifungal that is in consideration at the NCCCR in Qatar for prophylaxis against IFIs in the immunocompromised hematology patients. Within the context of this setting, the current research includes (i) the first cost-analysis simulation model of posaconazole and the resource utilization associated with it, and (ii) the first decision analytic cost-effectiveness simulation model of posaconazole versus fluconazole, in Qatar and the region. Internationally, the constructed models are comprehensive, and the first to consider ADR and the discontinuations associated with them, and they are also the first to follow up on specific alternative therapies to failures and discontinuations.

In the Qatari setting, 43% of patients on prophylactic posaconazole fail therapy due to IFIs, with the most common of which due to *Candida* infections. The overall cost of a patient on posaconazole was QAR 109,802, with the proportional cost per success being QAR 52,029 per patient. The main cost driver in the use of posaconazole was the patient pathway of success with major ADR, contributing to 30% of the total cost. Compared to posaconazole, fluconazole was associated with about similar rate of success without major ADR, but at a much-reduced cost. In 96% of cases, fluconazole saved over QAR 1,200,000 compared to posaconazole per lost case of success without major ADR.

The findings of this research are in contrast to the current practices at the NCCCR in Qatar, where posaconazole is the only systemic antifungal to be ever considered for prophylaxis. Based on the results in this study, particularly the comparative against fluconazole, it is possible that other antifungals, such as fluconazole, can be considered for

addition to the prophylactic arsenal in NCCCR, to maybe replace posaconazole in patients with high risk for ADR.

In addition, the research identified several aspects of methods where recommendations for future research were made. These included aspects about modeling and follow up, cost and perspective, comparators and outcomes, sensitivity analysis, and the quality of reporting.

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APPENDICES

Appendix 1. Ethical Approval Letter, Phase-I Of Thesis

مؤسسة حمد الطبية
Hamad Medical Corporation
HEALTH · EDUCATION · RESEARCH صحة · تعليم · بحوث

مركز البحوث الطبية
Medical Research Center

Ref No: MRC0271/2016
Date: 08 March 2016

Dr. Shereen Elazzazy
Asst. Director of Pharmacy
NCCCR
HMC

Dear Dr. Shereen,

Proposal #15378/15: "Analysis of the use of the systemic antifungal "posaconazole" for the prophylaxis from invasion fungal infection among cancer pateints at the National Center for Cancer Care & Research (NCCCR) - HMC"

This is in reference to your submission of the above titled proposal to the research center for review.

We would like to inform you that the Research Center has no objection for this Quality Improvement project to be conducted in HMC and published thereafter.

Yours sincerely,

Ms. Angela Ball,
Asst. Executive Director of Research and Business Development

Cc:
1. Dr. Daoud Al- Badriyeh, Qatar University
2. Dr. Ibrahim El Hijji, NCCCR, HMC
3. Dr. Amir Nounou, NCCCR, HMC
4. Ms. Wafa Ziad Al- Marridi, Qatar University
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Appendix 2. Qatar University Ethics Exemption Letter, Phase-I

جامعة قطر
QATAR UNIVERSITY

Qatar University Institutional Review Board
QU-IRB

November 6, 2016

Dr. Daoud Al-Badriyeh
College of Pharmacy
Qatar University
Tel.: 4403-5591
Email: Daoud.a@qu.edu.qa

Dear Dr. Daoud Al-Badriyeh,

Sub.: **Research Ethics Review Exemption**
Ref.: **Project titled, "Analysis of the use of the systematic antifungal 'posaconazole' for the prophylaxis from invasive fungal infection among cancer patients at the National Center for Cancer Care & Research (NCCCR) - HMC"**

We would like to inform you that your application along with the supporting documents provided for the above proposal, is reviewed and having met all the requirements, has been exempted from the full ethics review.

Please note that any changes/modification or additions to the original submitted protocol should be reported to the committee to seek approval prior to continuation.

Your Research Ethics Approval No. is: **QU-IRB 674-E/16**

Kindly refer to this number in all your future correspondence pertaining to this project.

Best wishes,

K. Hlali

Dr. Khalid Al-Ali
Chairperson, QU-IRB

Institutional Review Board
(IRB)
Office Of Academic Research

Appendix 3. Data Collection Form, Evaluation-I, Phase-I Of Thesis

Project title: cost-analysis study that evaluate the cost of resource utilization associated with the use of prophylaxis (posaconazole)

Table 1: Patient demographics			
Subject NO.	Patient age (years)	Sex (M=1, F=2)	Weight (KG)

Table 2: Medical information											
Underlying disease	Date of diagnosis with cancer	Current or previous history of proven or probable IFI (Yes=1, No=2)	Have used systemic antifungals within 7 days prior to commencing posaconazole	Chemotherapy protocol received	Date of admission	Date of discharge	Prophylaxis drug name	Dose (mg)	Formulation	Frequency (n/day)	Duration (day)

Table 3: Patient co-morbid conditions									
HIV/AIDS	Diabetes	HTN	CVD	Thyroid	Asthma	Arthritis	Epilepsy	Depression	None

Table 4: Smoking status			
Current	Never	Ex-smoker	Unknown

Table 5: Monitoring tests for side effects						
NO. of LFT (ALT/AST)	Notes	NO. of RT(creatinin)	Notes	NO. of CBC	Notes	Other tests

Table 6: Screening test for fungal infection (imaging)											
x-ray scan type	NO.	CT scan type	NO.	Ultrasound type	NO.	MRI type	No.	Nuclear medicine test type	No.	Cardiology procedures types	No.

Table 7: Screening test for fungal infection (pathology)								
Urine culture No.	Stool culture No	Blood culture No.	Parasites stool	Acid fast bacili culture	C. Diff toxin	C. Coli antigen test	Galactomannan test	PCR virology

Table 8: Patient outcome status		
alive W/O IFI after 112 days	alive with IFI before 112 days	death related/unrelated to IFI-date

Appendix 4. Questions for Expert Panel Discussions, Phase-I of Thesis

1. Availability of posaconazole in bottle (mg):
2. Availability of fluconazole tables in box:
3. Do you share bottles or boxes between patients if the amount allow that?
4. Based on your experiences in Qatar, in relation to patients taking posaconazole, what are types of fungal infection that you may see in addition to Aspergillus and Candida
    1. …
    2. …
    3. …

    4.1 What are the probabilities of these to happen?
        a. Aspergillosis :
        b. Candidiasis:
        c. Other #1:
        d. Other #2:
        e. Other #3:
        f. Other #4:

5. In relation to patients taking fluconazole, what are types of fungal infection that you see in addition to Aspergillus and Candida (flu is only given in lymphoid malignancy- same pathogens)

5.1 What are the probabilities of these to happen?

a. Aspergillosis:

b. Candidiasis:

c. Other #1:

d. Other #2:

e. Other #3:

f. Other #4:

6. If proven/ probable aspergillosis infection is detected during posaconazole prophylaxis, what antifungal therapy do you switch to:

    a. Drug name:

    b. Formulation:

    c. Dose:

    d. Frequency:

    e. Availability in bottle (mg):

7. If proven and probable IFI , may you provide alternative to flu in case of aspergillosis infection:

    a. Drug name:

    b. Formulation:

    c. Dose:

    d. Frequency:

    e. Availability in bottle (mg):

8. If proven and probable IFI , may you provide alternative to posa in case of candida infection:
    a. Drug name:
    b. Formulation:
    c. Dose:
    d. Frequency:
    e. Availability in bottle (mg):
9. If proven and probable IFI , may you provide alternative to flu in case of candida infection:
    a. Drug name:
    b. Formulation:
    c. Dose:
    d. Frequency:
    e. Availability in bottle (mg):
10. If proven and probable IFI , may you provide alternative to posa in case of other type of infection:
    a. Infection type#1:
    b. Drug name:
    c. Formulation:
    d. Dose:
    e. Frequency:
    f. Availability in bottle (mg):

11. If proven and probable IFI , may you provide alternative to posa in case of other type of infection:
    a. Infection type#2:
    b. Drug name:
    c. Formulation:
    d. Dose:
    e. Frequency:
    f. Availability in bottle (mg):
12. If proven and probable IFI , may you provide alternative to posa in case of other type of infection:
    a. Infection type#3:
    b. Drug name:
    c. Formulation:
    d. Dose:
    e. Frequency:
    f. Availability in bottle (mg):
13. If proven and probable IFI , may you provide alternative to flu in case of other type of infection:
    a. Infection type#1:
    b. Drug name:
    c. Formulation:
    d. Dose:
    e. Frequency:

f. Availability in bottle (mg):

14. If proven and probable IFI , may you provide alternative to flu in case of other type of infection:

    a. Infection type#2:
    b. Drug name:
    c. Formulation:
    d. Dose:
    e. Frequency:
    f. Availability in bottle (mg):

15. If proven and probable IFI , may you provide alternative to flu in case of other type of infection:

    a. Infection type#3:
    b. Drug name:
    c. Formulation:
    d. Dose:
    e. Frequency:
    f. Availability in bottle (mg):

16. Treatment of severe headache side effect during prophylactic posaconazole:

    a. Drug name:
    b. Formulation:
    c. Dose:
    d. Frequency:
    e. Duration (day):

f. Availability in bottle (mg):

17. Treatment of severe headache side effect during prophylactic Fluconazole:

a. Drug name:

b. Formulation:

c. Dose:

d. Frequency:

e. Duration (day):

f. Availability in bottle (mg):

18. Treatment of GI side effect (with posaconazole):

	Diarrhea	Nausea	Vomiting
Drug name			
Dose:			
Formulation:			
Frequency:			
Duration (day):			
Availability in bottle (mg):			

19. Treatment of GI side effect (with fluconazole):

	Diarrhea	Nausea	Vomiting
Drug name			
Dose:			
Formulation:			
Frequency:			
Duration (day):			
Availability in bottle (mg):			

20. Treatment of liver & biliary side effects due to antifungal therapy (with posaconazole):

	Bilirubinemia	Increased γ-glutamyltransferase	Increased hepatic enzymes	Increased aspartate aminotransferase	Increased alanine aminotransferase
Drug name					
Dose:					
Formulation:					
Frequency:					
Duration (day):					
Availability in bottle (mg):					

21. Treatment of liver & biliary side effects due to antifungal therapy (with fluconazole):

	Bilirubinemia	Increased γ-glutamyltransferase	Increased hepatic enzymes	Increased aspartate aminotransfera-se	Increased alanine aminotransferase
Drug name					
Dose:					
Formulation:					
Frequency:					
Duration (day):					
Availability in bottle (mg):					

22. Based on your experience in Qatar, what are adverse events with prophylactic posaconazole that can lead to therapy discontinuation and what is your estimation of the probabilities of these to happen?

SE#1: Probability:

SE#2: Probability:

For fluconazole :

23. How often does a patient discontinue due to oral therapy intolerance? And what do you give instead in case of posaconazole and fluconazole?
24. In your experience, during a hospital stay for immunocompromised patients with neutropenia with fever, how often would a patient spend a day in the **ICU**? (Average number of days per week or month)
25. **Info of tests done for patients:** Which of the following tests would you use to monitor for prophylaxis efficacy from invasive fungal infections, and how often do you use the tests for the same patient (per day, week or month)? (check all that apply)

Test	Applied or not	Frequency (in Ward)	Frequency (in ICU)
Chest X-Ray			
CT scan			
Ultrasound scan			
MRI scan			
Blood C&S			
Urin C&S			
Non-Blood C&S			
Bronchoscopy			
lung biopsy			
skin biopsy			
lung wedge resection			
lumbar puncture			
PCR			
Serology			
Histology			
full blood count			

renal function test			
liver function test			
Galactomannan test			
Coagulation test			
CRP			
fibrinogen			

Appendix 5. Search Strategy, Pubmed, Phase-Ii of Thesis

Search Strategy:

#	Searches	Results
1	("Antifungal Agents"[Mesh] OR "Pre-Exposure Prophylaxis"[Mesh] OR prophylaxis) AND ("Mycoses"[Mesh] OR "Lung Diseases, Fungal"[Mesh] OR "Immunocompromised Host"[Mesh] OR "Neoplasms"[Mesh] OR Systemic OR invasive OR) AND ("Cost-Benefit Analysis"[Mesh] OR "Economics"[Mesh] OR "Costs and Cost Analysis"[Mesh]). Limited to journal articles	5139
2	("Antifungal Agents"[Mesh] OR "Pre-Exposure Prophylaxis"[Mesh] OR prophylaxis) AND ("Mycoses"[Mesh] OR "Lung Diseases, Fungal"[Mesh] OR "Immunocompromised Host"[Mesh] OR "Neoplasms"[Mesh] OR Systemic OR invasive OR) AND ("Cost-Benefit Analysis"[Mesh] OR "Economics"[Mesh] OR "Costs and Cost Analysis"[Mesh]).	5132
3	Limit 1 to journal articles, human, English language, and title and abstract	385
4	Limit 2 to RCT, Comparative articles, systematic reviews, meta analysis,	191

Appendix 6. Literature Data Collection Form, Phase-Ii of Thesis

Record number:
Reviewer:
- Checked by:

Date of review:
Author (All):
Year of Paper:
Journal (Full, In Abbreviation):
Title:
Volume/issue:
Method of Economic Evaluation (Cost Minimization, Cost Effectiveness, Cost Utility, Cost Benefit, cost analysis):
Comparative: Y / N
Intervention:
Comparator:
Country:
Population (Disease):
Participants:
- Age:
- Inclusion:
- Exclusion:

Sample Size (Intervention, Comparators):

Clinical Effectiveness Component
Study setting:
Clinical Effectiveness Data:
- Clinical Measure:
    - Definition:

Source of Effectiveness Data:
Time Horizon of Follow up:
Analysis Used:
Clinical Outcome Results:

Economic Effectiveness Component
Perspective:
Study setting:
Date of Analysis:
Dates of Economic Data:
Type of Time Adjustment (Inflation, Discounting):
Discount Rate:
Source of Economic Data:
Modeling:
- Type (Decision Analysis, Markov Model)
- If Markov,

    - Health States Considered:
    - Utility of these:
- Structure (Branches and Different Pathways)

Direct Medical Costs:
Direct non-Medical Cost:
Indirect Costs:
Measure of Benefit Used in Economic Evaluation:
Treatment of Uncertainty (Sensitivity Analysis):

- Inputs Varied (Clinical, Cost, Utility):
- Range of Variation:
- Types of Sensitivity Analysis (One-Way, Mutivariate, Scenario):
- Graphical Presentation of Results:
- Conclusions of Sensitivity Analysis:

Statistical Analysis:
Main Economic Findings:
Outcome Category:

	Higher Effect	Same Effect	Lower Higher
Higher Cost			
Same Cost			
Lower Cost			

Authors Conclusions:
Reviewers Comments:

- Reviewer Name:
    - Comment:
- Reviewer Name:
    - Comment:

Initial Extraction Complete Yes___ No___
Revision Complete Yes___ No___

Appendix 7. Prisma 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

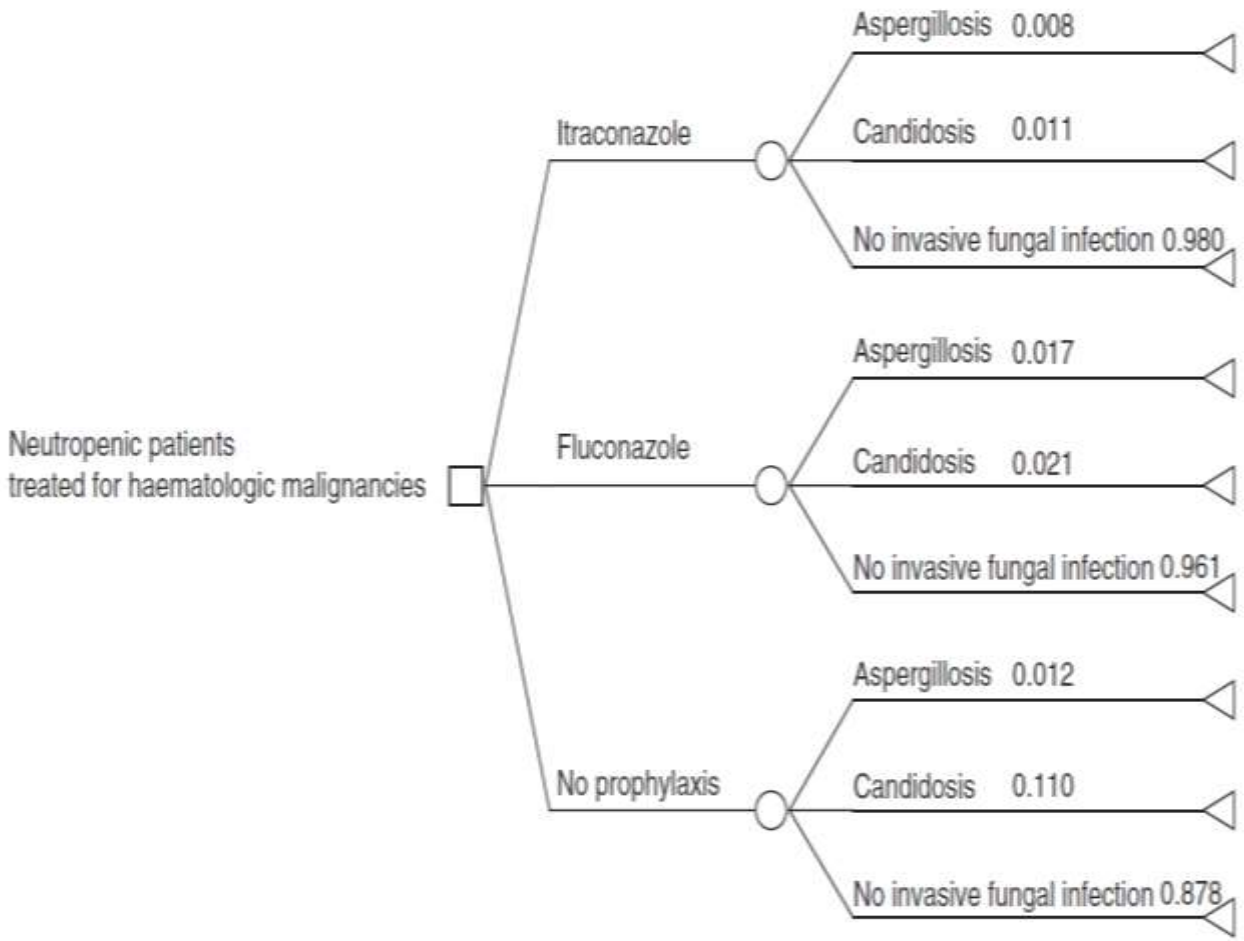
Appendix 8. Cheers Checklist

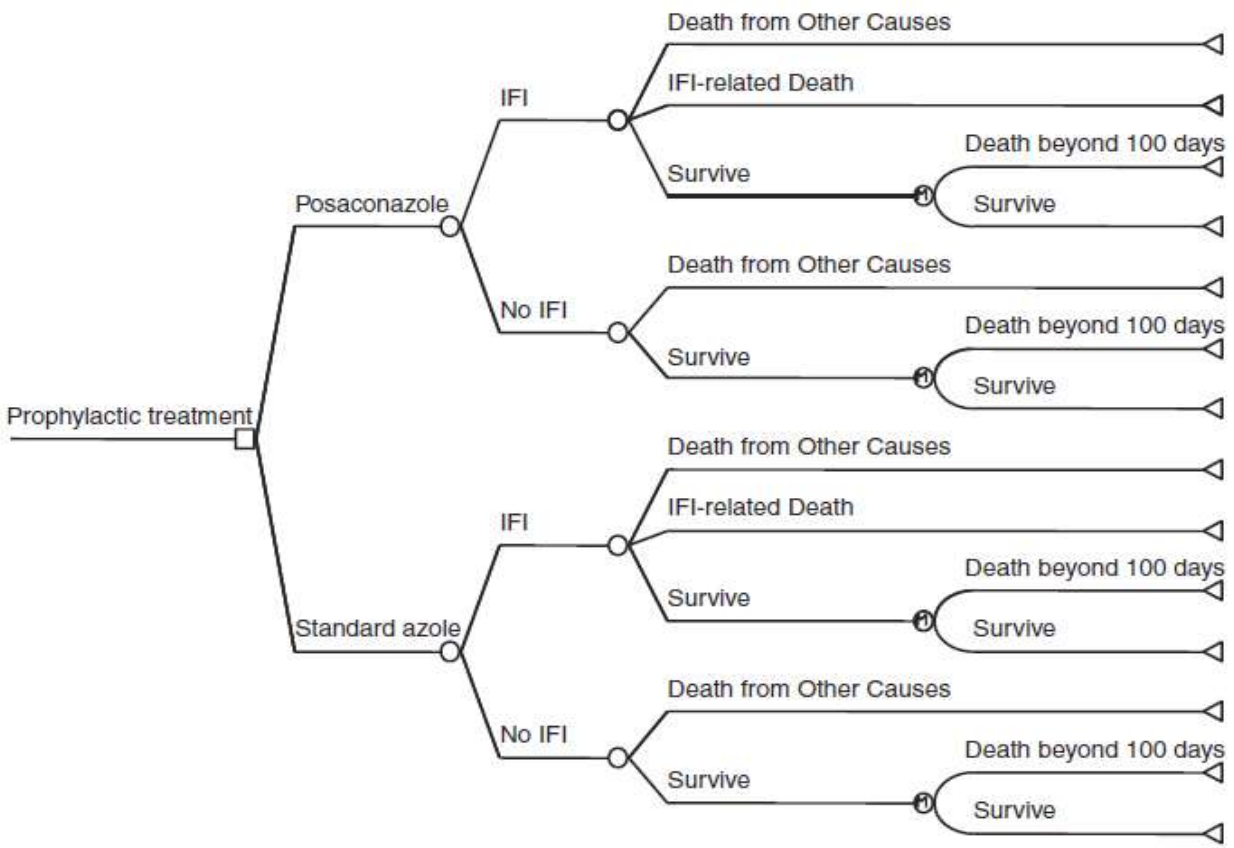
Section/item	Item No	Recommendation	Reported on page No/line No
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	

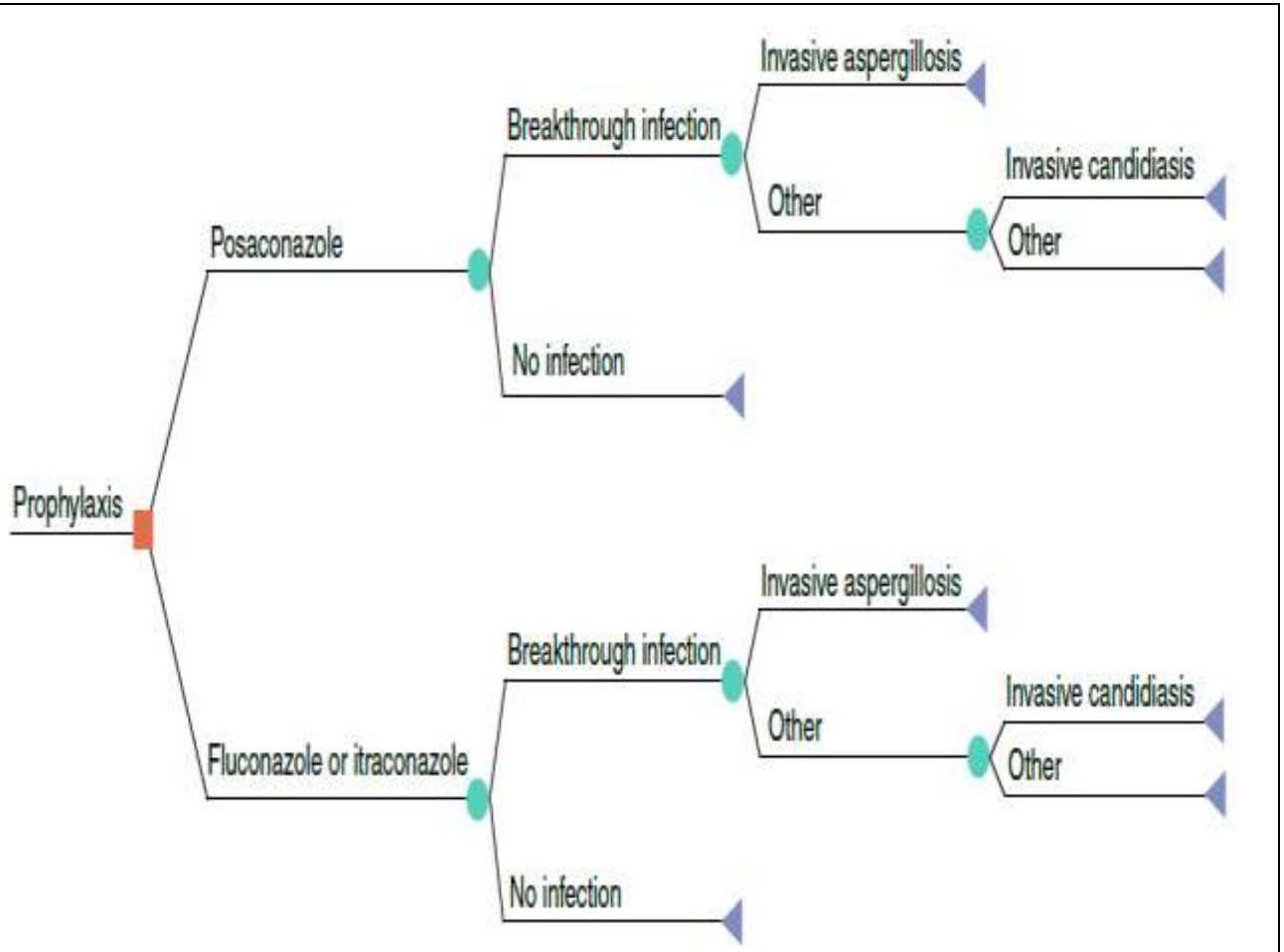
Section/item	Item No	Recommendation	Reported on page No/line No
Estimating costs and resources	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	

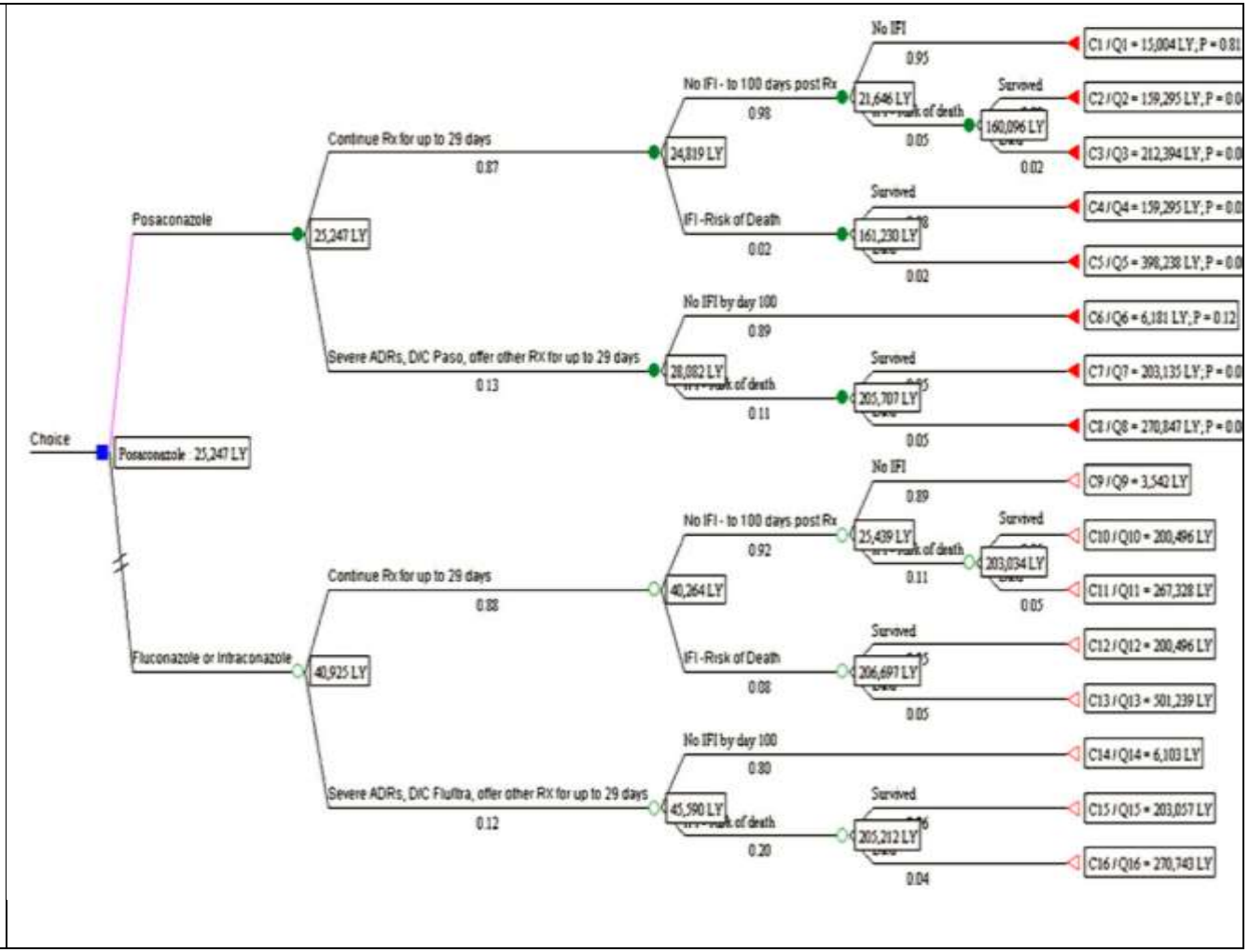
Section/item	Item No	Recommendation	Reported on page No/line No
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

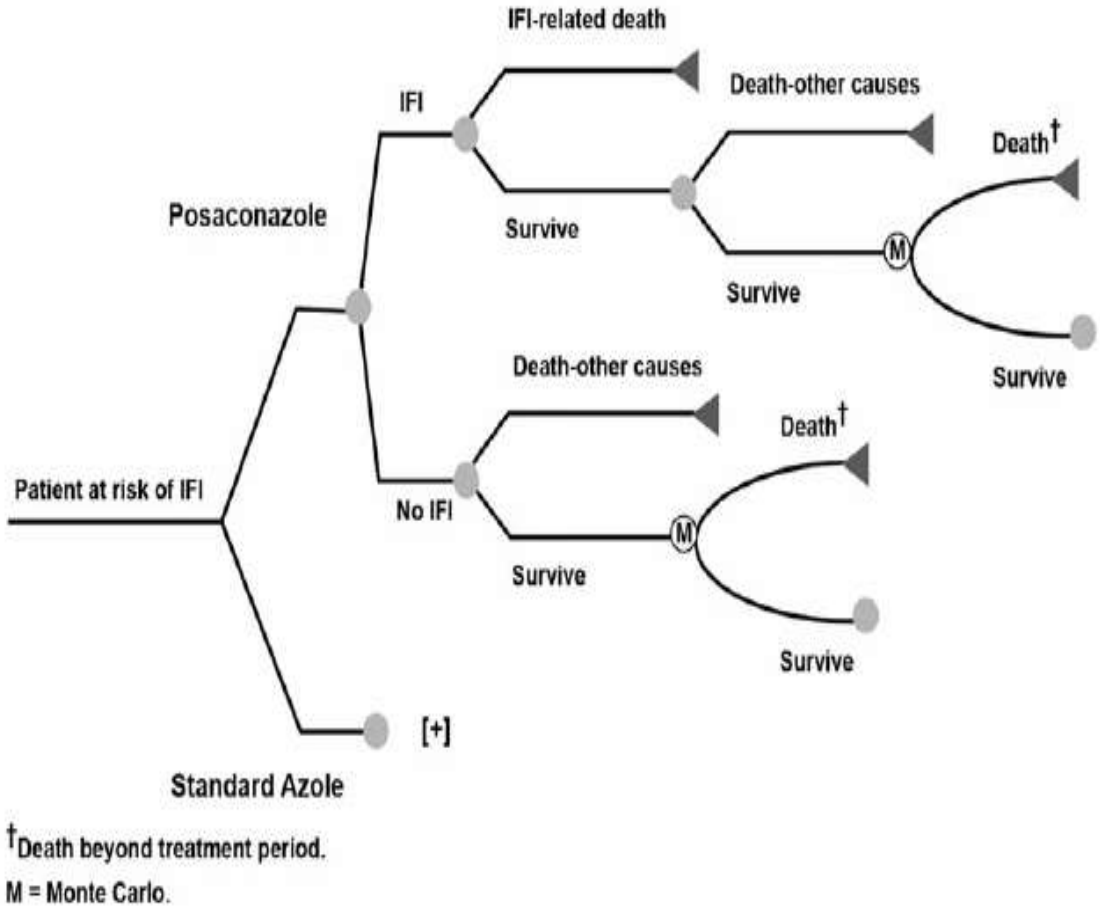
Appendix 9. Decision Trees as Presented in Included Systematic Review Articles, Phase-Ii of Thesis

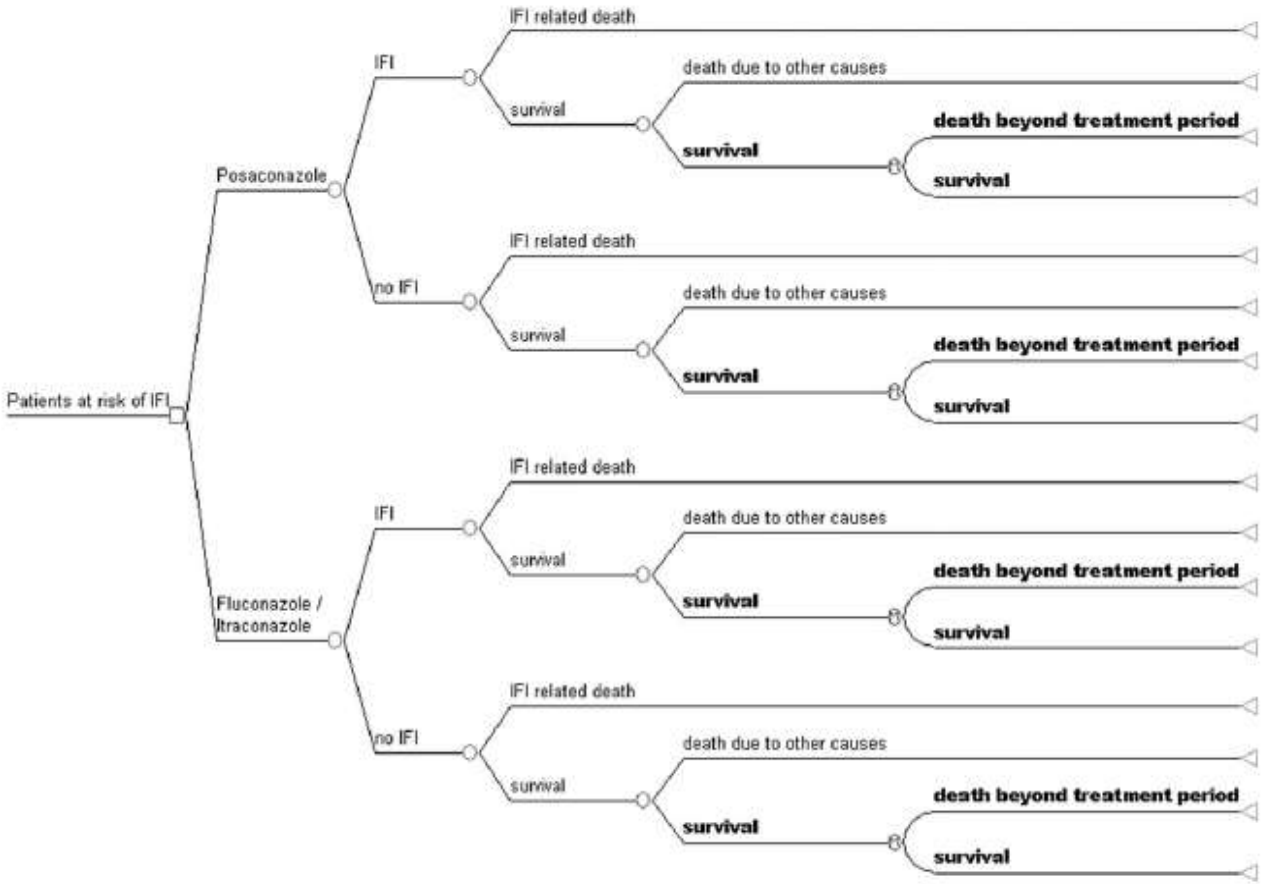
Record No.	Author's last name, year	Screenshot of decision tree
1	de Vries, 2006	

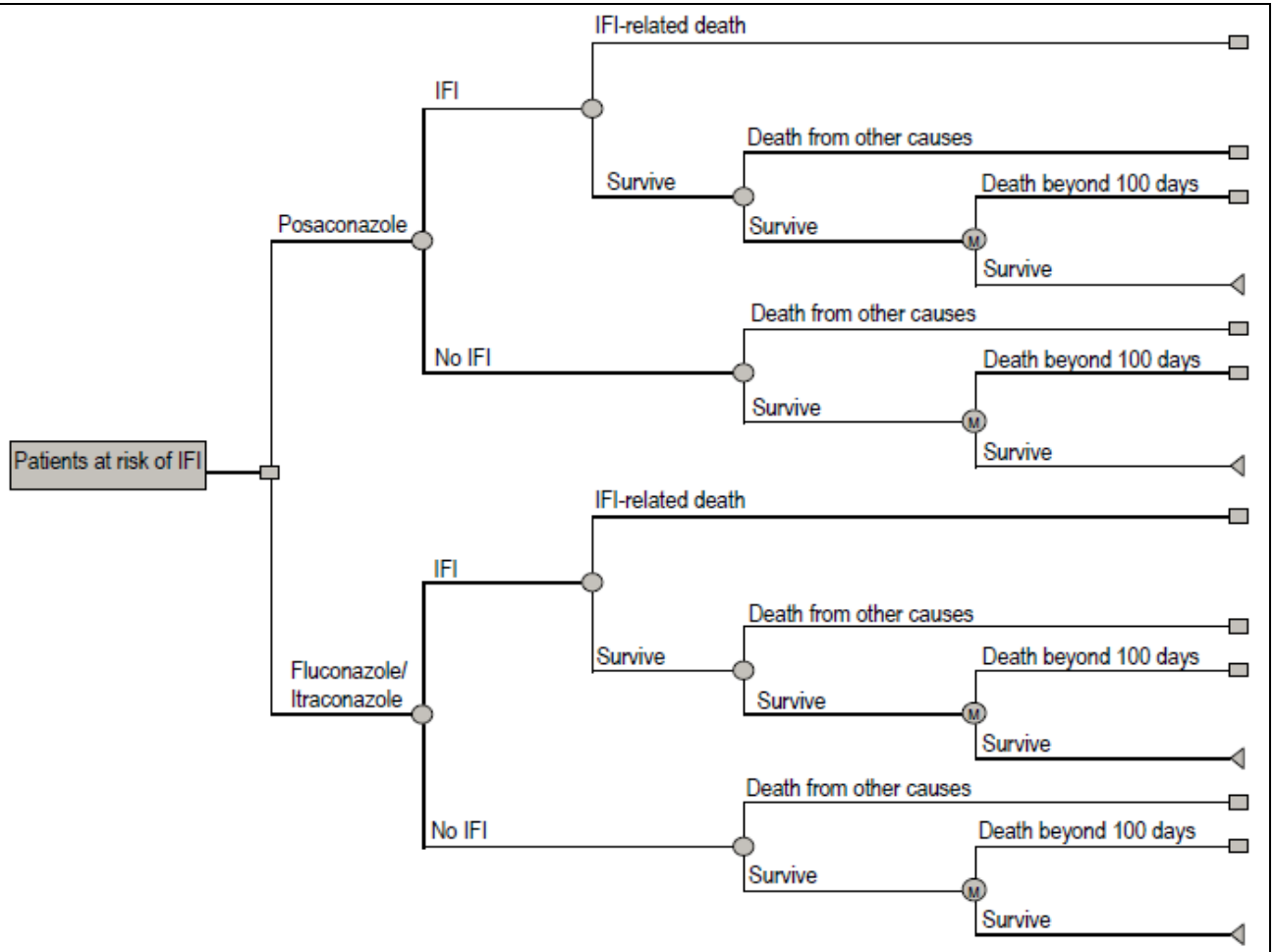
2	Stam, 2008	 Death from Other Causes IFI-related Death IFI Death beyond 100 days Survive Survive Posaconazole Death from Other Causes No IFI Death beyond 100 days Survive Survive Prophylactic treatment Death from Other Causes IFI-related Death IFI Death beyond 100 days Survive Survive Standard azole Death from Other Causes No IFI Death beyond 100 days Survive Survive

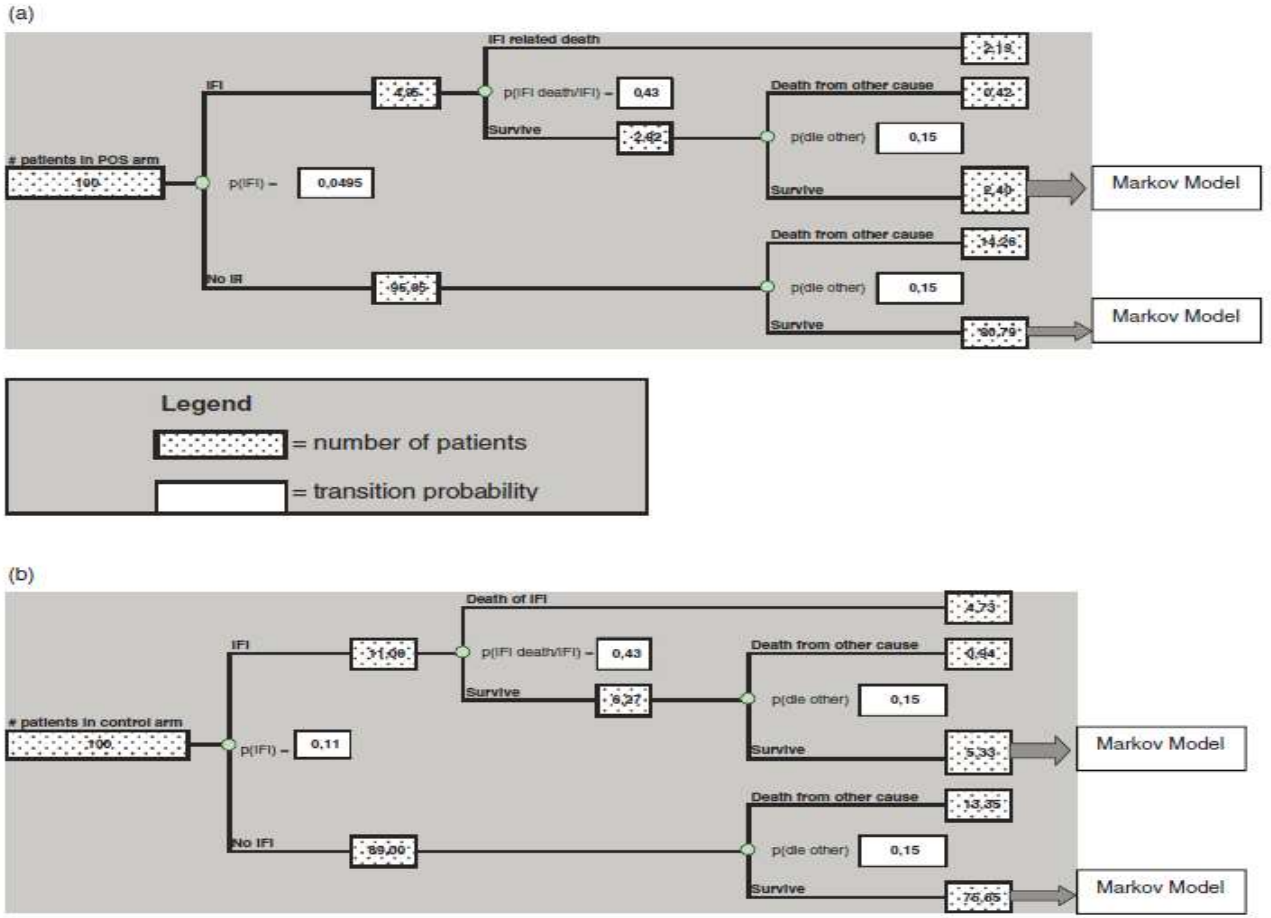
3	Collins, 2008	

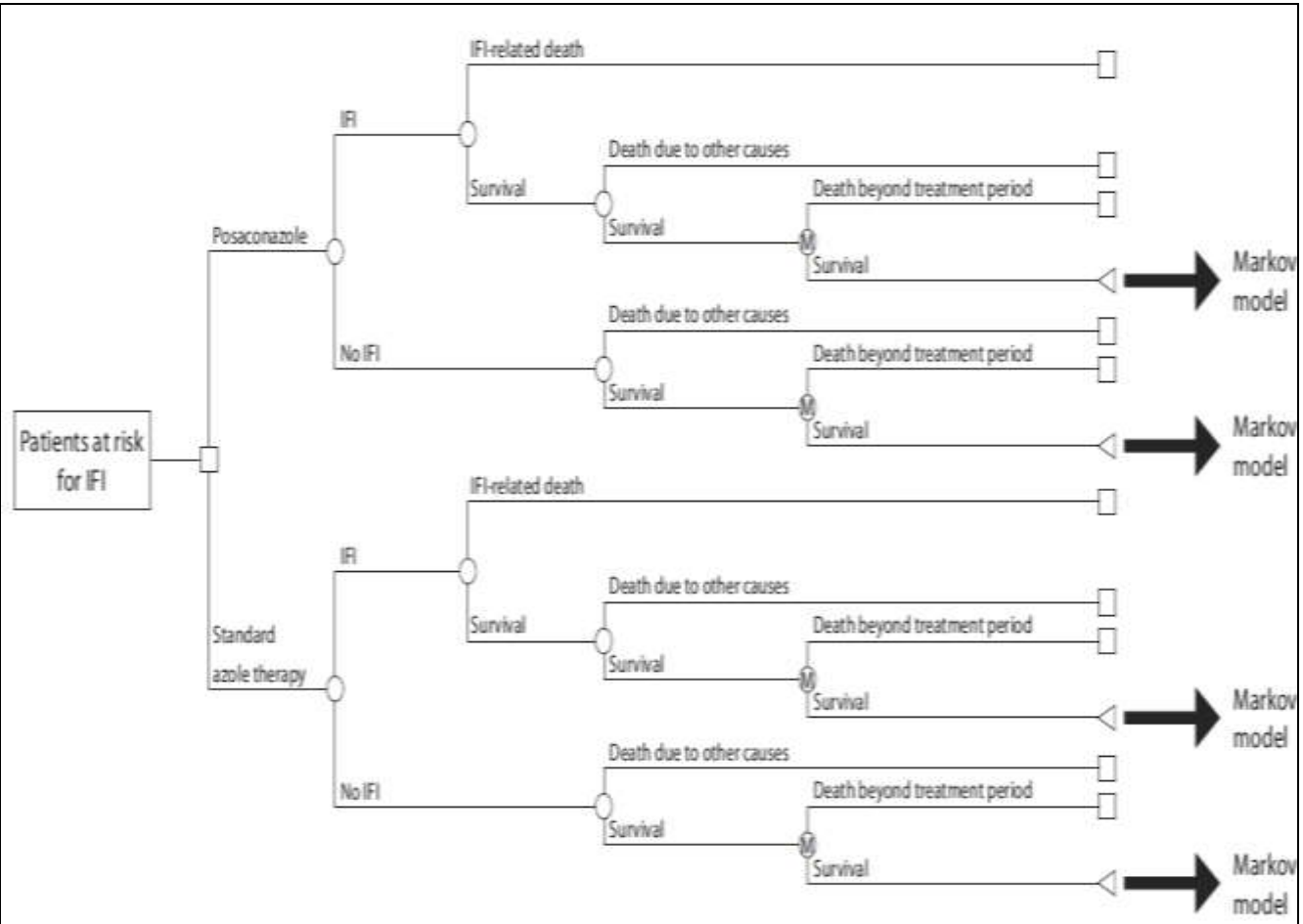
4	Dranitsaris, 2011	

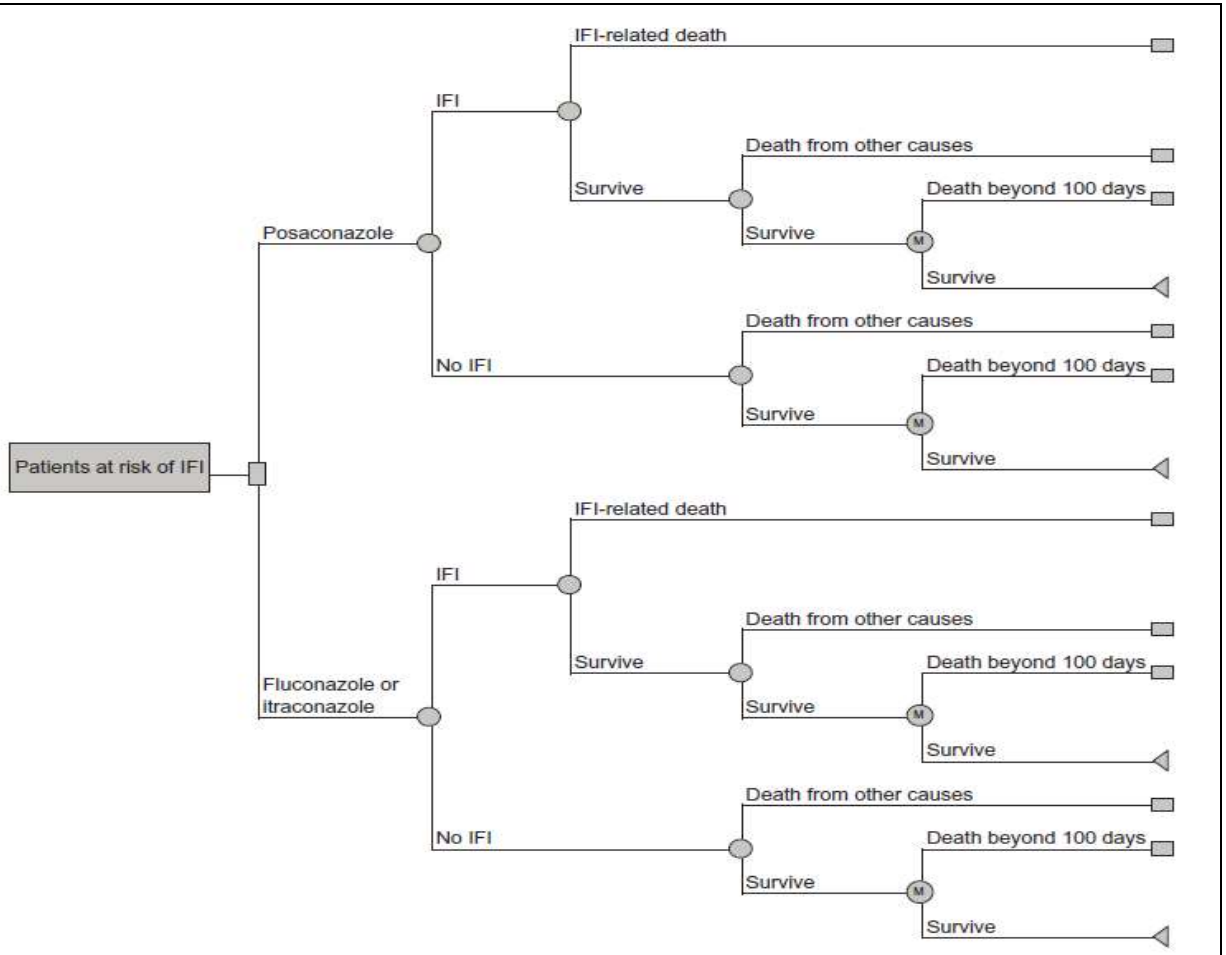
5	Papadopoulos, 2013	

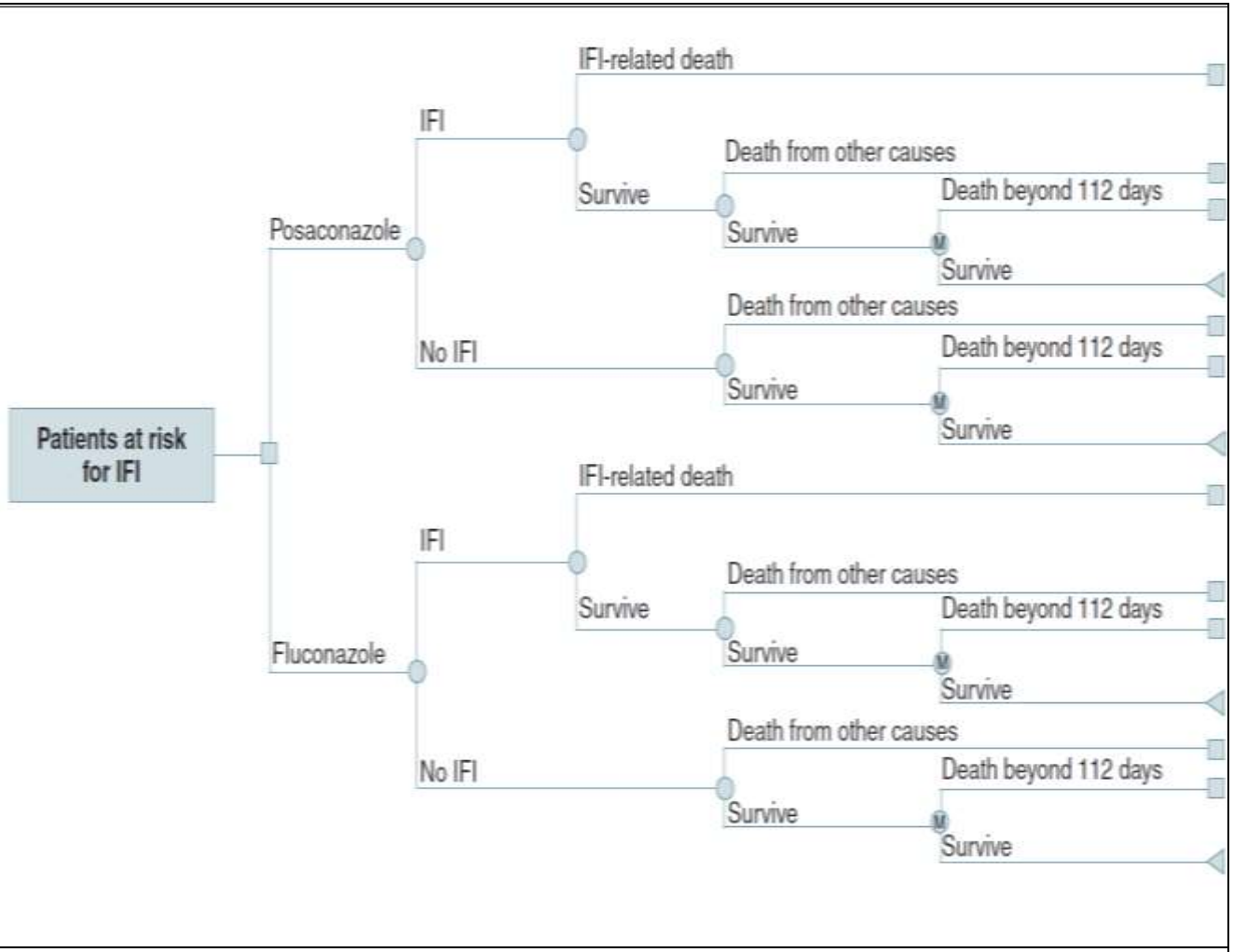
6	Athanasakis, 2013	

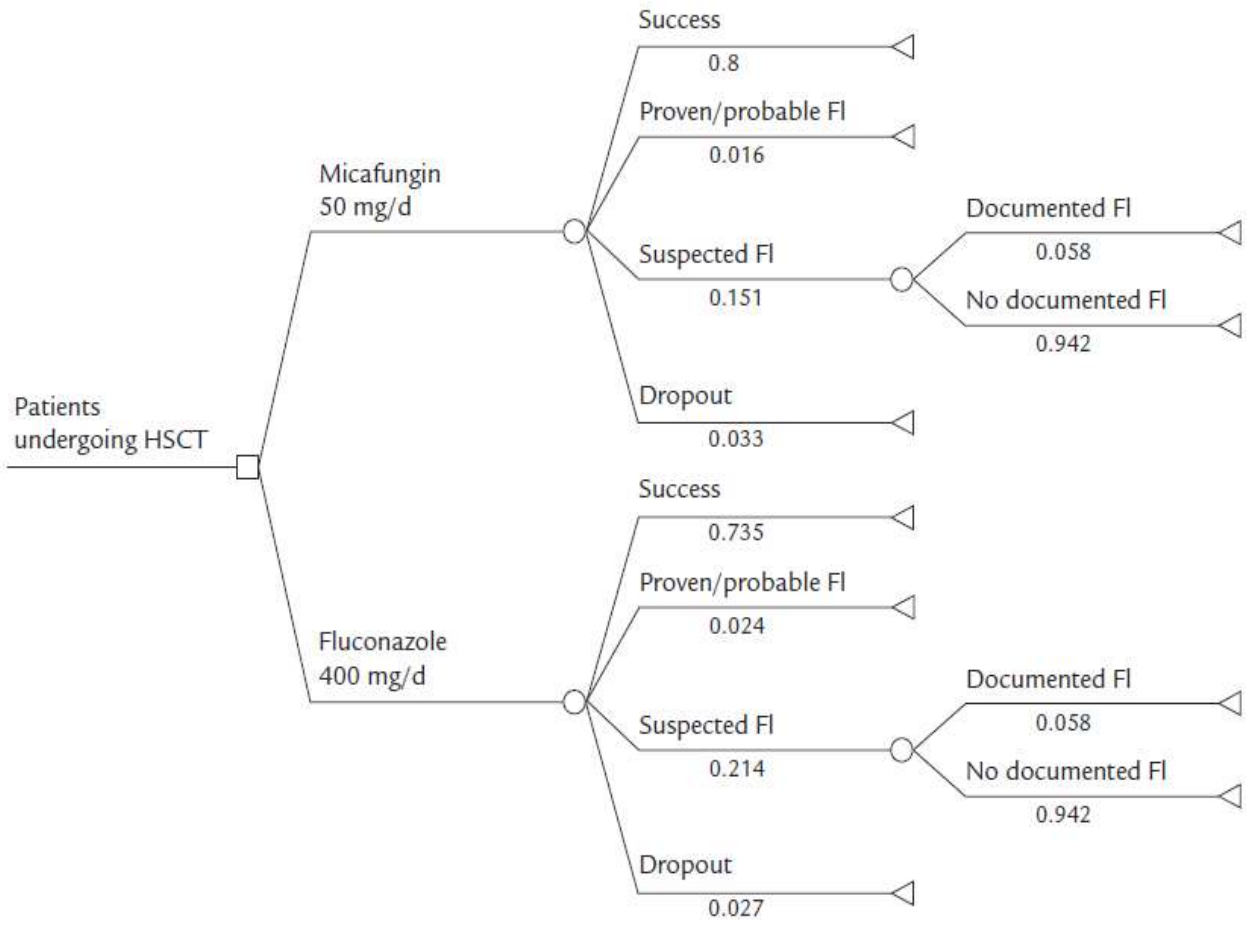
7	Grau, 2012	 Patients at risk of IFI Posaconazole Fluconazole/ Itraconazole IFI No IFI IFI-related death Survive Death from other causes Survive Death beyond 100 days Survive M

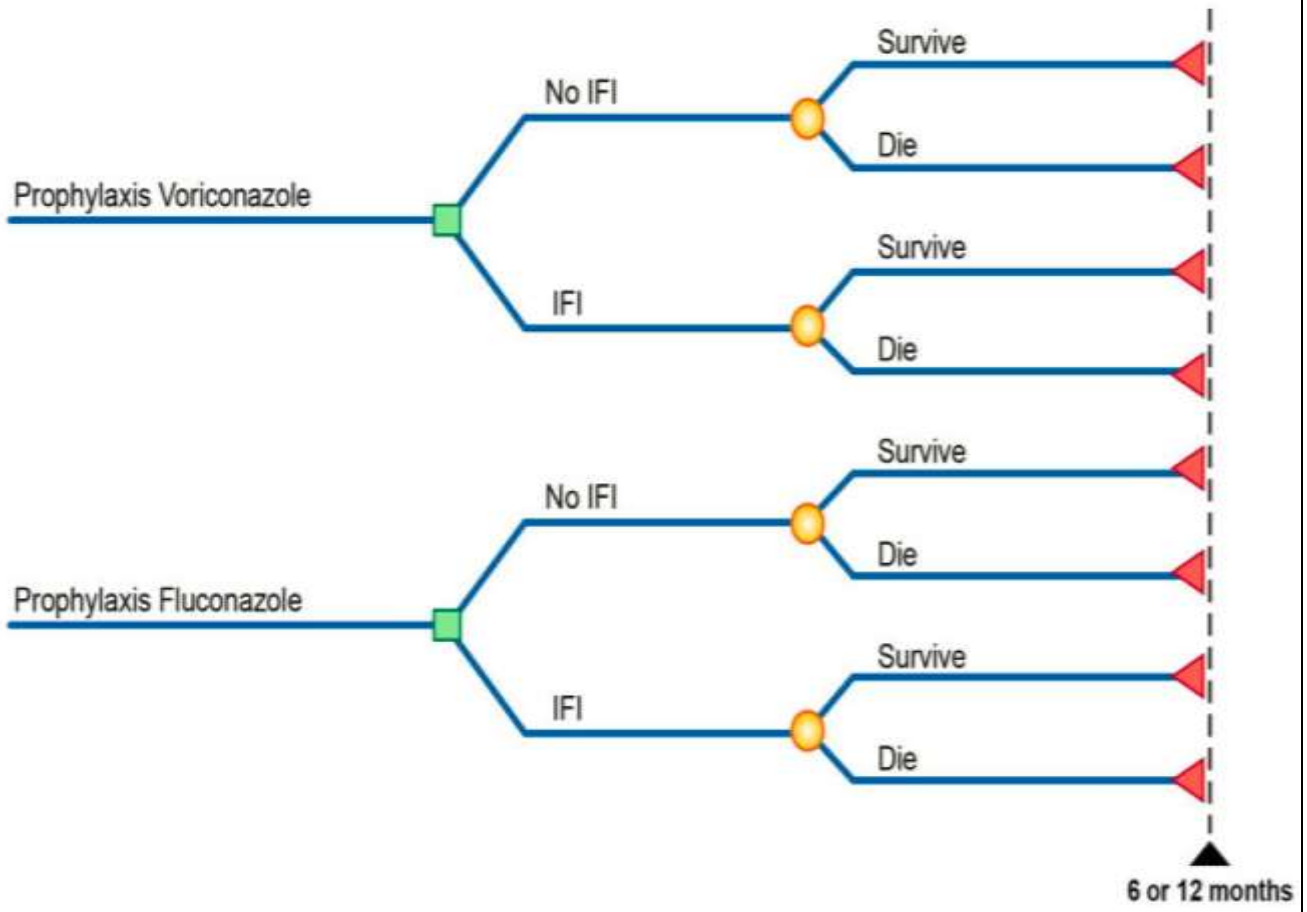
8	Michallet, 2011	

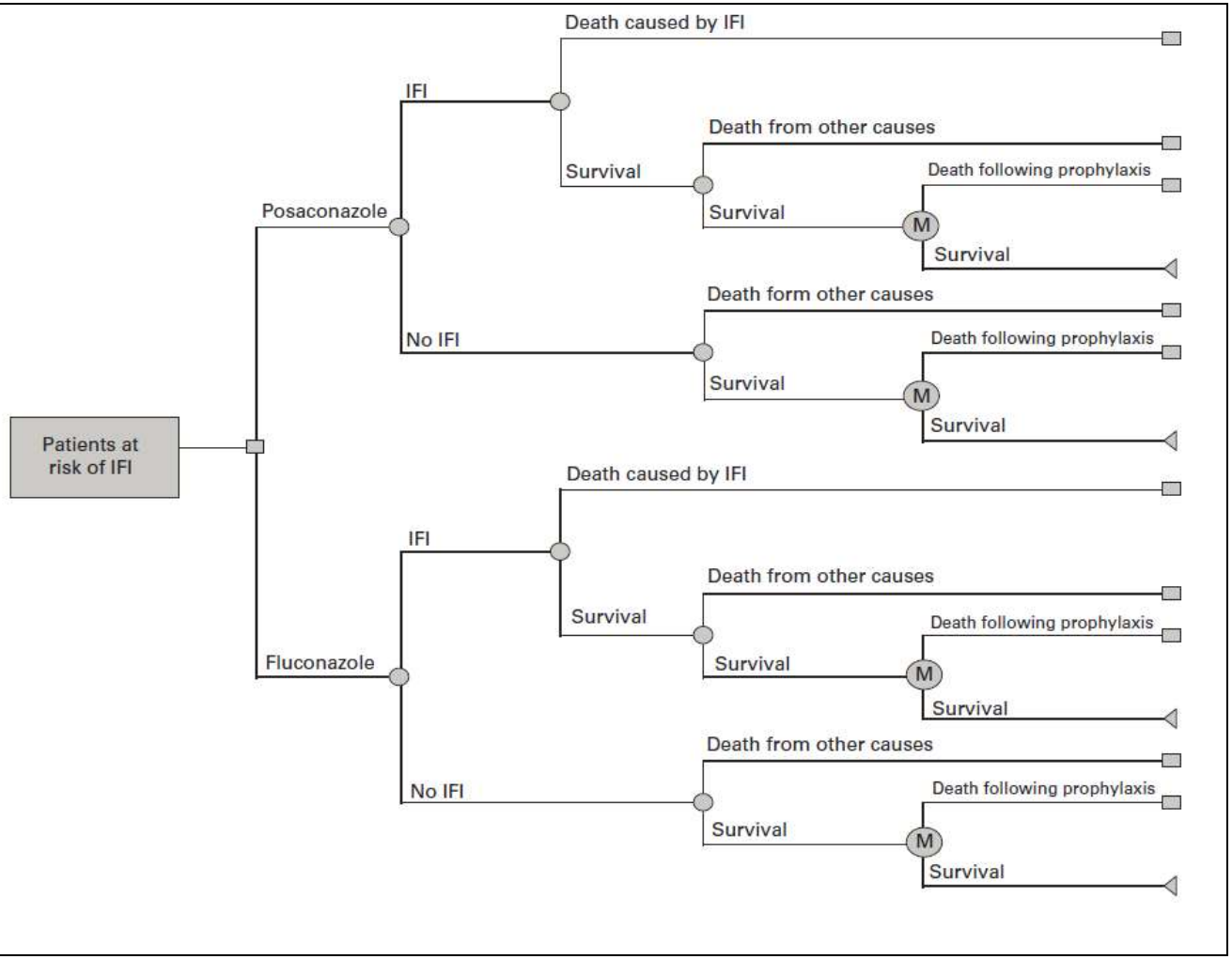
9	Greiner, 2010	

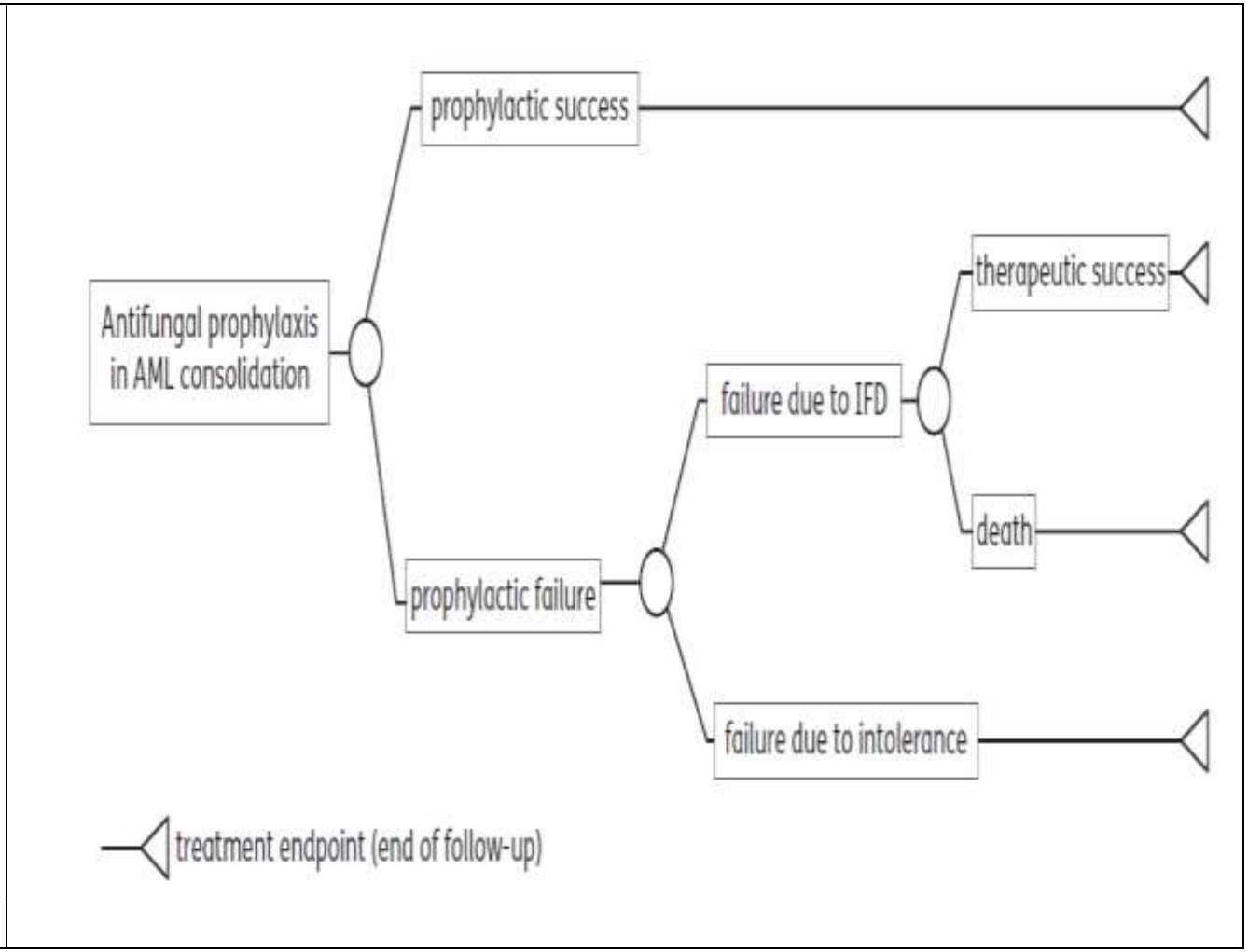
10	O'Sullivan, 2009	

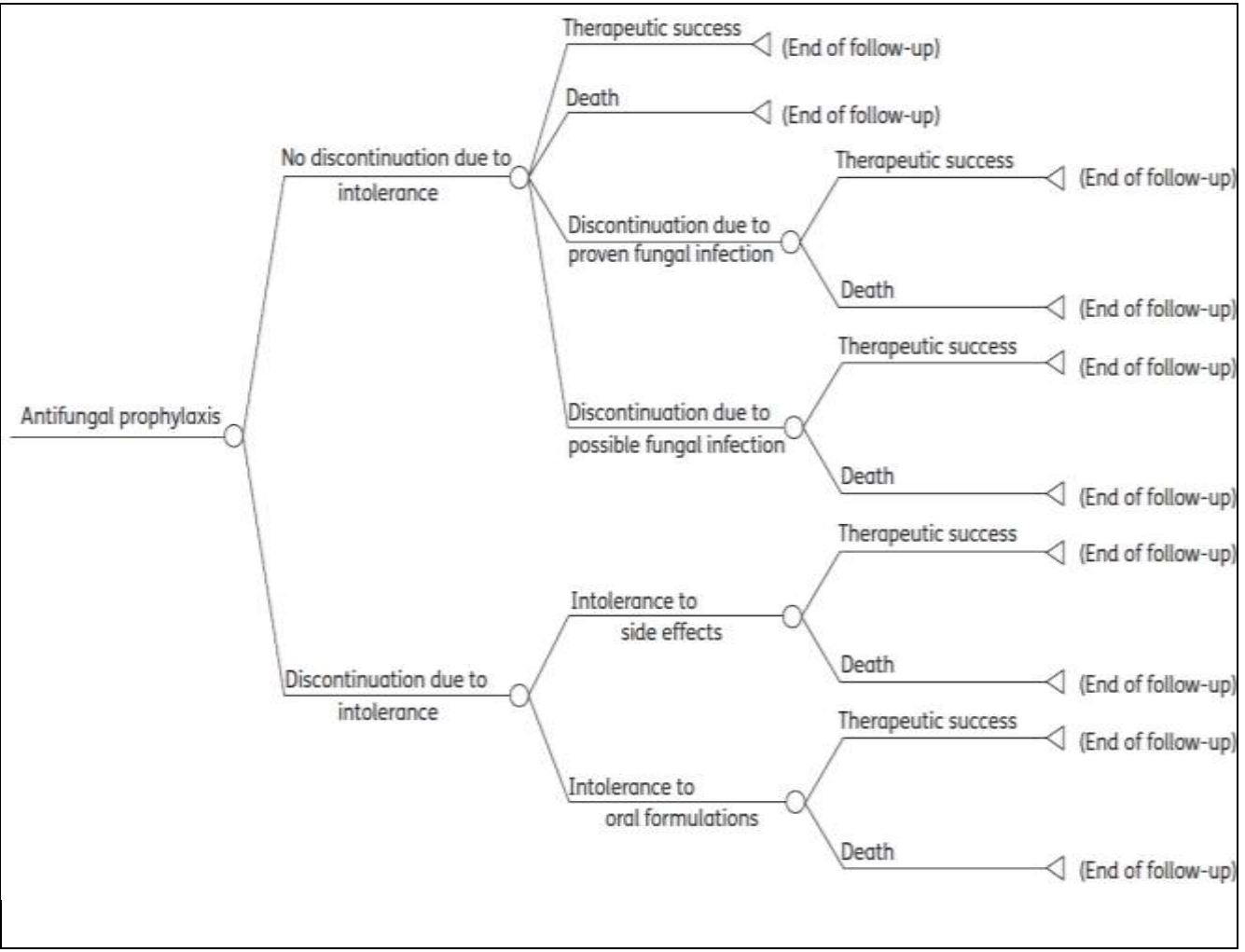
11	O'Sullivan, 2012	
12	Schonfeld, 2008	No tree provided

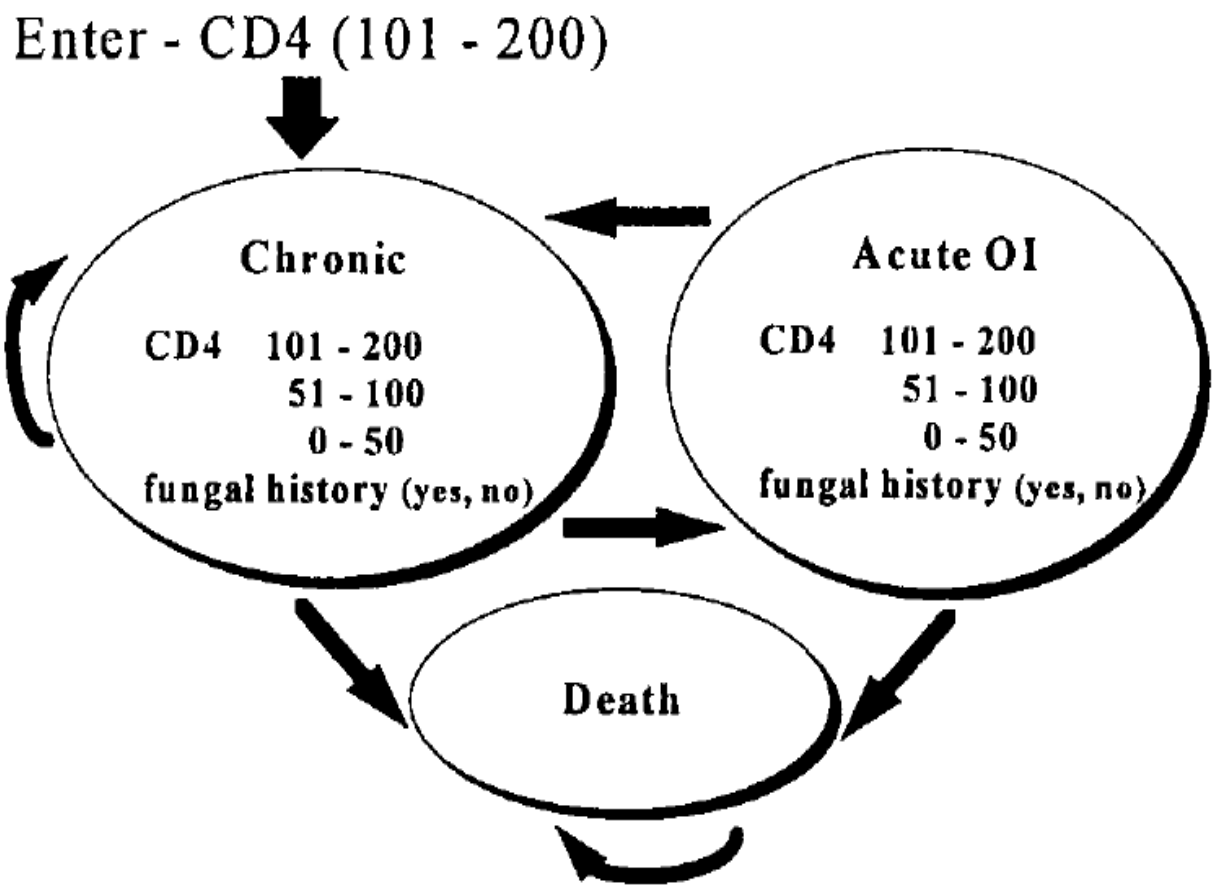
13	Sohn, 2009	 Success 0.8 Proven/probable FI 0.016 Micafungin 50 mg/d Documented FI 0.058 Suspected FI 0.151 No documented FI 0.942 Dropout 0.033 Patients undergoing HSCT Success 0.735 Proven/probable FI 0.024 Fluconazole 400 mg/d Documented FI 0.058 Suspected FI 0.214 No documented FI 0.942 Dropout 0.027

14	Mauskopf, 2013	
15	Sánchez-Ortega, 2013	No tree provided

16	de la Ca´mara, 2009	

17	Heng, 2013	 prophylactic success Antifungal prophylaxis in AML consolidation therapeutic success failure due to IFD death prophylactic failure failure due to intolerance treatment endpoint (end of follow-up)

18	Al-Badriyeh, 2010	

19	Scharfstein, 1997	

Appendix 10 Outcome Measure of All Included Systematic Review Articles, Phase-Ii of Thesis

Clinical Effectiveness Data				
Author's last name, year	**Study Setting**	**Clinical measure**	**Definition**	**Source of effectiveness data**
O'Sullivan, 2009	89 Clinical centers worldwide	Proven or probable invasive fungal infection IFI	According to consensus criteria of the European Organization for the Research and Treatment of Cancer and the Mycoses Study Group	Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348-59
Greiner, 2010	Hospital	IFI occurrence, IFI-related death and death from other causes	--	Wingard JR, Piantadosi S, Vogelsang GB, Farmer ER, Jabs DA, Levin LS, Beschorner WE, Cahill RA, Miller DF, Harrison D: Predictors of death from chronic graft-versushost disease after bone marrow transplantation. Blood 1989; 7 4: 1 428–1435. 1 Kantarjian H, Beran M, Cortes J, O'Brien S, Giles F, Pierce S, Shan J, Plunkett W, Keating M, Estey E: Long-term follow-up results of the combination of topotecan and cytarabine and other intensive chemotherapy regimens in myelodysplastic syndrome. Cancer 2006; 1 06: 1 099–1109. National Cancer Institute: SEER cancer statistics review 1975–2004. http://seer.cancer.gov/csr/1975_2004/sections.html (accessed January 15, 2008).
Sánchez-Ortega, 2013	Hospital	IFIs avoided and overall survival	Defined by the European Organization for Research and Treatment of Cancer criteria	They conducted an observational study at the Catalan Institute of Oncology, Hospital Duran i Reynals, Barcelona, Spain→ Sanchez-Ortega I, Patino B, Arnan M, et al. Clinical efficacy and safety of primary antifungal prophylaxis with posaconazole vs itraconazole in allogeneic blood and marrow transplantation. Bone Marrow Transplant 2011;46:733–9

Athanasakis, 2013	89 Clinical centers worldwide	Proven or probable invasive fungal infection IFI	According to consensus criteria of the European Organization for the Research and Treatment of Cancer and the Mycoses Study Group	Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348-59
Papadopoulos, 2013	89 Clinical centers worldwide	Proven or probable invasive fungal infection IFI	According to consensus criteria of the European Organization for the Research and Treatment of Cancer and the Mycoses Study Group	Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348-59
de Vries, 2006	Hospital	Occurrence of invasive fungal infection (candida or aspergillosis) during neutropenic state, which was assumed to be <1 year	-	(From 2 meta-analysis: (Rinaldi MG. Problems in the diagnosis of invasive fungal diseases. Rev Infect Dis 1991; 13: 493-5) + Kanda Y, Yamamoto R, Chizuka A, et al. Prophylactic action of oral fluconazole against fungal infection of neutropenic patients: a meta-analysis of 16 randomized, controlled trials. Cancer 2000; 89: 1611-25))
Dranitsaris, 2010	89 Clinical centers worldwide	Proven or probable invasive fungal infection IFI	According to consensus criteria of the European Organization for the Research and Treatment of Cancer and the MycosesStudy Group	Cornely OA, Maertens J, Winston DJ et al (2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 356:348–359
Michallet, 2011	89 Clinical centers worldwide	Proven or probable invasive fungal infection IFI	According to consensus criteria of the European Organization for the Research and Treatment of Cancer and the MycosesStudy Group	Cornely OA, Maertens J, Winston DJ et al (2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 356:348–359
Scharfstein, 1997	USA-endemic and non-endemic regions (not specified!)	Efficacy of fluconazole prophylaxis in IFI	A percentage reduction in the monthly probability of developing primary fungal infection (estimated as 70%)	Powderly WG, Finkelstein D, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. N Engl J Med 1995; 332:700-5.
Al-Badriyeh, 2010	Major Australian tertiary Hospital	Success	The absence of initial antifungal discontinuation for the duration of the induction stage	6 year (2003–09) retrospective chart review of AML patients
Stam, 2008	89 Clinical centers worldwide	Life years (no infection, breakthrough infection (invasive aspergillosis, Invasive candidiasis, others))	The expected life years per treatment arm were obtained by estimating the survival during as well as beyond the 100-d prophylactic period.	Cornely OA, Maertens J, Winston DJ et al (2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 356:348–359

de la Ca´mara, 2009	International , multicenter clinical trial	Survival	It was assumed that if patients with acute GVHD survived the 112 day following initiation of prophylaxis, the death rate due to chronic GVHD may be applied as surviving acute GVHD puts a patient at high risk for chronic GVHD	Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007; 356: 335–347.
O'Sullivan, 2012	89 Clinical centers worldwide	Probability of IFI, Probability of IFI-related death, Probability of death from other causes within 112 days, survival rate over 10 years, IFI treatment costs, daily drug cost, Mean duration of prophylaxis (days).	Survival means free of invasive fungal infections	Directly from randomized control trial.(Ullmann AJ, Lipton JH, Vesole DH et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med. 2007; 356:335-47.). some data were taken from secondary sources.
Soon Sohn, 2009	Hospital	Clinical outcome of prophylactic therapy in HSCT (Treatment success, Proven/probable FI or Suspected FI), Clinical outcome of empiric therapy, Mortality in HSCT, Life expectancy in HSCT (with or without fungal infection).	Treatment success was defined as the absence of proven, probable, or suspected systemic fungal infection through the end of prophylactic therapy and the entire analysis period. Proven infection was defined as biopsy-proven invasive or disseminated infection, or positive cultures of specimens obtained from the respiratory tract in conjunction with compatible findings on diagnostic imaging. Probable infection was considered present if diagnostic studies revealed fungal elements in conjunction with compatible clinical and radiographic findings. Proven/probable fungal infection was required to follow acute antifungal therapy. Suspected fungal infection was determined to exist if fevers persisted for >96 hours despite prophylactic antifungal treatment and if they required empiric therapy.	Park SH, Choi SM, Lee DG, et al. Current trends of infectious complications following hematopoietic stem cell transplantation in a single center. J Korean Med Sci. 2006; 21:199–207. Moeremans K, Annemans L, Ryu JS, et al. Economic evaluation of intravenous itraconazole for presumed systemic fungal infections in neutropenic patients in Korea. Int J Hematol. 2005;82:251–258. van Burik JH, Ratanatharathorn V, Stepan DE, et al, for the National Institute of Allergy and Infectious Diseases Mycoses Study Group. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis. 2004;39:1407– 1416. Min CK, Jeong W, Park SJ, et al. Stem cell transplantation in adult acute lymphoblastic leukemia. Korean J Hematopoietic Stem Cell Transplant. 1999;4:161–172. 13. Korea National Statistical Office. 2005 Life Tables of Korean Population. http://www.kosis.kr.

			Dropout was defined as loss to follow-up or death for any reason.	Accessed March 20, 2007. 14. Briggs A, Claxton K, Sculpher M. Decision Modeling for Health Economic Evaluation. New York, NY: Oxford University Press; 2006
Schonfeld, 2008	Hospital	Successful prophylaxis, Successful empiric therapy, Fungal infection candidiasis, Fungal infection aspergillosis, other fungal infection.	Treatment success, defined in the clinical trial as the absence of a proven, probable, or suspected systemic fungal infection through the end of the prophylaxis therapy, and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period.	Van Burik JA, Ratanatharathorn V, Stepan DE, et al, for the National Institute of Allergy and Infectious Diseases Mycoses Study Group. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis.* 2004;39:1407–1416.
Collins, 2008	89 Clinical centers worldwide	No infection, breakthrough infection (invasive aspergillosis, Invasive candidiasis, others)	Treatment failure was defined as the occurrence of a proven or probable invasive fungal infection; receipt of an intravenous study drug for 4 consecutive days or more or 10 days in total; receipt of any other systemic antifungal agent for 4 days or more for suspected invasive fungal infection; the occurrence of an adverse event possibly or probably related to the study treatment, resulting in the discontinuation of treatment; or withdrawal from the study with no additional follow-up	Cornely OA, Maertens J, Winston DJ et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med.* 2007; 356:348-59.
Mauskopf, 2013	Hospital	FFS(proven/probable/presumptive infections) or IFI (proven, probable or Presumptive)	FFS means alive and free from proven, probable, or presumptive IFI at 180 days post-transplant	Wingard JR, Carter SL, Walsh TJ et al., for the Blood and Marrow Transplant Clinical Trials Network. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood. 2010; 116:5111-8.
Grau, 2012	89 Clinical centers worldwide	Proven or probable invasive fungal infection IFI	According to consensus criteria of the European Organization for the Research and Treatment of Cancer and the Mycoses Study Group	Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al: Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007, 356:348-359

				Kantarjian H, Beran M, Cortes J, O'Brien S, Giles F, Pierce S, et al: Long-term follow-up results of the combination of topotecan and cytarabine and other intensive chemotherapy regimens in myelodysplastic syndrome. Cancer 2006, 106:1099-1109. General Spanish Council of Pharmacists. BOT database of pharmaceutical prices [http://www.botplusweb.portalfarma.com].
sHeng, 2013	Hospital	Success or failure (proven, probable, possible breakthrough IFD or intolerance)	Success was defined as completion of the designated full course of initial antifungal prophylaxis without breakthrough IFD. Failure was defined as the premature discontinuation of initial prophylaxis and switching to alternative therapy due to any of the following reasons: (i) proven, probable or possible breakthrough IFD, as defined by the European Organisation for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG), or empirical use of systemic antifungal treatment for clinically suspected IFD, or (ii) intolerance due to poor oral intake or gastrointestinal intolerance (e.g. diarrhoea, vomiting) or any other conditions that raised concern about oral absorption of the antifungal agent.	A retrospective chart review from Australian public hospital