The application of health technology assessment in Egypt: Case study using Hepatitis C.

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A dissertation presented by

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Summary

The application of health technology assessment in Egypt:

case study using hepatitis C

The staggering prevalence of Chronic hepatitis C virus (HCV) infection in Egypt ranging from 15-20% places tremendous demands on the health care system and the society. This fact made it a good example to use to measure the feasibility of pharmacoeconomic and health assessment research in Egypt. The study attempted to answer some of the questions that policy makers and physicians need to address and patients need to consider when undertaking treatment of HCV infection. A critical appraisal was also included to confront and to highlight some additional issues that need be addressed, amended and/or altered when undertaking treatment decisions regarding HCV.

In this study, cost of the disease was calculated as well as the cost effectiveness of the various treatment options available: the supportive treatment pathway and both standard interferon and pegylated interferon combination treatment pathways. Outpatients and inpatients with chronic hepatitis C liver cirrhosis frequenting the National Liver Institute, Menoufia, Egypt's largest and busiest public tertiary referral government health subsidized center. The mean annual cost per patient was assessed and the data computed using computer cohorts of 100 patients following the Markov models of the natural history of disease progression. It was found that the cost of pegylated interferon combination therapy over the full cycle of the disease was the most cost effective alternative amounting to 75 704.61LE versus 144 872.23LE and 92 155.61LE for the supportive and the standard interferon treatment pathways respectively and thus its cost effectiveness values were negative compared to the other pathways. The same results were true for patients visiting private profit and non profit medical settings. This in turn helps to emphasize the importance of adopting health economic evaluations in the determination of efficiency of the health care services and policies in Egypt.

It was concluded that it was more cost effective to use antiviral therapy in relation to the cheaper supportive option where not only cost effectiveness ratio was negative for both the regular interferon and the pegylated interferon alternatives but also 10% and 14% of lives were saved respectively. The study proves the feasibility and the importance of implementing health economics and health technology assessment studies towards health improvement in Egypt. It further highlights that informed decision makers can have a positive effect on the health budget and consequently on unwritten social contract and ethical guidelines they have with their communities and society at large.

Declaration

I, May M. ElBatran certify that this research has not already been accepted in substance for any degree or award, and is not being concurrently submitted in candidature for any degree or award.

Date: ---------- ----------

May M. ElBatran

Statement

This investigation was conducted entirely by me. The data was collected mainly from the National Liver Institute, Menoufia University, Egypt. I also included in my research two other private hospitals. The first is a private non profit hospital dedicated solely for liver disease having inpatients and outpatients. The second was particularly important because it is the only private hospital that performs liver transplants in Egypt. Moreover, data and costs about outpatients private and for profit clinics were collected from three specialized outpatient centers. All the data collection, analysis, writing of the thesis and any other work concerned by this work was undertaken by me.

Date: ----------

May M. ElBatran

Statement of availability

I, May M. ElBatran, hereby give my consent for my thesis to be available for photocopying, for interlibrary loan and for the title and summary to be made available to outside organizations.

Date: ----------

May M. ElBatran

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Mother, you are my light and my support, without your help and guidance this would not have come to life.

Father, you are my backbone and safety net, your perseverance was always inspiring to me.

Ossama, I expect a dedication in your PhD or whatever you do too!!

I love you all

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Glossary of Terms

Abbreviation	Term
AC	Average cost
ALT	Alanine aminotransferase
AWP	Average wholesale price
AWAP	Average wholesale adjusted price
CBA	Cost-benefit analysis
CBE	Central Bank of Egypt
CE	Cost Effectiveness
CEA	Cost-effectiveness analysis
CF	Cost function
CMA	Cost-minimization analysis
Comp	Compensated
CUA	Cost-utility analysis
Decomp	Decompensated
EASL	The European Association for the Study of the Liver
EBHC	Evidence based healthcare
EBM	Evidence based medicine
FC	Fixed cost
FDA	Food and Drug Administration
GTP	Guanosine triphosphate
HBV	Hepatitis b virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis c virus
HTA	Health technology assessment
HYE	Healthy years equivalent
IFN	Interferon
IL	Interleukin
IVDU	Intravenous drug use
LE	Egyptian pounds
LTx	Liver Transplantation

MC	Marginal cost
MOH	Ministry of Health and Population
NHS	National Health System
NHL	Non-Hodgkin's lymphoma
NICE	National Institute for Clinical Excellence
NIH	National Institute of Health
NLI	National Liver Institute
NR	No Response
OECD	Organization for Economic Co-operation and Development
Pts	Patients
PAT	Parenteral Schistosomal Therapy
PCR	Polymerase chain reaction
PEG IFN	Pegylated Interferon
QALY	Quality-adjusted life-year
QOL	Quality of life
R	Respond
RCT	Randomized controlled trial
RNA	Ribonucleic acid
SEER	Surveillance, Epidemiology, and End Results
SF	Short Form
SVR	Sustained virological response
TC	Total cost
ttt	Treatment
US	United States
VA	Veteran association
VC	Variable cost
WHO	World Health Organization

Chapter 1

Introduction and Aim of Work

Health services and the amount of resources required for their provision is among the most controversial and debatable social and political issues of our time. However, aside from the short-term political controversies, the more fundamental issue of the health service dilemma has been taxing the minds of all governments in the developed world and is increasingly becoming apparent in developing countries (Phillips and Prowle, 1992; Phillips, 2003 and Palfrey *et al*, 2004). This health service (or healthcare) dilemma is part of a wider economic problem which affects individuals, organizations, societies, economies and ultimately the global community. The attempts to deal with health and healthcare problems, to reduce the magnitude of their negative effects and to achieve a closer fit between the supply of services and demand for healthcare both constitute a challenge for healthcare officials and decision makers. Egypt, unlike developed and western countries, has very little practical or theoretical experience to incorporate cost issues within clinical decisions and guidelines. Taking into consideration that rich countries able to devote significantly greater levels of resources to healthcare services provision, are increasingly utilizing health economic techniques alongside evidence based approaches to inform decision-making bodies and to establish priorities in relation to healthcare. The question arises whether developing countries, such as Egypt, where the levels of resources are even more limited should consider the need to embrace such techniques in seeking to maximize the healthcare benefits for their societies / residents. In addressing this issue, the feasibility of employing evidence-based approaches and health economic techniques in the decision-making process, within a culture not only dominated by the perception of the medical community to provide treatment for all, but also which is severely constrained by resource availability, has to be established.

It is important to stress at the outset that health economics as emphasized in this research is not necessarily concerned about controlling expenditure, but it is rather a set of tools or a technique which can be utilized to ensure that whatever available resources are allocated to generate the maximum benefits for society (Jefferson *et al,* 2000). In addition, these tools and/or technique can be regarded as key for doctors, decision-makers and other healthcare professionals ensuring that they do the most good that could be done with the available resources (Williams, 1993). Moreover, the adoption of these tools does not compromise the medical profession's desire to provide treatment as such, but encourages healthcare professionals to address the existence of ineffectiveness and inefficiencies in service provision and to consider costs issues in their clinical decisions. This leads to best allocate the available resources and to secure the greatest health benefits for their patients and ultimately their whole community.

The adoption of a more evidence-based perspective alongside health economic techniques by policy makers will result in an explicit approach to priority setting becoming evident. This in turn may affect current thinking and decision-making at all levels and will require a fundamental cultural change. Alternatively it will yield a more efficient allocation of healthcare resources. Being a developing country, Egypt and its government, is no exception in its attempts to offer remedies and solutions for an increasingly complex set of problems.

Aims and objectives

This project aims to assess the extent to which health technology assessment might contribute to the decision-making process relating to healthcare provision and delivery in Egypt, using hepatitis C as a case study. In addition this project aims to

identify treatment alternatives of HCV, measure and value their costs and compare them against each other. The specific objectives are to:

- assess the cost of hepatitis C virus (HCV) treatment in Egypt
- evaluate the effectiveness of treatment strategies for HCV in Egypt by adopting evidence-based guidelines
- calculate the cost effectiveness of the various treatment options
- apply health technology assessment as a methodology aid to healthcare policy and decision making in Egypt
- maximize effective delivery of appropriate healthcare methodology in Egypt
- explore means for increasing the use of health technology assessment techniques in healthcare policy making and expenditure decisions in Egypt.
- answer some of the questions that physicians need to address and patients need to consider relating to the cost of the disease and effectiveness of treatment when undertaking treatment of HCV infection.

The rationale for using HCV as a case study, derives from the significant burden that it places on the Egyptian healthcare system (Strickland, 2006), and the exorbitant costs of alternative treatment strategies available for managing the condition. This study, to the best knowledge of the author, is amongst the first studies to assess cost effectiveness of HCV treatment in Egypt. In essence, this study provides both the theoretical background and the practical applications required to assess the value of HCV treatment in Egypt.

The literature review begins with introducing health economics as a concept; and health technology assessment as an essential methodology aid for dealing with healthcare issues and for capitalizing on healthcare systems' effectiveness worldwide. This is then followed by a dissertation on HCV, as a disease and its health

implications from a global perspective. The systematic review of evidence in this study then considers the available interventions for HCV treatment and examines their effectiveness. The explanation of the uniqueness of the Egyptian situation comes next in terms of the prevalence of HCV, the reasons for it, the implications and burden of HCV and finally current treatment patterns and services. The proposed design and methodology starts with choosing the medical settings for the field research, it then, leads to assessing the cost components of treatment which include drugs and services given to HCV patients in Egypt and ends with the estimation of the disease cost. The Markov models from published literature were used for the analysis of the cost effectiveness of available treatments. The collected data was computed and costs' components of the treatment alternatives were first calculated and then discussed in relation to the international costs of HCV treatments. The cost components and effectiveness data calculated emphasized the importance of health assessment benefits within the boundaries of the Egyptian healthcare system. The conclusion ends with the implications of assessing the effectiveness of HCV's best treatment alternative and its cost effectiveness. The study highlights the feasibility and the importance of implementing health economics and technology health assessment studies towards health improvement in Egypt. This fact is accentuated by the initiation and implementation of the national new mandatory HCV interferon treatment centres throughout the country.

Chapter 2

Healthcare Economics

And Health Technology

Assessment

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2.1. Background

Resource allocation and healthcare

The exponential augmentation of demands placed on healthcare services against limited resources available to meet them, is the core of the decision making dilemma and a major concern for those at all echelons of policy and decision-making. The global problem the decision-maker faces is too complicated to solve directly, he should reduce it to a series of simpler problems, solve each of them, and then combine these solutions in a consistent and reasonable way to solve the original problem (Williams, 1974). In any decision making situation, choosing an option depends on two key factors: the decision maker's *uncertainty* about what will happen if an option is chosen; and the relative *desirability* of the possible outcomes (Robinson, 1993 a).

The utilization of economic evaluation techniques and other approaches, in the form of health service research which most directly pertains to decisions about the allocation of resources, should be explored and indeed be used by Egyptian decision makers, to assist them in their struggle to balance the competing claims made on limited resources by a variety of parties, each of whom have strong and worthy rationales to underpin their particular case (Drummond, 1987).

Health economics is a logical and explicit framework to aid healthcare workers, decision makers, governments, or societies at large, to make decisions on how best to use resources (Jefferson *et al,* 2000). It represents a way of thinking about the problems relating to the allocation of limited healthcare resources and how to generate the most beneficial outcomes for society as a whole.

Health economics is itself relatively young; the first book on this subject was published in 1973 with barely any systemic reference mention before the mid sixties (Cooper and Culyer, 1973). The term pharmacoeconomics has an even more recent

history, and although primarily used by the pharmaceutical industry and academic institutions, it was later used with outcomes research by pharmacy practitioners to assess the value of pharmacy compared to the rest of the healthcare system and to society. Pharmacoeconomics and outcomes research identify, measure and compare the cost (all resources consumed both direct and indirect ones) and consequences (clinical, humanistic, economic and social) of pharmaceutical products and medical services. Clemens *et al*, (1993) reported a definition that incorporated pharmacoeconomic research into the process of drug development from inception (pre phase one) up to phase four when post marketing surveillance is taking place. They reported that pharmacoeconomics research "assesses the implications of projected outcomes and costs of pharmaceutical products for the decision whether to continue or to stop development of a drug and for global pricing strategy" (Clemens *et al*, 1993). Furthermore, with soaring healthcare budgets, attention has turned to the economic efficiency or so called "cost-effectiveness" of diagnostic and therapeutic medical interventions; consequently pharmacoeconomics has emerged as an increasingly important area of research.

New drug evaluations traditionally involved phase I studies of drug safety and dosing for a particular condition, followed by phase II and III randomized controlled trials to evaluate drug efficacy. Occasionally, a post marketing surveillance study might be performed to evaluate drug effectiveness in a less controlled setting (Wong, 1999). Pharmacoeconomics research has been directed towards not only the refinement of the research methods and their application to evaluating pharmaceutical services and specific drug therapies, but also towards helping in making important clinical and managerial decisions, whereupon pharmacoeconomics' role does not remain the same during the different phases of drug development. In the early phases, it helps the

identification of commercially viable options with their respective market niches which could be profitably exploited (commercially) emphasizing on informing pro and con decisions about product development. While in later phases (stages), it affects decision making by supplying the necessary information regarding both the appropriate use and the rational prescription of the developed drugs, thus acting as a tool of management used in strategic and operational decisions about pharmaceutical development, production or consumption and ultimately ensuring the most efficient use of limited resources.

As such pharmacoeconomics is evolving as a new discipline that can help many people, every day, with many important health and lifestyle decisions. Pharmacoeconomics is a branch of health economics which aims to address the concern of the value of drug and medical therapy, which is a function of its benefits as well as its costs, and it also aims to ensure that resources are allocated to effective interventions. To continue to define pharmacoeconomics and what it means to do high-quality health economic research; there is an opportunity and indeed an obligation to apply knowledge and skills at the patient's bedside, work place, and home. Knowledge of economics, outcomes, and quality of life is taken, and involved with patients directly and more completely in their healthcare decision making (Drummond, 1996).

Prioritizing healthcare resources has become both inevitable and necessary. A harsh fact that is emphasized by the scarcity of resources and the almost insatiable demands made on them (Spiegelhalter *et al*, 1992). To effectively prioritize, some measures of output from healthcare must be first established; bearing in mind that in choosing to use resources in one healthcare program or treatment, the opportunity is sacrificed to use the same resources in another competing activity and to obtain some other benefit.

Hence, the idea of opportunity cost; that is the cost of using healthcare resources in one area or field is the value of the benefits they would have generated in their best alternative use (Drummond *et al*, 1987). The aim of providing "the best" within the constraint of available resources is, however, an objective to which the health service ought to ascribe. The definition of best here allows for scarcity of means and policy-making (Mooney *et al*, 1986). The three fundamental issues confronting the policy makers and decision-makers in the health service are:

(1) The need to determine what services to provide, when and at what level of provision

(2) The need to determine how and where to provide such services

(3) The need to determine who should get the services (Mooney *et al*, 1986)

In essence, there is scope for considerable improvement in decision making and that the issues of what to provide, how and to whom, which are central to both the problems of the health service and the discipline of economics, can be helped by injection of both the philosophy and the techniques of economics (Mooney *et al*, 1986) bearing in mind that the issue in this research relates to a developing country still experimenting this "new" philosophy and "modern" techniques. Extra complications arise because there is essentially a mix of systems and methods for decision making, among which are planning decisions, made on behalf of the community by healthcare jurisdictions. These decisions concern issues such as whether particular public health programs (such as screening or immunization schemes) should be funded and occasionally decisions concerning individual medical procedures. In addition, there is resource allocation process which involves clinical decisions, made by practitioners on behalf of individual patients (Drummond *et al*, 1987). Although clinical decisions may be partially constrained by the facilities

provided, they are mainly made without reference to those planning, managing or funding the healthcare system. This presents obvious problems for those trying to ensure a rational use of healthcare resources.

Samuelson's definition of economics goes a long way to explain why economic theory is relevant to the evaluation of new drugs and therapies, "Economics is the study of how men and society end up choosing, with or without the use of money, to employ scarce productive resources that could have alternative uses, to produce various commodities and distribute them for consumption, now or in the future, among various people and groups in society. It analyses the costs and benefits of improving patterns of resource allocation" (Samuelson, 1976). Put in these terms, economics should not appear threatening. It is not primarily concerned with reducing financial costs but considers both costs and benefits in broader terms than simply money. The key issue is that economics focuses on productive resources and their scarcity (demand exceeds supply) and therefore someone must make a choice about how the resources can be used to produce as much benefit as possible. Economics can help in making these decisions by clarifying what the costs and benefits of different interventions may be (McGhan, 1996). In economics there are two types of choice to be made. First, when the decision to meet need X has been taken and we are evaluating the most efficient way of meeting it. This is called technical or X efficiency evaluation (Williams, 1974). Economic evaluation has a large part to play in such technical decisions. Then when the many needs to be met have to be defined and we must compare the costs and benefits of each alternative, this is called allocative efficiency evaluation (Williams, 1974 and Jefferson *et al,* 2000).

As Maynard, (1994) remarked that "the pursuit of efficient practice is not merely about reducing costs. If it were, the most efficient procedure would be to do nothing,

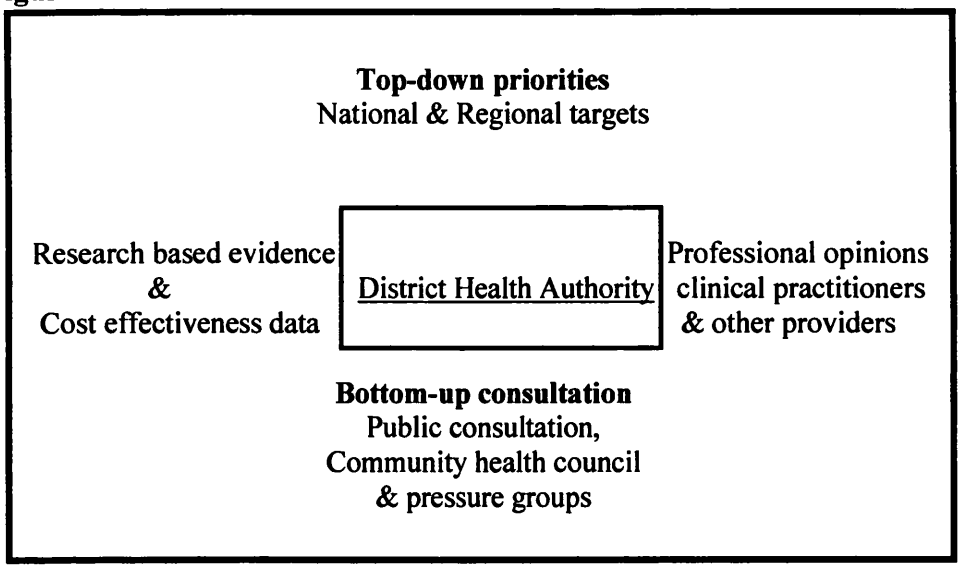
as that pushes costs to zero". To this should be added the concepts of equality and equity, along with effectiveness and efficiency recognized by Cochrane, (1972) and other think-tanks and bodies (Commonwealth Fund Commission on a High Performance Health System, 2006 and Gauthier *et al,* 2006). One such body - the Institute of Medicine in the US – has outlined a useful agenda for healthcare system improvement (Institute of Medicine, 2001), known as the "S-T-E-E-E-P" goals (Berwick, 2004):

- safety (reducing medical injuries to patients);
- timeliness (reducing waits and delays throughout the system);
- effectiveness (increasing the reliability of evidence based care);
- efficiency (reducing the total cost of care); and
- equity (closing racial and socioeconomic gaps in health status)
- patient centeredness (giving patients and carers far more voice, control and competence in self-management);

The existence of ineffectiveness and inefficiencies in service provision presents serious obstacles to delivering better healthcare. Irrespective of funding levels, choices always have to be made regarding the allocation of resources. In making such choices, decision-makers need to establish a definite set of priorities while professionals' and societies' attitudes need to be changed. The recognition of the need to generate evidence relating to resource utilisation and the most beneficial utilisation of available resources is also very important.

In making decisions about the allocation of resources, health authorities need to draw on several sources of information (Cochrane *et al*, 1991 and Gilbody and Petticrew, 1999). These may be summarized as top down priorities, bottom up consultation, professional opinion, and research based evidence (figure 1).

Figure 1: Health authorities' sources of information



Derived from Cochrane *et al*, (1991)

2.2. Health Technology Assessment

HTA dates from the late 1970s when the expansion of technology and health-care costs began to capture the attention of decision-makers (Jonsson, 2002). Decision-makers needed a more comprehensive approach to set priorities and obtain maximum benefit from limited resources, without compromising the ethical and social values underpinning health systems (Hutton *et al,* 2006). The growth and development of HTA reflected this demand for well-founded information to support decisions on the development, uptake and diffusion of health technologies.

Assessment in healthcare has developed greatly in the last decade; it became a process with methodological concepts underlying its many stages. Health economic assessments coupled with portfolios of effectiveness evidence have been progressively used in recent years by decision-making bodies that increasingly relied on such evaluations. Eventually, health technology assessment has become a recognized academic discipline and a recipient of large scale research funds. An

HTA's principal aim is to provide a range of stakeholders (typically those involved in the funding, planning, purchasing and investment of healthcare) with accessible, usable and evidence-based information to guide decisions about the use and diffusion of technology and the efficient allocation of resources. In light of these objectives, HTA has been called "the bridge between evidence and policy-making", as it provides information for health-care decision-makers at macro-, meso- and micro-levels (Battista & Hodge, 1999). HTA also contributes greatly to the knowledge base for improving quality of care, especially by supporting the development (or updating) of clinical practice guidelines and standards for health-service provision (Zentner *et al,* 2005). HTA provides important benefits by empowering governments to make value-driven decisions, supporting innovation and providing patients and physicians with the information for making the best treatment choices.

On a broad level, HTA was regarded by Sorenson and colleagues as "The systematic evaluation of the properties, effects, and/or other impacts of healthcare technology" (Sorenson *et al,* 2008).

More specifically, HTA involves the evaluation of an intervention through the production, synthesis and/or systematic review of a range of scientific and non-scientific evidence. The type of evidence considered typically includes the safety, efficacy, cost and cost-effectiveness of a product. However, HTA is also concerned with the societal, organizational, legal and ethical implications of implementing health technologies or interventions within the health system (Velasco-Garrido & Busse, 2005). For example, HTA often considers health technologies' broader macroeconomic impacts on national health-care budgets; resource allocation among different health programs; regulation; and other policy changes for technological innovation, investment, technology transfer and employment (Goodman, 1998).

In addition to ascertaining technologies of value, an effective HTA can reduce or eliminate the use of interventions that are not safe and/or effective, or have insufficient cost-benefits. HTA can also be used to identify existing technologies that may be harmful or ineffective. Less commonly, HTA can also identify underused technologies (e.g. preventive screening, smoking-cessation interventions) and the reasons for this (Asch *et al,* 2000 and McNeil, 2001).

Since the 1970s, HTA has broadened to encompass a wide range of health technologies including drugs; medical devices; medical and surgical procedures; and the organizational and support systems for care provision (Jonsson, 2002). However, the majority of HTAs have been conducted on pharmaceuticals rather than other technologies such as medical devices and surgical procedures (Hutton *et al,* 2006).

In particular, assessments often differ according to the:

- type of economic assessment required
- classification of product benefit (benefit versus harm) – hierarchy of evidence
- choice of comparator
- specification of the outcome variable
- costs included in the analysis
- discounting
- use of cost effectiveness threshold
- allowance for uncertainty
- missing and incomplete data

(Zentner *et al,* 2005)

Methodologies can also differ on sub-group analyses; time horizons; instruments to measure quality of life; and methods for calculating costs (Sorenson *et al,* 2008).

The appraisal or assessment of a health technology is divided into three distinct phases starting with the scoping, passing through assessment and ending with appraisal.

A. Scoping

During this process, not only are the issues of interest defined as clearly as possible to have clear boundaries for the appraisal, but also the parameters to be investigated are stated plainly. The scope is then developed into a protocol, the main frame for the technology assessment.

B. Assessment

This process is a systematic and independent evaluation of the relevant evidence available on the technology. The aim is to produce an estimate, including uncertainty, of its clinical and cost effectiveness for a specific indication. Assessment has two mutually dependent components: a systemic review of the evidence and an economic evaluation. This process requires an understanding of the appraisal question and the context within which it is addressed, covering for example, currently available care, any alternative technologies, and appropriate methods of comparing the technologies etc.... This assessment, therefore, consists of an objective analysis of the quality, the findings, and the implications of the (mainly research) evidence available as it relates to the appraisal question and context, strengths, weaknesses and gaps in the evidence which are identified and evaluated.

C. Appraisal

The appraisal process is a consideration of the outputs of the assessment process within the context of the additional information supplied by consultants, commentators, clinical specialist and patient experts. The appraisal committee first considers the evidence available in the assessment reports and elsewhere, it then formulates an appraisal decision, applying judgments on the importance of a range of factors differing from one appraisal to the next. The boundary between assessment

and appraisal, while present is not clearly defined; the judgment in the assessment process will influence the appraisal process.

The wide variation in approaches and methods employed in economic evaluation and HTAs has led to the adoption of a reference case of core methods to be used (Gold *et al,* 1996 and National Institute of Clinical Excellence, 2004). In some instances, there may be some barriers to the application of the reference case methods, and data required to present reference case results may not be available. In such situations, NICE and other similar bodies requires the submission of well specified and justified reasons for the inability to meet the reference case requirements along with the quantification of the likely implications.

However, the success of such approaches is highly dependent on other factors influencing the quality of the decision-making process. Among which are (Moore *et al,* 2006):

- evidence on effectiveness;
- evidence on cost; and
- evidence on how to make a change

The reference case specifies the methods considered by the NHS to be the most appropriate for the appraisal purpose and consistent with the objective of maximising health gain from limited resources. The key elements are summarized in table 1.

Table1: NICE Reference Case

(from National Institute of Clinical Excellence, 2004)

Element of Health Technology Assessment	Reference Case
Defining the decision problem	The scope developed by NICE for the appraisal
Comparator	Alternative therapies routinely used in the NHS
Perspective on costs	National Health Service and Personal Social Services
Perspective on outcomes	All health effects on individuals
Type of economic evaluation	Cost-effectiveness analysis
Synthesis of evidence on outcomes	Based on systematic review
Measure of health benefits	QALYs
Description of health states for calculation of QALYs	Health states described using a standardized and validated generic instrument
Method of preference elicitation for health state valuation	Choice-based method, for example, time trade-off, standard gamble (not rating scale)
Source of preference data	Representative sample of the public
Discount rate	An annual rate of 3.5% on both costs and health effects
Equity position	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit

It is essential, to think about the use of evidence relating to effectiveness and cost-effectiveness without considering the organizational context is 'to miss a good part of the story' (Weiss 1998), for example, that the organizational climate is conducive to ensure that 'patients get the right care at the right time and in the right setting' (McCannon *et al,* 2006) and what constitutes best evidence within the context of the evidence-based organization must take into account the circumstances and conditions prevailing within the organization's environment (Palfrey *et al,* 2004). While evidence answers the question *does it work*, and economics will inform whether *it is worth it,* the *can it work* question is where quality decision-making comes in (Haynes, 1999).

2.3. Health economics and evidence-based healthcare

The ever increasing demands placed on healthcare services against limited resources available to meet them, continues to be a major concern for those at all echelons of

policy, decision-making, and delivery of healthcare services. This fact helps to highlight the contribution of economic techniques and approaches in relation to decision making. It initially considers the relationship between economics and evidence-based healthcare, and the need for both to be involved in the decision-making process if some degree of quality is to be achieved. The development of policies and strategies based on what has been proven to be clinically effective has been advocated for some time on the international arena. Terms such as evidence-based healthcare and clinical effectiveness are now common in healthcare circles. The need to ensure that limited resources are channelled into effective interventions coupled by the belief that the way to reduce cost pressures in healthcare is to focus on effectiveness and proven quality has both provided the incentive to promote evidence-based practice (Marwick, 1997).

Health management requires what Phillips, (2005) referred to as *joined-up thinking,* and employs a whole-systems approach, one which is broadly focused and not only driven by budgets, and with due consideration for the impact of decisions on the consequences for patients and healthcare provision in general. The burgeoning growth in the quantity and quality of evidence available for decision-makers has not removed the need for a whole systems approach to decision-making (Bell *et al*, 2006; Commonwealth Fund Commission on a High Performance Health System, 2006 and Gauthier *et al,* 2006). Berwick, (2005) have concisely and conveniently summarized what a quality health system should aim to represent:

- No needless deaths – don't kill me
- No needless pain – don't hurt me
- No helplessness – do help me
- No unwanted waiting – don't keep me waiting

- No waste – don't waste resources

The relationship between health economics and evidence-based medicine is one that has aroused interest among health economists (Maynard, 1996; Vale *et al,* 2000 and Birch, 2002) and leading advocates of evidence-based healthcare (Sackett *et al,*1996). Evidence based healthcare (EBHC) and health technology assessment (HTA) play a significant role in informing decision-making bodies at an organizational and healthcare system level across many countries.

The widely used definition of evidence based medicine (EBM,) which has been widely used, is that provided by Sackett and colleagues (1996): "Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett *et al,* 1996).

Hill, (1997) along with Nutley and Webb, (2000) both described the rational policy process cycle, by including the notion of evaluation and review, as well as the notion of implication research and evidence. Evaluation is defined as being "concerned with judging merit against some yardstick" and involving "the collection, analysis and interpretation of data.....attempts to measure the extent to which certain outcomes can be validly correlated with inputs and/or outputs" (Phillips *et al,* 1994).

The EBM movement has gone through the stage of being an evolutionary process which then led policy-makers to create the notion of clinical governance among other facets of healthcare policy to establish and deliver quality and monitor performance against agreed standards. This notion was introduced in 1998 as a new approach to the quality improvement in the UK NHS, on the basis that it would be the framework within which healthcare organisations at every level of the NHS would be "accountable for monitoring and improving the quality of their services" and it was also intended to "safeguard high standards of care by creating an environment in

which excellence in clinical care will flourish" (NHS Executive, 1998). It should be noted, however, for the sake of the argument that a search of the literature concluded that "as yet, there are no studies providing evidence showing that the adoption of clinical governance improves the quality of healthcare and of patient care (Thomas, 2001).

2.3.1. Characteristics and application of good evidence

The success of quality initiatives is highly dependent on the quality of the information sources which are available. In its attempt to stimulate 'professional policy making'; the Cabinet Office, (1999) in England, sought to emphasize the importance of evidence and defined the range of sources as expert knowledge; existing domestic and international research; existing statistics; stakeholder consultation; evaluation of previous policies; new research, if appropriate; or secondary sources, including the Internet.....outcome of consultation, cost calculation of policy options and the results of economic or statistical modelling. (Cabinet Office, 1999; paras 7.1 and 7.2) However, the debate regarding the attributes of good evidence reflects the wide range of views relating to the particular hypothesis and perspective employed in medical and social science research.

Type and strength of evidence (from McQuay and Moore, 1998)

I. Strong evidence from at least one systematic review of multiple well-designed randomized controlled trials

II. Strong evidence from at least one properly designed randomized controlled trial of appropriate size

III. Evidence from well-designed trials without randomization, single group pre-post, cohort, time series or matched case-controlled studies

IV. Evidence from well-designed non-experimental studies from more than one centre or research group

V. Opinions of respected authorities, based on clinical evidence, descriptive studies or reports of expert committees

Nevertheless, the increase in quality reviews in other fields might contribute to "improve the evidence base and increasing its influence on policy and practice in the public services" (Davies *et al,* 2000). It is also important to emphasize whether the evidence can fulfil three basic requirements:

(1) Are the results valid? Can they be believed, have the studies conformed to recognized practice and procedures, to what extent have bias and other external factors impacted on the research, which outcomes were considered and are they meaningful?

(2) What are the results: does the intervention work as intended, what are the risks that the intervention will cause harm, how precise are they, is there wide variation across the findings?

(3) How relevant are the results: can they apply in different environments and different settings?

Moreover, within the evidence-based organization, if an intervention is unsuccessful, the evidence should help to determine whether the intervention was inherently faulty (that is, failure of intervention concept or theory), or just badly delivered (failure of implementation)" (Rychetnik *et al*, 2002).

Concisely, what constitutes best evidence within the context of the evidence-based organization takes into account the circumstances and conditions prevailing with the

organization and its environment. Furthermore, the three requirements highlighted above need to be supplemented by other factors such as:

- What are the implications of applying these findings within the current organizational dynamics?
- To what extent would the implications of findings cause de-stabilisation within the organization?
- Would there need to be significant change if these findings were to be implemented?
- What would be the reaction of service users and other stakeholders to the findings?
- What are the resource implications resulting from implementing such evidence?
- Are there alternative perspectives that need to be considered?

A major stipulation, to the success of evidence and quality in policy documentation, is organizational environments. The adjustability of those environments to facilitate policy approaches along with the implementation of suitable guideline recommendations and relevant research findings to become part of standard policy making practice is also an issue. More effort and studies are still needed to assess the effectiveness of intra-organizational, inter-organizational, inter-professional, collaborative and partnership approaches to the organization and delivery of services (El Ansari *et al*, 2001 and El Ansari and Phillips, 2001), to complement the wealth of research evidence relating to practice. In spite of this, Weiss, (1998) demonstrated that the quantity of research information appears to have very little or no impact on practice because availability does not mean accessibility by practitioners (NHS CRD, 1999). Then again, Nutley and Davies, (2000) concluded that, "there is much to be

gained from viewing evidence-influenced practice as a partnership activity" and advocated an approach that combines:

- insights from systems thinking (in terms of setting the contexts within which evidence is to be used);
- understanding of individual decision making and behaviour change (which acknowledges the importance of craft routines and tacit knowledge by professionals);
- awareness that the nature of the innovation being promulgated will influence its diffusion (and in particular, the 'fit' between the innovation, the context and those who are potential adopters);
- ownership of evidence through partnerships in the evidence generation process.

The evidence-base for the effectiveness of interventions and management strategies should be continuously developed. However, health economics alone is not going to result in better decisions being made. Health economists tend to fall into the trap of being narrowly focused on efficiency issues, by condensing outcomes into a single measure and failing to grasp the bigger picture (Phillips, 2005). Coast, (2004) advocated a broader perspective and set of approaches, whereby the economic framework would enable decision makers (on behalf of society) to assign their own values to the profile of costs and consequences, which could and would differ according to the context, and where decision makers would be able to clearly identify alternatives.

The integration of evidence relating to effectiveness and resource utilisation can be brought together in a matrix (Donaldson *et al*, 2002) as shown in figure 2 below.

Figure 2: Integration of effectiveness and resource utilisation evidence [based on Donaldson *et al*, 2002]

Declining effectiveness →					
Increasing cost ↓		**1**	**2**	**3**	**4**
	A	**Y**	**Y**	**J**	**n**
	B	**Y**	**y/n**	**N**	**N**
	C	**J**	**N**	**N**	**N**
	D	**N**	**N**	**N**	**N**

y = yes adopt
n = no reject
y/n = indifferent
j= judgement needed
EFFECTIVENESS
Compared with control the intervention has:
1 evidence of greater effectiveness
2 evidence of no difference in effectiveness
3 evidence of less effectiveness
4 not enough evidence of effectiveness
COST
Compared with control the intervention has:
A evidence of cost savings
B evidence of no difference in costs
C evidence of greater costs
D not enough evidence on costs

There are many criteria that should be considered before making clinical decisions: including comparison for the suffering, the likelihood of benefit and the effectiveness and efficiency of the intervention. The use of decision matrices as important tools for decision makers due to their emphasis on integrating effectiveness and resource utilization evidence as well as their recognition of the importance of trade-offs (Stevens *et al,* 1995 and Donaldson *et al,* 2002).

Phillips, (2005) commented on the exponential increase in demand for healthcare services concurrently occurring with increased pressures on governments and funding agencies to carefully manage the resources available for healthcare services. Phillips added that as the addition of resources would help, it would not completely solve the problem. Decision-makers need to apply themselves to removing hurdles to new adaptive ways of working, to change attitudes and to supply supportive structures to

explicit set of priorities, which integrate and sustain new initiatives and modern activities if the benefits resulting from evidence-based healthcare and health economics are to accrue (Weiss, 1998). In addition, the enhanced recognition of the need to generate evidence relating to resource utilization, effectiveness of interventions and the most beneficial utilization management strategies of available resources is encouraging and the emphasis attached to evidence-based medicine and evidence-based healthcare has, in all likelihood, reduced the size of the service provision gaps and defects, but efforts need to be maintained to ensure that the right momentum is preserved (Donald, 2001 and Walshe, 2001), and that the journey along the road to better healthcare is not merely based on hope, but on secure knowledge that the proportion of resources allocated to interventions and services that are *effective*, is continually increasing.

2.4. Doctors and health economists: Different perspectives

Health professionals, administrators and the policy-makers as well as the pharmaceutical industry shapers are all concerned with the use of the economics in relation to drug therapy and policy (McGhan, 1996). The professionals and healthcare administrators are both keen to make best use of limited resources. They can use health economics to define the areas where resources can best be used for maximum health gain. Far from cutting costs, health economics, may identify areas where there is under supply of resources and may even increase costs in some areas. Health professionals and healthcare administrators bring different perspectives as the former will tend to consider the benefit of the individual patient as most important, while the latter tend to consider the benefit of populations of patients. There are tensions between these two perspectives, and a balance must be struck between the two (McGhan, 1996). Doctors sometimes think it unethical to consider the economics of

treating a patient: but in reality, not to consider this, risks the inefficient and wasteful use of limited resources. What more could be unethical? Clinicians frequently equate health economics with rationing or cost cutting and fail to perceive its potential value in improving patient care and exposing areas of deficiencies and under funding (Walley and Davey, 1995). Many doctors, therefore, reject as a matter of principle the whole process and condemn its application as being unethical (Walley and Davey, 1995). While such an approach does not stand up to serious analysis (Walley and Davey, 1995 and McGhan, 1996), it must be recognized that there is a potential conflict between the traditional Hippocratic medical ethic (what is best for the individual patient) and the less traditional utilitarian ethics (what is best for any given population of patients). The tension between the two approaches must not be allowed to stifle debate but rather can be constructive in advancing our thinking on the future of health services. Ultimately, health economics' mission is to promote health and alleviate suffering (Williams, 1974). The pharmaceutical industry is increasingly aware of the need to provide not just evidence of safety and efficacy of their products but also of their costs effectiveness. The use of health economics in industry is quite comprehensive. It includes identifying markets, supporting promotional activities, making or justifying pricing decisions, and possibly making crucial go or no go decisions in drug development.

Health economists are often perceived by doctors as not appreciating the complexity of clinical decisions. Ironically, health economists are most likely to criticize doctors for not appreciating the complexity of healthcare as a whole (McGhan, 1996) Furthermore tensions, do exist on how resources are allocated, not only because of incompatibility between the ethics of two sciences, medicine and economics, but also because of tensions between different perspectives within the same science: medicine.

Culyer, (1991) defined two forms of medical narrow mindedness: monotechnics and romantics. The former are obsessed with technology to the extend that they fail to consider any of the other complex elements which determine need for treatment, while the latter refuse to face the fact that decisions about resource allocation must and will be made.

In somewhat similar tones, the British Medical Association's Handbook of Medical Ethics makes essentially the same point: "As the resources available are limited, the doctor has a general duty to advice on their equitable allocation and efficient utilization. " It then adds: "This duty is subordinate to the doctor's professional duty to the individual who seeks his clinical advice" (British Medical Association, 1984).

Mooney, (1992) made a few observations from an economist standpoint on the subject and practice of medical ethics. He highlighted the "uncomfortable fact" that, as practiced, medical ethics, particularly in the form of clinical freedom, tends to breed inefficiency. He went on to say that it sometimes provides a convenient escape mechanism for the romantic member of the medical profession neither to pursue efficiency nor to attempt any rationalization at all of the potential of pursuing efficiency in healthcare. In the absence of such clear thinking, doctors may make illogical decisions based on personal opinion, on prejudice, even, for instance, influenced by a patient's socioeconomic circumstances (McGhan, 1996). Six potential strategies are considered when seeking to minimize the extent of the conflict between a doctor's responsibilities to the individual patient and his responsibilities to society all of which require "more and better evidence," (Sackett, 1996):

1. eliminate useless or harmful clinical manoeuvres;
2. expand effective, cost-saving clinical manoeuvres;
3. use equally effective but less expensive alternative clinical manoeuvres;

4. determine and apply the cost-utility properties of clinical manoeuvres;
5. inform the public;
6. be explicit about the presence and nature of conflicts.

Conversely, the aspect and point of view, where the aims of medical practice is to achieve best results for patients, match those of health economics, which are to achieve greatest benefits for given resources (McGhan, 1996). Both require evidence of clinical outcomes, and both will help to improve the quality of patient care.

Nonetheless, clinical pharmacologists have recognized the complexity of clinical decision making, and the need for a systemic approach to analysis of response to treatment. Systemic studies of outcomes of treatment, both clinical and social, help to define the benefits of interventions, and are the beginning of the process which will allow us to identify priorities in treatment.

However, economists go further than considering outcomes: they also identify the costs of interventions, not in financial terms but in terms of what have been decided to forgo so as to use resources in one particular way: economists term this "opportunity cost". They recognize that when resources are used for one intervention, there is less available for others. One of the great values of health economics to clinicians is that it makes such costs of a treatment explicit, so that they can weigh its value in comparison with other interventions. The description of the alternative uses of productive resources is clearly relevant to practical drug therapy, including decisions about whether benefits should occur now or in the future (e.g. prevention versus treatment of established disease). Moreover, economics offers a range of rigorous research techniques for investigating complex clinical and resource allocation problems. It can also provide clinical pharmacologists with some very practical techniques which are essential to a realistic understanding of the costs and value of

drug therapy, including the costs of treatment failure and adverse reactions (Davey *et al,* 1994; MacDonald *et al*, 1995 and McGhan, 1996).

The increasingly commonplace discussions among clinicians regarding the economic consequences of clinical decision making is evidence that the fields of economics and clinical medicine are rapidly moving toward the common goal of cost-effective medical practice (McKinlay, 1981; Eddy and Billings, 1988; Sloan, 1995 and McCombs, 1998). The increase in the frequency of involvement of healthcare workers and doctors in the process of economic evaluation is due to several reasons. While resources dedicated to healthcare may have increased, they are still limited and under increasing pressure, as such doctors and healthcare providers and payers find themselves frequently asking which technology should be provided and to what point the need for healthcare should be met. This is due to the constantly changing state of medical technology, which has made it incumbent on medical professionals to evaluate the cost-effectiveness of new medical technologies and innovation to update and improve clinical practice guidelines. Health economists have become an integral factor in this new dialogue. Though some scepticism still remains regarding this role, economists are rapidly becoming accepted as vital to furthering the discussion on health-care resource allocation. Although physicians remain the key decision makers in this deliberative process, economists provide data and insights (McCombs, 1998). The healthcare workers involvement should ensure that all dimensions of evaluation are taken into account in a multidimensional approach which includes equity and humanity as well as effectiveness and economic convenience. The value health economists bring to the thorny issue of how to allocate limited healthcare resources across the competing patients' needs in a fiscally restrained healthcare environment is valuable and is proven by the fact that treatment decisions are now known as rational

resource allocation decisions (McCombs, 1998). As such, this study with its very integrative Hepatitis C virus example emphasizes that the healthcare worker holding managerial functions of ever-increasing complexity has to acquire a basic understanding of the principles underlying economic evaluations and is forced to become the health economist with the increasingly important role of providing data and insights key to the deliberative process of comparing the costs and benefits of medical care, not just in terms of reduced healthcare costs but also in terms of efficiency of treatment.

2.5. Methods of healthcare economic evaluation

Methods of economic evaluation have been developed to assist the choices that inevitably must be made about the allocation of scarce resources. Within the healthcare sector there have been considerable advances in developing methods of increasing sophistication to provide a firmer evidential basis for a growing number of decisions in the health sector (Drummond *et al*, 1997; Duthie *et al*, 1999; Hill *et al*, 2000; Hoffman and Graf von der Schulenburg, 2000; Hoffman *et al*, 2002; Drummond, 2003; Speigel *et al*, 2004 and Wu *et al*, 2004).

Within the healthcare sector, economic evaluation (or economic appraisal as it is sometimes called) is used as a generic term for a range of techniques that may be used to assemble evidence on the expected costs and consequences of different procedures or programs. All methods of economic evaluation have this principle in common as they examine one (or more) possible interventions and compare the inputs or resources necessary to carry out such interventions with their consequences or effects (Williams, 1974 and Langley, 1997). Those who plan, provide, receive, or pay for health services face an incessant barrage of questions about:

- Who should do what to whom,

- With what healthcare resources, and
- With what relation to other health services?

The answers to these questions are strongly influenced by estimates of the relative merit or value of the alternative courses of action they pose. There are strategies and tactics whereby these estimates of relative value can be ascertained and interpreted, that is, with the evaluation of health services. In this type of evaluation many questions are asked (Drummond *et al,* 2001):

- Is this health procedure, service, or program worth doing compared with other things that could be done with these same resources?
- Is there satisfaction that the healthcare resources (required to make the procedure, service, or program available to those who could benefit from it) should be spent in this way rather than some other way?

It is imperative to note that although economic evaluation provides important information to decision-makers, it addresses only one dimension of healthcare program decisions. Nevertheless, economic evaluation is most useful and appropriate when preceded by three other types of evaluation, each of which addresses a different question (Williams, 1974; Mooney *et al,* 1986 and Drummond *et al,* 2001):

1- Can it work? Does the health procedure, service, or program do more good than harm to people who fully comply with the associated recommendations or treatments? *This type of evaluation is concerned with efficacy.*

2- Does it work? Does the procedure, services, or programs do more good than harm to those people to whom it is offered? This form of healthcare evaluation, which consider both the efficacy of a service and its acceptance by those to whom it is offered, is *the evaluation of effectiveness or usefulness.*

3- Is it reaching those who need it? Is the procedure, service, or program accessible to all people who could benefit from it? *Evaluation of this type is concerned with availability.*

Methodological criteria for assessing efficacy, effectiveness, and availability evaluations, from which the above questions have been drawn, have been described by Sackett, (1980).

The use of economic analyses as they pertain to the practice of medicine has become increasingly common place; these analyses have the potential to answer many of the questions posed by the delivery of healthcare in light of the accountability demanded by both the public and the funders of healthcare in a fiscally responsible era; but considerable scepticism as to their relevance and role in the assessment and evaluation of healthcare technologies and programs still remains due to major obstacles to increasing their usage and contribution to the decision-making process relating to the accessibility, generalisability, validity and quality of health economic studies represent (Drummond *et al,* 1997; Duthie *et al,*1999; Hoffman and Graf von der Schulenburg, 2000; Hoffman *et al*, 2002 and Wu *et al*, 2004).

To this end, there are a number of tools in the practice of pharmacoeconomics having as their outcome the development of a medical decision model or decision tree (Sloan, 1995 and McCombs, 1998).

The various methods of economic evaluation differ in the way they itemize and value inputs and consequences. Such differences reflect different aims and view points of the decision-making problems (Williams, 1974). The four main approaches that are currently in use are (Alan, 1974 and Robinson, 1993 a, b, c and d):

- Cost-minimization analysis
- Cost-effectiveness analysis

- Cost-utility analysis
- Cost-benefit analysis

Each of these approaches involves the systemic identification, measurement, and, where appropriate, valuation of the all relevant costs and consequences of the various options (table 2).

The issue of cost is one which is often at the forefront of decisions made in relation to healthcare service provision. However, it is essential to stress that cost, in economic terms, is not only concerned with the financial imperatives. Health economics is not necessarily about saving money and reducing expenditure. If it was it would only focus on programs and policies that contributed to achieving an improvement in financial budgets, rather than an improvement in the health of patients. In purely monetary terms the cheapest patient is a dead patient!

Therefore, the costs of an intervention or service are not only the staff inputs, materials, drugs and equipment contributed by providers; the costs to other agencies resulting from healthcare provision; and, the costs to patients and their families due to travel to and from healthcare facilities among other expenses. There are, in addition, the indirect costs or productivity costs associated with healthcare. These occur outside the healthcare sector and relate to losses of production, due to absenteeism and reduced productivity. The costs incurred through the informal care process should also be taken in consideration –as a result of a carer giving up paid employment to provide care, which would otherwise have been provided by formal care agencies.

However, it is the impact of health problems on the quality of life of patients, their families and communities that provide the biggest headache in determining the real cost. These aspects cannot be contained within any financial statement but are essential components of the balance-sheet connected with healthcare services.

Table 2: Methods of economic evaluation and the consequences (outcomes) measured

Type of study	Measurement of consequences
Cost minimization analysis	Outcome the same between options; no measurement necessary
Cost effectiveness analysis	Outcomes measured in natural units e.g. life years gained e.g. mm of Hg
Cost utility analysis	Utility measures e.g. QALYs
Cost benefit analysis	Outcomes valued in money terms

All relevant costs are measured in monetary terms.

2.6. Perspective of healthcare economic evaluation

It is important to determine at the outset from whose viewpoint an economic evaluation is to be carried out (Robinson, 1993e and Walley and Davey, 1995). The viewpoint or vantage point, known as perspective establishes the context for the appraisal by determining which types of outcome measures and which categories of cost are relevant and meaningful (Elshakhs, 2001). It may be based on one or more of the following: the view point of an individual patient, the hospitals or other providers, the government, or the society in general. The broadest perspective is that of society in general, as this will include all the costs and benefits leading to optimal decisions, given that the aim of economic analysis is to make the best use of all of society's resources. Bonk (1999), classified the different perspectives for an economic evaluation and came out with four Ps; the patient receiving the service or treatment, the provider of the service, the payer who covers expenditures and the public in general (Table 3). In each perspective category different issues take precedence over others. Hence defining perspective at the outset of pharmacoeconomic studies remains crucial to obtaining useful results (Bonk, 1999 and Elshakhs, 2001).

Table 3: Relevant Issues by Perspective

Perspective	Relevant Issue
Patient	Which therapeutic option works best for me? What costs must I pay? How will I feel if I subject myself to this therapy?
Provider	How will my patient fare with the chosen therapy? Will the patients insurance cover these expenditures? Will the patient be compliant with this treatment?
Payer	Which treatment should we cover in our formulary? How do we adjust actuarial tables for high risk groups? How do legislation and lawsuits affect our decisions?
Public	Will our tax base handle costs for the indigent? Does this disease decrease worker productivity? Could we better expend our limited funds for other uses?

Source: Adapted from Bonk (1999).

Adopting a broad approach has two main implications which distinguish it from approaches with more limited perspectives. Firstly, it usually involves measuring and valuing items that do not have market prices attached to them, such as the time costs that patients incur when undergoing treatment and recuperating. Secondly, it means that certain costs, or cost savings, or both, should not be included in the evaluation because they are transfers from one sector to another rather than a net cost on society (Robinson, 1993 a and e).

However economics is not about cutting cost, it is about securing the maximum benefits and efficiency given the level of resources available. This directly relates to the aim of this study in terms of assessing HCV costs, highlighting how to handle the produced results to maximize the benefit of expenditures and informing decision makers as to the impact of their policies on the performance of the financial process of the Ministry of Health and Population and consequently on the general societal and ultimately on the national health benefit. The nature of information resulting from this study would depend on the standard of the health outcome evidence it uses (Moore *et*

al, 2006) and would be essential as long as it is evidenced that correct methodologies and sound techniques have been followed and as long as the integrity of the team members and their adherence to the research and scientific ethics is not in question. This economic study would act as a framework that would enable decision makers (on behalf of society) to accredit values to the profile of costs and consequences of HCV, which could differ from other profiles elsewhere according to Egyptian local context, whereby the evidenced results would be a good guide to emphasize weak points or strengths in the implications of followed health policies.

2.7. Cost Categories

Categories of costs often termed expenditures do not explicitly depend on a specific type of pharmacoeconomic evaluation. Instead, costs provide a commonality across the study types and despite their different outcomes component; they all include some quantification of costs (Robinson, 1993 a).

Drummond *et al,* (1997) and Bonk, (1999) divided costs into four basic categories, stratified by two parameters: directly or indirectly (intangible) related to the disease, to the treatment, or to the program, and medical or non-medical in nature (Table 4).

Table 4: Examples of categorized costs

Relationship to disease, treatment, or program	**Relevant issues**	
	Medical	**Non-medical**
Direct	Hospital fees, drugs, equipment, supplies, and professional fees.	Transportation, lodging for family, and additional homecare.
Indirect	Earnings lost during illness or treatment, and from disability.	Intangible effects such as quality of life and psychological tolls.

Source: Adapted from Bonk (1999)

2.7.1. Direct costs and benefits

These terms have been used in the past to denote the resources consumed (costs) or saved (benefits) by the program. In general these would be resources in the healthcare sector, but sometimes would include patients' out of pocket expenses, resources from other statutory agencies and voluntary bodies. However, use of the term is not consistent across studies, which sometimes causes confusion.

2.7.2. Indirect costs and benefits

These terms have been used in the past to denote patients' time consumed or freed by the program. In general focus has been on work time and indirect costs and benefits have been synonymous with productivity gains and losses. The term has often caused confusion as it is used by accountants to denote overhead costs. Strictly speaking, economic evaluation should seek to value all inputs in terms of their opportunity costs, that is, their value in their next best use. Indirect costs, for which there are no market prices, pose a more difficult problem of valuation. Shadow pricing and time costs provide a good example of methods used to impute indirect cost values. When time is spent in hospital by a patient, or on caring at home by a relative and this displaces work time, it is usual practice to use the relevant wage to value the lost time (Robinson, 1993 a).

2.7.3. Average costs

The major significance of the average-cost distinction to the evaluation is as follows First, when making a comparison of two or more programs it is worth asking independently of each, what would be the costs (and consequences) of having a little more or a little less? Second, when examining the effects (on cost) of small changes in output, it is likely that these will differ from average costs (Drummond *et al*, 1997).

For example, the extra cost of keeping patients in hospital for another day at the end of their treatment might be less than the average daily cost for the whole stay.

2.7.4. Marginal or incremental costs

The terms marginal and incremental are often used interchangeably in the literature. They both refer to a change in the scale of an activity. Strictly speaking, the marginal cost relates to the cost of producing one extra unit of output (Drummond *et al*, 1997). However, it is often used to refer to the cost of producing the next logical batch of output. The term incremental is sometimes also used to refer to such a change, but more often used to refer to the difference, in cost or effect, between the two or more programs being compared in the evaluation.

Various definitions of cost

Total cost (TC): Cost of producing a particular quantity of cost.

Fixed cost (FC): Costs which do not vary with the quality of output in the short run. That is, costs which vary with time, rather than quality.

Variable cost (VC): Costs which vary with the level of output.

Average cost (AC): TC/Q, the average cost per unit of output.

Marginal Cost (MC): (TC of X + 1 units) – (TC of X units)

The extra cost of producing one extra unit of output.

2.7.5. Overhead and shared costs

The term overhead cost is an accounting term for resources that serve many different departments and programs. If individual programs are to be costed, these shared costs may need to be attributed to programs. The main point at the outset is that there is no unambiguously right way to apportion such costs. The approach favoured by economists is to employ marginal costs (Drummond *et al*, 1997).

2.7.6. Capital costs

Investments in buildings, plant, and equipments that yield a flow of services over a number of years give rise to capital costs. Generally, investment expenditure will be undertaken at the beginning of a project but the use of items of capital equipment will generate annual capital costs over the lifetime of the asset (Robinson, 1993 a).

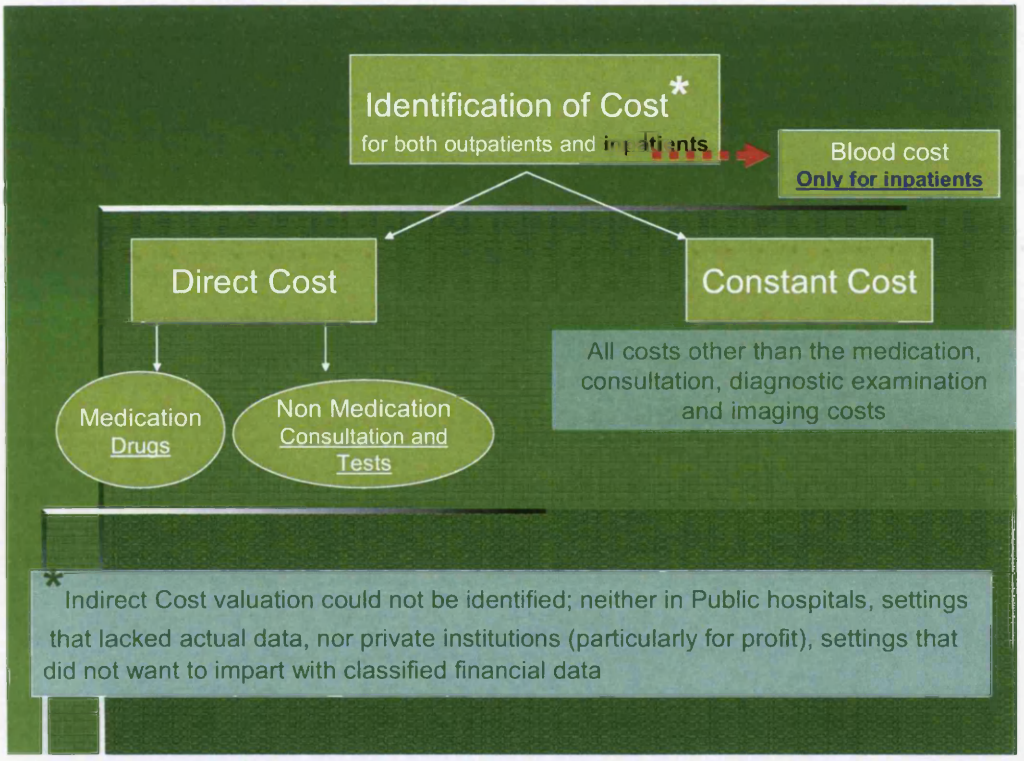
These costs have two components, namely, interest and depreciation. Interest costs should be included even if the asset was not acquired with borrowed money because tying up money in an item of capital equipment involves an opportunity cost, that is, interest forgone. Depreciation costs arise because of the wear and tear that an asset receives through use and consequent reduction in the length of its useful life. Sometimes an item of capital expenditure is unique to a particular use and has little or no alternative use value (opportunity cost). In such cases, it is referred to as a "sunk cost".

2.7.7. Measures of Cost in *This Study*

The international cost parameters were identified and defined in the above section. The actual on the ground availability of data and its sorting made the abiding to the international known nomenclature difficult. This led to the following division of costs (Figure 3). The direct costs were broken down to direct medication cost (actual drugs prescribed to each patient and hand copied from their prescriptions) and direct non medication costs which included tests, diagnostics and procedures performed to the patients under study as well as the consultation fees paid (in case of private patients). It is noteworthy to mention that there were no kept records anywhere to prescriptions data or procedures performed so physical presence in the outpatient clinics in NLI was necessary to obtain this data; some data was available in accounting sheets for the inpatients which made the job of cost calculation a little easier for that sector.

Constant costs were also included instead of indirect costs to cover all overhead costs that are not directly paid for by the patient nor by the payer of the service, such as the subsidy paid by the government to each patient. There were no indirect costs identifications in the research because in the case of public sector there were no such data available and in the case of the private sector such detailed information was too financially classified to impart with.

Figure 3: Cost categorization (special adaptation for the study)



2.7.8. Discounting

The current operating costs associated with most projects can be expected to extend over a number of years into the future, but their time profiles may differ. Where a condition impacts health and treatment utilization for over one year it is considered good practice to employ discounting to assess appropriately the changes in costs and benefits over time (OECD, 2003). Discounting offers a means of standardizing different cost time profiles so that total costs can be compared (Robinson, 1993 a and

Drummond *et al,* 1997). Discounting is based on the assumption that costs incurred in the immediate future are of greater importance than costs incurred in the distant future. This is because earlier access to finance would permit investment at a positive rate of interest, thereby yielding a larger sum in the future (opportunity cost) or simply because people and society attach more importance to current opportunities than to future ones "positive time preference". For these reasons, economic evaluation "weights" costs by a discount rate, according to the year in which they accrue, before adding them up and expressing total costs in present value terms. Discounting is particularly relevant to analyses of the cost of HCV because anti-HCV infection treatment costs occur now, and the costs of potential end-stage liver disease occur in the future. This was considered due to the long life cycle of the disease and the high immediate cost of the treatment.

Almost all HTA bodies employ discounting in assessments, typically applying an annual rate between 2.5% and 10% to both costs and benefits (Zentner *et al,* 2005 and OECD, 2003).

2.7.9. Inflation

Most programs that extend over several years will be affected by inflation. It is important, however to distinguish between changes in the general price level and changes in relative prices. For the general level, there will be no change in the relative cost of inputs and all future inputs can be valued at current prices and discounted by a real (excluding inflationary effect) rate of interest (Robinson, 1993a). If, however, some input prices are expected to increase more than others there will be relative changes in their opportunity costs and these need to be taken into account (Robinson, 1993a).

2.8. Development of drugs and role of technology appraisal

Evaluation designs that have been described value consequences either by assuming them as equivalent such is the case of cost-minimization analysis (CMA) or in utilities as is the case for cost-utility analysis (CUA) or in natural units for the cost-effectiveness analysis (CEA), while cost benefit analysis (CBA) values them in monetary units. Several approaches to valuation have been used. These falls into two broad categories: individual or societal preference and human capital. The human capital approach to valuation is based on the fact that human beings are similar to capital equipment as they represent a productive resource to society and this worth is calculated on the basis of their present and future earnings. Illness diminishes that person's productive capacity, which is usually valued in this approach by the loss of earnings. Life, for instance, has been valued on the basis of its expectancy multiplied by the annual average income of that person or that social class. Loss of life has been valued as the loss of projected earnings from the date of death to the projected date of retirement.

2.9. Cost-minimization Analysis

It is an appropriate form of evaluation to use when there is reason to believe that the outcomes of the procedures under consideration are the same or similar, whether through established literature or from parallel clinical trials (Robinson, 1993 a; Drummond *et al,* 1997 and ElShakhs, 2001). Only then should treatment costs be compared, thereby identifying the treatment associated with the lower cost; albeit with the same likelihood of producing the intended therapeutic outcome. In this case, minimization of costs refers not to techniques for driving down expenditures explicitly, but rather to a comparison of costs for alternative interventions with equivalent outcomes (Bonk, 1999 and ElShakhs, 2001). Incorrect supposition of

outcome equivalency, however, could indeed, undermine the validity of an otherwise sound pharmacoeconomic study. It is noteworthy to mention that Walley and Haycox, (1997) indicated that it is the most restrictive form of analysis that focuses entirely upon costs, usually only to the health service (Walley and Haycox, 1997); and McCombs, (1998) supported this by saying "it is the most limited type of health economic analysis" (McCombs, 1998).

2.10. Cost-benefit analysis

At times it is necessary to take decisions on the allocation of resources of large and far reaching interventions which have costs and consequences for more than one section of society. We may also have to make decisions about whether an intervention is worth making at all. Healthcare interventions may be competing for resources with other programs, not necessarily directly linked to health. The type of economic evaluation which can assist planners and decision-makers on such issues is cost-benefit analysis (CBA), which is the first analytical study design to have been introduced in health economics (its origins date back to the 1930s) (Williams, 1974). CBA compares the discounted future streams of incremental program benefits with incremental programs costs; the difference between these two streams being the net social benefit of the program (Drummond *et al,* 1997). In simple terms, the goal of this analysis is to identify whether a program's benefit exceeds its costs. A positive net social benefit indicating that a program is worthwhile and its outcomes exceed requisite financial investment for its implementation. CBA aims to compare all social costs and consequences across different interventions or against a "do nothing" option. At the basis of CBA is the concept that social welfare exists and can be maximized by moving additional productive resources to aspects of production where there is greater social benefit at the margin. The key to CBA is the systematic

calculations of all costs and consequences accruing to society from different options and the expression of their values in monetary terms. Translating health consequences in monetary values is far from easy, and such difficulties have contributed to the relative fall from grace of CBA design. Usually, healthcare programs evaluated by CBA extend several years into an uncertain future and have immediate sizeable effect on resources but long-term effects on health. These types of programs may still have to be compared and their values translated into a single current measure which represents their present value. Such a value is usually calculated by discounting their future costs and consequences in time. Discounting takes account of observed economic behaviour which shows a positive preference for benefits now and costs later. Discounted benefits and costs are valued less the further onto the future they accrue (Williams, 1974).

2.11. Cost-effectiveness analysis

The term refers to a particular type of evaluation in which the health benefits can be defined and measured in natural units (e.g. years of life saved, life years gained, ulcers healed, pain or symptom free day, blood pressure mm Hg decreased ...) and the costs are measured in monetary terms (Walley and Haycox, 1997). CEA therefore compares therapies which can be measured on a common scale of outcomes but perhaps exhibit different success rates (Williams, 1974; Robinson, 1993 b and Walley and Haycox, 1997). Unlike CBA, it avoids the complication of reducing all outcomes to a monetary basis (ElShakhs, 2001). The typical logical setting for CEA is one in which a decision to intervene in a particular problem has already been taken and CEA is carried out in order to identify the most efficient way of achieving the desired objective, and it is for this reason that economists say that CEA is used to assess "technical efficiency"(Williams, 1974).

CEA, born in 1960's (Williams, 1974 and Gold *et al,* 1996) has quickly supplanted cost-benefit analysis popularity up to the point where the term "cost-effectiveness analysis" is often used as synonymous with economic evaluation (Williams, 1974; and Walley and Haycox, 1997), and at times, North American economists use the term CEA to include both CMA and CUA. Furthermore, Walley and Haycox, (1997) mentioned that CEA is the most commonly applied form of economic analysis but it does not allow comparisons to be made between two totally different areas of medicine with different outcomes (Walley and Haycox, 1997). It is also noteworthy to report that Mooney, Russel and Weir, (1986) wrote in their book that cost effectiveness analysis is essentially concerned with the "how" of policy. It can assist in decisions on the techniques of care delivery (Mooney *et al,* 1986).

McCombs, (1998) noted the limitation of this approach by emphasizing the fact that all years of life as a unit of outcome are valued equally without adjustment; for the quality of life enjoyed by the patient. Clearly, society values a year of life at full function higher than a year of life in a comatose state. To account for this, economists and other practitioners of patient outcome research are attempting to measure the utility of the effects achieved in an analysis referred to as cost-utility analysis.

2.12. Measures of effectiveness

Decision about resource allocation must be made, and indeed are made, every day by all healthcare workers. As economics is but one of the many dimensions that decision-makers have to take into consideration, often economics play "second" to or "third fiddle" to other dimensions such as effectiveness, safety of interventions and politics. In order to carry out a cost-effectiveness analysis it is necessary to have suitable measures of effectiveness. These will depend on the objectives of the particular interventions under review. In all cost effectiveness analyses, however, measures of

effectiveness should be defined in appropriate natural units and, ideally, in a single dimension which would permit direct comparison between alternative procedures in terms of their marginal cost per unit of outcome. Sometimes, however, the alternatives under examination have multiple outcomes (Table 5). Nonetheless, many of these choices can be dealt with within the cost-effectiveness analysis framework (Robinson, 1993 b). Furthermore, economic evaluation should be undertaken alongside clinical trials so that the appropriate data collection can be built in as an integral part of the study. Unfortunately this is rarely the case, and hepatitis C virus is but one example and so existing medical publications usually provides the main source of data on effectiveness and outcomes (Robinson, 1993 a).

Table 5: Examples of measures of effectiveness used in literature

Examples of measures of effectiveness	• Cases treated appropriately • Lives saved • Life years gained • Pain or symptoms free days • Cases successfully diagnosed • Complications avoided

2.13. Obtaining effectiveness data

Ideally, economic evaluation should be built alongside clinical trials so that relevant data on costs and effectiveness can be collected at the same time. However, setting up and conducting appropriate trials is often time consuming and expensive (Robinson, 1993b). Another route for obtaining effectiveness data for CEA is from the existing medical literature.

Unfortunately though, there is often a lack of good epidemiological evidence relating health inputs to outputs, particularly in the case of new technologies, which are the focus of economic evaluation (Culyer, 1982 and Robinson, 1993b). Even when data are available it is important to ensure that they are relevant to the context in which an evaluation is being carried out. If neither specifically designed clinical trials nor the existing published work provide the necessary data in full, an economic evaluation may have to rely on assumptions about clinical evidence (Robinson, 1993b and Drummond *et al,* 1997). Although this may seem like a dangerous practice, there is often a range of situations in which cost considerations dominate, and so variations in effectiveness are unlikely to alter the preferred option. In such cases, however, the results must be subjected to a range of different assumptions about effectiveness. This is done by sensitivity analysis. McCombs, (1998) adds a few other data sources among which are retrospective data, which are a good source of healthcare costs and effectiveness reflecting real world practice. In particular, real world transition probabilities (effectiveness) may vary significantly from the efficacy measured in RCT. "Prospective studies that mimic real world practice and measures definitive patient outcomes in addition to clinical outcomes are becoming the gold standard in cost effectiveness analysis", he wrote. McCombs, (1998) also mentions expert opinion to fill in missing data (McCombs, 1998).

The validity of data for this study is sound even though this is not a randomized clinical trial (RCT) nor the data has been previously published. Moreover, the evidence of the effectiveness of treatment is also seen in the difference between the health state and quality of life (QOL) experienced by the patient receiving it; this is endorsed by clinicians and expert opinion as well as the medical norms and literature

and international consensus. These endorsements have quality, relevance and reliability (Palfrey *et al,* 2004).

2.14. Sensitivity Analysis

The final piece of any good clinical economic analysis is the sensitivity analysis (Mulahy and Manning, 1995 and McCombs, 1998). Much of the data necessary to completely specify the medical decision analytic model are not available, thus requiring that gaps in knowledge be fitted in by assumptions and expert opinion (Briggs, 2001). A good clinical evaluation will clearly identify those assumptions that are critical to the results and test the sensitivity of the results to changes in these assumptions (McCombs, 1998).

2.15. Cost-utility Analysis

Cost-utility is a form of economic evaluation in which the outcomes of alternative procedures or programs are expressed in terms of a single, "Utility based" unit of measurement. Utility is a term used by health economists to refer to the subjective level of well being, or improvement in health status, as measured by the preferences of individuals or society (Robinson, 1993c). It actually derives from the work of the early nineteenth century economist and philosopher Jeremy Bentham, who developed the "utilitarian" school of thought (Robinson, 1993 a). The most widely used utility based measure in cost-utility analysis is the quality-adjusted life-year (QALY) but that does not exempt other utility based measures and variants such as healthy years equivalent (YHE) (Robinson, 1993 c and Drummond *et al,* 1997). To calculate the number of QALYs resulting from a particular intervention, the number of additional years of life obtained is combined with a measure of the quality of life in each of these years to obtain a composite index of outcome. Comparison between alternative

procedures or programs can then be based on the marginal cost per QALY gained (Robinson, 1993 c).

In cost-effectiveness analysis, typically the main outcome (measured in program specific unit) is designated as the primary effectiveness measure and used as the denominator in the cost/effectiveness ratio. There are three problems; first, because the measure of primary effectiveness may differ from program to program, cost-effectiveness analysis cannot be used to make comparisons across a broad set of interventions. Second, in any one program there is often more than one outcome of interest. In fact, normally there are a large number of relevant outcomes; for example, outcomes of any specific intervention often include life extension, long term quality of life changes, side effects both major and minor from the interventions, as well as the short term quality of life effects of the intervention itself. Third, some outcomes are more important, or more valued, than others. Cost-utility analysis was developed to address these problems. It enables a broad range of relevant outcomes to be included by providing a method through which the various disparate outcomes can be combined into a single composite summary outcome. This, in turn, allows broad comparisons across widely differing programs. And, finally, cost-utility analysis provides a method to attach values to the outcomes so the more important outcomes are weighted more heavily (Drummond *et al*, 1997). By converting the effectiveness data to a common unit of measure, like QALYs gained, CUA is able to incorporate simultaneously both the changes in the quality of life (morbidity) and the changes in the quality of survival (mortality), considering that this type of consequence is not rare in health interventions (Drummond *et al,* 1997). In the QALY approach, the quality adjustment is based on an act of values or weights called utilities, one for each possible health state, that reflect the relative desirability of the health state.

Drummond and colleagues, reported, that technically, CUA can be seen as simply a specific type of CEA (Drummond *et al,* 1997). Jefferson and colleagues, (2000) wrote that CUA is a specialized variant of CEA in which consequences are expressed in utilities instead of in natural units as in CEA (Jefferson *et al,* 2000). However, unlike authors in the United States, Gold *et al,* (1996) as well as Weinstein and Stason, (1997), continued to use the separate label, giving several reasons for their choice. First, they mentioned that the separate label clearly distinguishes between those studies that use a generic measure of outcome and thus are potentially comparable across studies (CUA), and those that use a measure of outcome specific to the program under study (CEA). They added that it highlights the crucial role of consumer preferences (utilities) in valuing the outcomes. They concluded their reasoning by emphasizing the need to incorporate the consumer preferences, which makes CUA special (Gold *et al,* 1996 and Weinstein and Stason, 1997).

2.16. The role of randomized controlled trials and modelling

In the evaluation of pharmaceutical interventions the most usual way to undertake economic assessments has been randomized controlled trials (RCTs). However, the limited scope for generalization to every-day patient management of RCTs) results and the fact that they may not represent the real world of clinical practice. In addition, the follow-up period within a RCT is often relatively short in relation to the natural progression of the disease (Phillips, 2005).

The limitations of randomized controlled trials lead to the notion of lifetime or long-term modelling being "an important and necessary component of cost effectiveness analysis" (Kuntz and Weinstein, 2001) and health economics (Rittenhouse, 1996; Sheldon, 1996; Buxton *et al,* 1997; Kuntz and Weinstein, 2001; Weinstein *et al,* 2001 and Siebert *et al,* 2003).

A model is a simplified picture of reality providing useful frameworks for understanding the important parameters involved in achieving a certain outcome. There are several reasons for building models; they start with the fact that models help in describing problems, leading to models helping in analyzing problems. A Markov charts patient progression and then through the model layout seeing how treatment will impact patient progression. Furthermore Markov is a way to assess effectiveness as once the treatment comes in it induces a different profile because the probability of a patient moving from one stage to the next will change.

Models, defined by Bender, (2000) as simply "something that mimics relevant features of a system being studied" can assist with decision making in a descriptive, heuristic, or prescriptive (identifying optimal choice) sense (Bender, 2000). Models can also help to integrate data from different sources, as well as assist with disease risk assessment and the formulation of hypotheses, and can additionally act as a bridge between pharmacoepidemiological data and the processes of decision-making. A specialized set of models called decision analytic models go a step further than this by assisting with the identification of optimal choices in decision modelling scenarios (Patten and Lee, 2002).

Some chronic diseases are not reversible, and some are recurrent. In these circumstances prevalence will be determined by incidence and duration. Models that incorporate these concepts may be termed "incidence-prevalence models. Changes in probability of disease and nature of health status over time are evaluated using Markov models and stochastic (probabilistic) models.

Models and their use in disease risk assessment and medical decision making are discussed in many papers (Beck and Pauker, 1983; Moolgavkar *et al*, 1988; Dewanji *et al*, 1989; Sonnenberg and Beck, 1993 and Dewanji *et al*, 1999).

2.17. Case Study Approach

Use of the case study originated only in the early 20th century as a distinct approach to research and their popularity as research tools has developed only in recent decades. The Oxford English Dictionary traces the phrase *case study* or *case-study* back as far as 1934, after the establishment of the concept of a *case history* in medicine. Case study methods involve an in-depth, longitudinal examination of a single instance or event: a case (HCV health burden in Egypt). They also provide a systematic way of looking at events, collecting data (cost of various treatment pathways) and, analyzing information (processed, calculated data and evidence), and reporting the results. As a result a sharpened understanding is gained of what and/or why might become important to look at more extensively in future research (Stake, 1995). As Flyvbjerg, (2006) put it; case studies lend themselves to both generating and testing hypotheses (Flyvbjerg, 2006), and in this study, the implementation of HTA within the Egyptian healthcare system. Case studies can generate a great deal of data that may defy straightforward analysis a fact that comes in handy with HCV as an expensive disease and heavy burden on the Egyptian government. Yin and Lamnek both noted that case studies can be based on any mix of quantitative and qualitative evidence (Yin, 2002 and Lamnek, 2005).

2.18. Debating health economics and issues in evaluating healthcare interventions from the economic perspective

The decision-making process to determine which services and treatments should be provided is highly complex and involves a number of different, often conflicting, factors. Health economic techniques help to contribute to the process of healthcare priorities determination and to ensure the most efficient use of available resources within the limited healthcare budgets. Most importantly those techniques assist

decision makers to assess information relating to the effectiveness and efficiency of an intervention. However, limitations to application of economic evaluations include both the cost and the time required render them unfeasible in the context of many decisions (Mitton and Donaldson, 2004). It has also been argued that the assumptions underlying the current methods fail to consider all society's health objectives and are too complex for policy makers to use. In addition, it is argued that "Even aside from doubts over the existence of this mythical decision maker with a clear set of objectives, the desire to maximize health seems to be largely the objective of economists rather than society" and "by generating a pseudoscientific aura around economic evaluation, they camouflage critical weaknesses in current techniques" (Coast, 2004).

Ideally, resource allocation decisions should not be solely based on the capitalization of healthcare benefits, rather, on many other factors such as equity, need, access, and others. If not resources would never be allocated to services provided for extremely rare conditions, with poor survival and quality of life outcomes. In addition, attempts to restrict the benefits derived from healthcare services into a single outcome measure also fail to do justice to the wide ranging impact that healthcare improvements can have on the other determinants of health model (Evans and Stoddart, 1990), among which are patients, their families, their communities and ultimately society as a whole. Furthermore, the emphasis on cost-effectiveness may lead paradoxically to over-spending (Mitton and Donaldson, 2004). The limitations of health economic evaluations highlighted above, together with the time and resources involved in their production, mean that while they can provide useful information relating to specific interventions or programs, they are of less use in the context of decision making, especially in relation to making choices as to where additional resources should be

placed, or which areas should bear the brunt of any cutbacks, within healthcare organizations.

The human capital approach has been applied in the valuation of health benefits in cases of both avoidable morbidity and mortality. There have, however, been various criticisms, as many people have strong ethical objections to monetary values being placed on human life. Other criticisms have centred on the use of rates of pay as a measure of value. At the same time, valuing benefits in terms of rates of pay, neglects the health benefits that accrue to people who are not employed. It also ignores the non-financial costs of pain, suffering and grief often associated with illness (Alan, 1974). This human capital method of valuing health status has been used for many years (Mushkin, 1978 and Drummond *et al,* 1997).

There are technical issues surrounding economic approaches to priority setting but they should not be allowed to detract from the fact that they provide a rational framework within which other concerns, such as considerations of equity and public and professional opinions can be embraced and priorities established. Irrespective of how crude or limited the techniques and tools of health economics are, as Maynard, (1994) put it attempts to set priorities within the context of a transparent and relatively rational framework "should be welcomed as a challenge to the covert, imprecise and inconsistent practice of prioritization which exist in all healthcare systems today" (Maynard, 1994).

Chapter 3

Hepatitis C Virus And Its Management

Contents of Chapter

3.1. Introduction: History and epidemiology

Hepatitis C virus is an enormous present and future health burden to the world (Wong *et al,* 2000). Choo *et al,* in 1989, identified hepatitis C virus and found it to be the cause of disease for the majority of patients with non A non B hepatitis (Choo *et al,* 1989). It is estimated that 170 million people worldwide approximately 3% of the world's population is infected with hepatitis C virus (Alter, 1997; WHO, 1997 and Thomas *et al,* 2000) and this population approximately approach 2.7 million infections in the USA (Alter *et al,* 1999), an estimated 5 million are in Western Europe, and 7.8 million infections in Egypt, nearly 12.8 % of the population, this is the highest prevalence of HCV in the world. Hepatitis C virus represents the most frequent etiology of cirrhosis in the developed world (Alter *et al,* 1999; WHO, 1999; Thomas *et al,* 2000 and Alberti *et al,* 2002) and is the leading cause of liver transplantation in Europe and the USA (Alter *et al,* 1999). Fortunately the incidence of Hepatitis C virus infection appears to be declining since its peak in 1989. Currently, approximately 30,000 acute new infections are estimated to occur each year, about 25% - 30% of which are diagnosed (Wong *et al,* 2000). Allowing for failing prevalence, a huge backlog of infected patients will still be progressing towards cirrhosis and hepatocellular carcinoma. Even if it were possible at the present time to treat all those infected and to slow down the progression towards chronic severe liver disease, the cost of such large scale investigations and therapy would be enormous. One of the most prominent characteristics of HCV infection is its high rate of evolution to chronicity. The virus is cleared only in less than 15% of exposed individuals; in the remaining, the infection produces chronic hepatitis, which can lead, later on, to cirrhosis and eventually, hepatocellular carcinoma (Di Bisceglie, 1998 and

Thomas *et al,* 2000). In contrast to hepatitis A and B, there is no effective vaccine to prevent acquisition of Hepatitis C virus infection.

3.2. The Natural history of hepatitis c virus

3.2.1. The Virus

HCV is a small enveloped RNA virus belonging to the family flaviridae (Dusheiko *et al,* 2000). The replication of HCV takes place in the cytoplasm (Di Bisceglie, 1998). Individual isolates consist of closely related yet heterogeneous populations of viral genomes (quasispecies) (Domingo *et al,* 1996). Comparing the genomic nucleotide sequences from different HCV isolates enables classification of viruses into several genotypes and many more subtypes. The mutations rate of the polymerase RNA-dependent of HCV is of $1/10^4$ to $1/10^5$ nucleotides; that means one mutation per each genome is transcribed (Rodriguez-Rosada *et al,* 2001). This diversity has allowed the distinction of genotypes and subtypes. For HCV six main genotypes and at least 30 subtypes have been described by Brechot, (1994) and Simmonds, (1995) within three subtypes, the viruses' pond in one infected subject also show significant differences among their sequences. The great genetic variability allows HCV to quickly develop mechanisms to improve its adaptation to the environment, and in this way evade any immune surveillance or pharmacologic pressure, leading to a high rate of chronic infection. This is the reason why the most heterogenous regions of both viruses are those codifying the envelope, which is the most immunogenic part (Brechot, 1994; Simmonds, 1995 and Rodriguez-Rosada *et al,* 2001). The extensive genetic heterogeneity of HCV has important diagnostic and clinical implications, perhaps explaining variations in clinical course, difficulties in vaccine development, and lack of response to therapy.

3.2.2. Transmission

Hepatitis C virus is transmitted primarily by the parenteral route, and sources of infection include injection drug use, needle-stick accidents, and transfusion of blood or blood products. Since 1990, following the introduction of sensitive and effective blood tests for the detection of HCV, the risk of new cases of post transfusion HCV have virtually disappeared (NIH, 1997). The majority of HCV infections in developed and developing countries are, or have been, caused by intravenous drug use, transfusion of unscreened blood and blood products, nosocomial transmission from inadequately sterilized instruments or unsafe injections, chronic haemodialysis, and possibly high risk sexual practices (Dusheiko *et al,* 2000). Vertical transmission rates drive the trends among children and adolescent, with active carriers born to mothers with HCV infection with 1 % to 5% likelihood (Younossi *et al,* 1999). Prospective studies could help determine the relative contribution of vertical and horizontal transmission of HCV infections observed in these children (Zanetti *et al,* 1999).

3.2.3. Vaccination

HCV is a worthy adversary, changing continually to avoid immune surveillance by the host. A traditional vaccine is unlikely to become available in the foreseeable future. HCV infrequently induces an effective protective immune response. Neutralizing antibodies, CD4 and CD8 T cells are poorly elicited by natural infection. The difficulties of preparing a protective vaccine are:

(a) Only man and the chimpanzee are infected, and better animal models are needed;

(b) HCV replicates poorly *in vitro*;

(c) The viral envelope proteins (E1/E2) are highly mutable; antibodies against them fail to provide long term protective immunity.

3.3. A "Typical" patient with chronic HCV infection

The typical patient for whom therapy is well established is an adult who has a chronic HCV infection (evidence of infection for at least 6 months) and increased serum levels of transaminases, detectable serum HCV RNA, and histologic evidence for liver injury in the absence of cirrhosis. Also, other liver diseases and compounding co-morbid conditions have been excluded (Zein and Zein, 2002).

3.4. Course of infection and disease progression

The health states were based on liver histology, presence or absence of hepatitis C viraemia, decompensated liver disease, hepatocellular carcinoma, or liver transplantation. The three histologic states considered were mild hepatitis, moderate hepatitis and a cirrhotic stage (Alter and Mast, 1994).

From each histologic state, individuals could progress over time to a more advanced clinical or histologic state or remain in the same state of health. For example, each year, individuals with mild chronic hepatitis could develop moderate chronic hepatitis or remain stable with mild chronic hepatitis.

Likewise, individuals with moderate chronic hepatitis could progress to either hepatocellular carcinoma or one of three modes of hepatic decompensation: (1) ascitis, (2) variceal hemorrhage, or (3) hepatic encephalopathy. Once individuals developed decompensated cirrhosis, they could die from liver disease, receive a liver transplant, or remain alive with liver failure. The likelihood of these health status transitions was based on probabilities derived from a review of the literature in which actuarial techniques were used; expert opinion was used when such data was unavailable. The natural history of this disease appears to differ according to geography, alcohol use, virus characteristics (e.g., genotype, viral load), co infection

with other viruses, and other unexplained factors (Hoofnagle, 1997 and Centres for disease contol and prevention, 1998).

3.4.1. Acute infection

After initial exposure, HCV RNA can be detected in blood in one to three weeks. Within an average of 50 days (ranges betwen 15 - 150 days), virtually all patients develop liver cell injury, as shown by elevation of serum alanine aminotransferase (ALT). The majority of patients are asymptomatic and anicteric. Only 25% - 35% develops malaise, weakness, or anorexia, and some become icteric. Fulminant liver failure following HCV infection has been reported but is a rare occurrence.

Antibodies to HCV (anti-HCV) almost invariably become detectable during the course of illness. Anti-HCV can be detected in 50% - 70% of patients at the onset of symptoms and in approximately 90% of patients 3 months after onset of infection.

HCV infection is self-limited in only 15% of cases. Recovery is characterized by disappearance of HCV RNA from blood and return of liver enzymes to normal (Hoofnagle, 1997; NIH, 1997 and EASL, 1999).

3.4.2. Chronic infection

About 85 % of HCV-infected individuals fail to clear the virus by 6 months and develop chronic hepatitis with persistent, although sometimes intermittent, viremia. This capacity to produce chronic hepatitis is one of the most striking features of HCV infection. The majority of patients with chronic infection have abnormalities in ALT levels that can fluctuate widely. About one-third of patients have persistently normal serum ALT levels. Antibodies to HCV or circulating viral RNA can be demonstrated in virtually all patients. Chronic hepatitis C virus is typically an insidious process, progressing, if at all, at a slow rate without symptoms or physical signs in the majority of patients during the first two decades after infection. A small proportion of patients

with chronic hepatitis C virus, perhaps less than 20% develops nonspecific symptoms, including mild intermittent fatigue and malaise. Symptoms first appear in many patients with chronic hepatitis C virus at the time of development of advanced liver disease (NIH, 1997 and EASL, 1999).

In chronic hepatitis, inflammatory cells infiltrate the portal tracts and may also collect in small clusters in the parenchyma. The latter instance is usually accompanied by focal liver cell necrosis. The margin of the parenchyma and portal tracts may become inflamed, with liver cell necrosis at this site (interface hepatitis). If and when the disease progresses, the inflammation and liver cell death may lead to fibrosis. Mild fibrosis is confined to the portal tracts and immediately adjacent parenchyma. More severe fibrosis leads to bridging between portal tracts and hepatic veins. Such fibrosis can progress to cirrhosis, defined as a state of diffuse fibrosis in which fibrous septae separate clusters of liver cells into nodules. The extent of fibrosis determines the stage of disease and can be reliably assessed. Severe fibrosis and necro inflammatory changes predict progression to cirrhosis. Once cirrhosis is established, complications can ensue that are secondary to liver failure and / or to portal hypertension, such as jaundice, ascitis, variceal hemorrhage, and encephalopathy. The development of any of these complications marks the transition from compensated to decompensated cirrhosis.

The rate of progression is highly variable, long-term studies suggest that most patients with progressive liver disease who develop cirrhosis have detectable ALT elevations; these can, however, be intermittent. The relationship is inconsistent between ALT levels and disease severity as judged histologically. Although patients with HCV infection and normal ALT levels have been referred to as "healthy" HCV carriers,

liver biopsies can show histological evidence of chronic hepatitis in many of these patients.

3.4.3. Cirrhosis

Chronic HCV infection leads to cirrhosis in at least 20 % of patients within two decades of the onset of infection. Cirrhosis and end-stage liver disease may occasionally develop rapidly, especially among patients with concomitant alcohol use.

3.4.4. Hepatocellular carcinoma

Chronic infection by HCV is associated with an increased risk of liver cancer. The prevailing concept is that hepatocellular carcinoma (HCC) occurs against a background of inflammation and regeneration associated with chronic hepatitis over the course of approximately three or more decades. Most cases of HCV related HCC occur in the presence of cirrhosis. The risk that a person with chronic HCV will develop HCC appears to be 1% - 5% after twenty years, with striking variations in rates in different geographic areas of the world. Once cirrhosis is established, the rate of development of HCC increases to 1% - 4% per year. Among patients with cirrhosis due to hepatitis C virus, HCC develops more commonly in men than in women and in older than in younger *patients* (NIH, 1997 and EASL, 1999).

3.4.5. Extra hepatic manifestations of HCV

Patients with chronic HCV occasionally present with extra hepatic manifestations or syndromes considered to be of immunologic origin, including arthritis, keratoconjunctivitis sicca, lichen planus, glomerulonephritis, and essential mixed cryoglobulinemia. Cryoglobulins may be detected in the serum of about one third of patients with HCV, but the clinical features of essential mixed cryoglobulinemia develop in only about 1% - 2% of patients. Chronic HCV may be a major underlying cause of porphyria cutanea tarda (NIH, 1997 and EASL, 1999).

3.4.6. Mortality

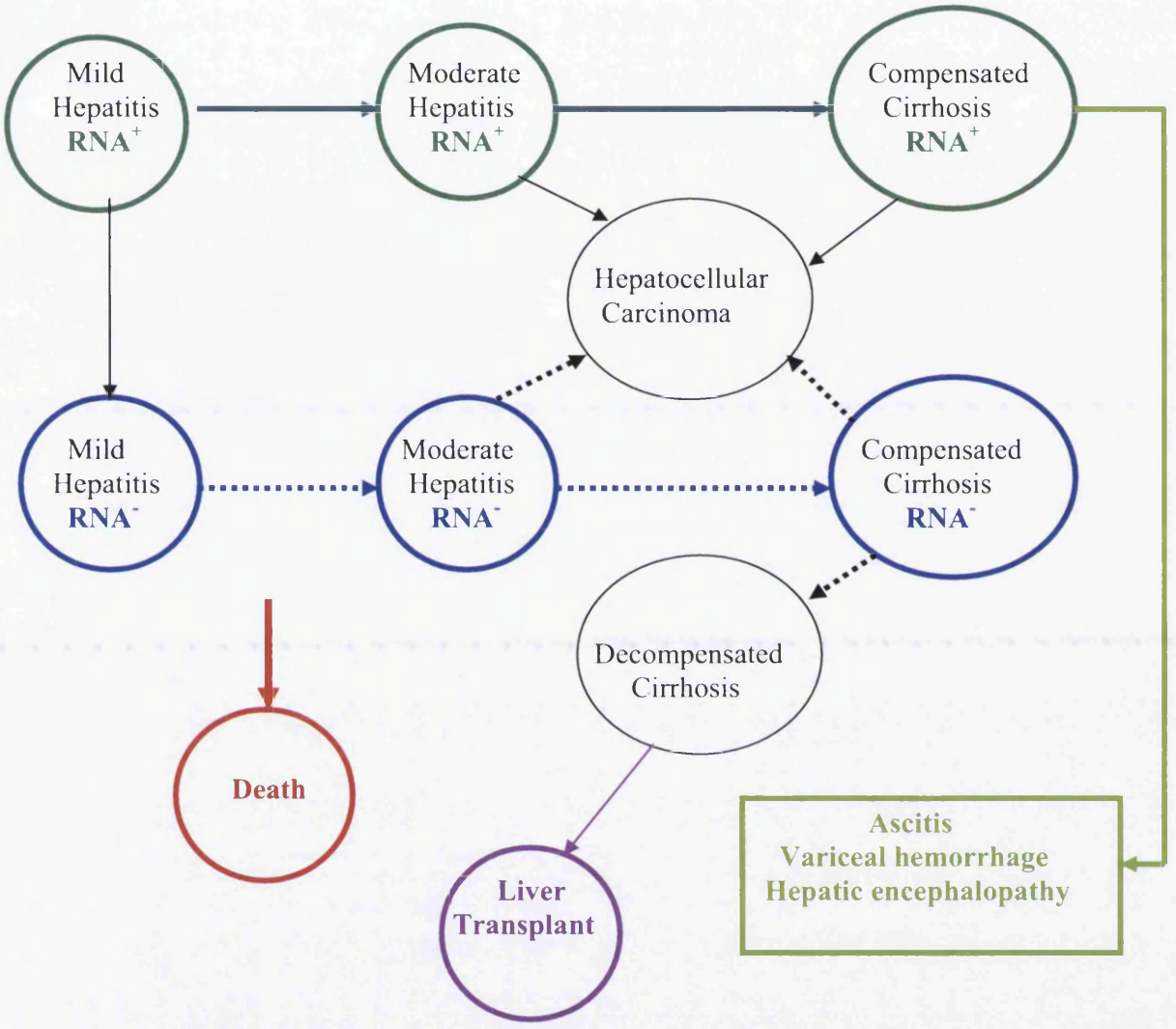
After an average follow up of eighteen years, a prospective study of patients who received blood transfusions showed no difference in overall mortality between HCV-infected cases and non infected controls. Liver-related mortality, although rare, was twice as high in the cases (3.2 % versus 1.5 %) (Wong *et al,* 2000).

A European study showed that survival among HCV patients with compensated cirrhosis was 91 % after five years and 79 % after ten years. Among patients developing decompensated cirrhosis, however, five years survival was only 50% (Thomas *et al,* 2000).

3.5. Clinical implications of hepatitis C viral kinetics

From serial measurements of changes in viremia, kinetic information on the dynamics of HCV replication was obtained. Calculations revealed a minimum virus production and clearance per day in patients with chronic HCV of approximately 10^{10} x 2013; 10^{12} virions per day and an *in vivo* half life of the virus is measured in the order of a few hours. The high turnover rate of HCV explains the rapid generation of viral diversity and the opportunity for viral escape from the host immune surveillance and antiviral therapy (Thomas *et al,* 2000 and Zeuzem, 2002). The implications derived from HCV kinetics comprise the consideration of more aggressive initial design regimens, the possibility to optimize therapy individually not only according to pretreatment parameters but also according to the initial decline of viral load and the perception that eradication of the virus will rely on the half life of infected cells.

Figure 4: Simplified schematic of Markov model (Wong *et al*, 2000)



Note: Overall, there were 190 states of health. Each circle represents a state of health for a segment of the population with chronic HCV. Each arrow represents possible changes in health status that may occur each year. Dotted arrow represent lower probabilities of transition, reflecting the viral-negative state (the odds-likelihood ratio for progression is reduced by 0.0002 for mild hepatitis, 0.001 for moderate hepatitis. 0.4 for cirrhosis to hepatocellular carcinoma, and 0.32 for cirrhosis to decompensated cirrhosis). The decompensated cirrhosis state represents separate states of health in the model for diuretic-sensitive and diuretic refractory ascites, first year and subsequent years after initial variceal hemorrhage, and first year and subsequent years after initial hepatic encephalopathy. Similarly, the liver transplant state has separate status of health for the first year and subsequent years postransplant. For individuals who are Hepatitis C virus RNA-positive with mild hepatitis, moderate hepatitis or compensated cirrhosis, additional separate states of health exist for those with normal transaminases and those with elevated transaminases. For those with elevated transaminases, separate states of health exist for those known to have chronic HCV and those whose infection is unknown and clinically silent unless they develop decompensated cirrhosis of hepatocellular carcinoma. Individuals in any state of health may die from causes related to their age and sex as occurs in the general population, and individuals with decompensated cirrhosis or hepatocellular carcinoma may die from liver-related causes.

3.6. Treatment and management of hepatitis C Virus

3.6.1. Treatment considerations

Not all HCV-infected individuals develop complications, so treating all patients subjects some individuals to unnecessary treatment has potential adverse effects. However, except for alcohol ingestion, male sex, older age and elevated transaminases, it is not currently possible to reliably identify those individuals likely to progress. Moreover, the degree of transminase elevation does not consistently indicate the severity of the underlying liver histology (Bacon, 2002). Patients with low platelet counts, elevated prothrombin times and low albumin levels already have results suggesting advanced liver disease. Noninvasive measures of liver inflammation and fibrosis remain under investigation. Consequently, liver biopsy with its attendant risks for morbidity, mortality and costs is necessary to accurately assess the extent of the hepatic inflammation and, more importantly, fibrosis (Dienstag, 2002). The necessity of liver biopsy prior to antiviral treatment is controversial (Bain *et al,* 2004; Almasio *et al,* 2005 and Herrine and Friedman, 2005) as although liver biopsy might avoid treatment for patients with healthy histology and maybe those with mild histology, one study suggests that pre-treatment liver biopsy might increase the cost of managing patients with chronic HCV infection and would not necessarily improve health outcomes unless the patient or physician valued the prognostic information afforded by the biopsy (Wong *et al,* 1998).

Once decompensated cirrhosis occurs, treatment options are limited to liver transplantation and by the availability of donor organs. Ideally, antiviral drug treatment should be initiated prior to the development of compensated cirrhosis or bridging fibrosis because the likelihood of response is lower once histologic progression has occurred added to the fact that is going to be proven in the course of

this research that the overall cost of treatment with the less than perfect effectiveness percentages are cheaper in the long run than the cost of no treatment. The results shown below would agree that patients with elevated transaminases and moderate inflammatory or fibrotic hepatitis should be treated because they may progress to bridging fibrosis or cirrhosis (Wong and Koff, 2000 and National Institutes of Health, 2002). On the other hand they would disagree with the fact that those with healthy liver biopsies would be unlikely to be treated unless their QOL was felt to be severely impaired by HCV and viral eradication was expected to improve patient symptoms (Foster, 1999 and National Institutes of Health, 2002). The agreement and disagreement with the literatures mentioned is a general pro treatment for patients without decompensated liver cirrhosis.

The most controversial indication for antiviral drug treatment involves patients with mild hepatitis, where some advocate monitoring with periodic liver biopsies for those patients unwilling to undergo treatment but for others, biopsy adds costs and a small risk for morbidity and mortality. Moreover, the potential for advancing liver disease and age while undergoing biopsy management may decrease the likelihood of response to subsequent antiviral drug treatment (Foster *et al,* 1997; Levine, 1998; Wong and Koff, 2000 and Freeman *et al,* 2001). These recommendations are somewhat outdated and were made when interferon monotherapy was the standard treatment and without looking at costs as was done on this research, which was done using combination therapy of both interferon and peginterferon with ribavirin. This was reinforced by the fact that despite numerous drugs under development, no further therapeutic innovations appear imminent, beyond peginterferon combined with ribavirin (Wong, 2006).

3.7. Should patients with chronic HCV be treated?

Progress in our understanding of HCV infection has depended on the support of the pharmaceutical industry, particularly in physician education and in evaluating therapy in large clinical trials.

Theoretically, all patients with chronic HCV infection are candidates for antiviral therapy. However, only a subgroup of these patients has a clear indication for therapy. The restriction for treatment arises due to the naturally slow progression course of the infection (Buti *et al,* 1998 and Buti *et al,* 2000), the expense of the treatment, the occurrence of adverse effects, and the relative ineffectiveness of the treatment. Currently, treatment is recommended for patients with persistently elevated aminotransferase levels, HCV viremia, and findings of fibrosis and inflammation on liver biopsy (Buti *et al,* 2000).

Patients with detectable levels of HCV RNA and persistently high concentrations of aminotransferase or transaminase, and with liver biopsy specimens that show fibrosis or at least moderate necrosis and inflammation have a high risk of disease progression. The standard recommended therapy consists of the combination of interferon α–2b, 3 million units three times weekly, plus ribavirin, 1000 -1200 mg daily for 6 - 12 months. For other groups of patients, the indications for treatment are less clear and decisions should be made on a case-by-case basis (Zaraski, 1999; Dusheiko *et al,* 2000 and Zein and Zein, 2002).

There are several drugs available for the treatment of this disease, the most ubiquitous is interferon. Hypothetically, all patients should be given 24 weeks of treatment. If HCV RNA is detected at 24 weeks, therapy should be discontinued. Patients infected with HCV genotypes II or III usually can stop therapy if the PCR assay for HCV is negative at 24 weeks. An additional 24 weeks of treatment is suggested for patients

with other genotypes (I, IV, V and VI) and a negative PCR assay. Further recommendations can be made about the length of therapy depending on other factors associated with a favorable response to therapy such as the pretreatment HCV RNA level. However, it should be taken into consideration that combination therapy given for 48 weeks entails more severe adverse effects and the risk that therapy will be discontinued (Zein and Zein, 2002).

The etiology for 40 % of all chronic liver disease, hepatitis C virus accounts to some extend for the increasing incidence of hepatocellular carcinoma (El-Serag and Mason, 1999 and Wong, 1999), and it is the leading cause for liver transplantation. It can result in decompensated cirrhosis and ultimately liver-related death (Wong, 1999). Infection with hepatitis C virus does not usually resolve, and 60% - 80% of acute infections persist. Chronic hepatitis can cause progressive fibrosis of the liver, leading to cirrhosis in 20% - 30% (Dienstag, 1997 and Dusheiko *et al,* 2000) which rarely becomes detectable before the second or third decade of infection (Poynard *et al,* 1997 and Dusheiko *et al,* 2000). It is argued that as a slowly progressive disease, requiring twenty to thirty years for some patients to develop cirrhosis; treatment is effective in only a proportion of patients entailing potential side effects; and current treatments are relatively expensive. Others, however, contend that interferon treatment can eliminate viraemia, improve or stabilize histology, decrease the risk for hepatocellular carcinoma, and perhaps prolong survival (Wong, 1999 and Colombo, 2000).

3.8. Interferon

Interferons are a group of low-molecular-weight proteins produced by leukocytes (interferon-α), fibroblasts (interferon -β), and T lymphocytes (interferon-γ). Interferons have antiviral effects that seem to operate through several mechanisms,

including inhibition of viral replication, inhibition of viral protein production, and prevention of the release of virions from infected cells. In addition, the immunoregulatory property of interferons facilitates viral eradication. Interferon-α has been the basis of all effective regimens against HCV infection since the discovery of the virus.

Four types of interferon-α are available commercially: recombinant interferon-α-2a (Roferan, Hoffman-La-Roche Inc., Nutley, NJ), recombinant interferon-α - 2b (Intron A, Schering – Plough, Kenilworth, NJ), natural interferon α-n3 (alferon N, Purdue Fredrich Company, Norwelly, CT), and consensus interferon (In Pergen, Aurgen Inc., Thousand Oaks, CA).

3.8.1. Interferon's side effects and shortcomings

Interferon based therapy is expensive, has to be administered subcutaneously, has limited efficacy and is associated with numerous side effects (table 6) (Dusheiko, 1997 and Dusheiko *et al,* 2000). Many, but not all, of the side effects are dose dependent. A flu like syndrome is the most common side effects of interferon and occurs in 60% - 80% of patients but usually disappears after 2 - 4 weeks of therapy. These flu like symptoms can be ameliorated with acetaminophen given before interferon is injected. Long-term side effects include fatigue, weight loss, alopecia (reversible), and psychologic changes. Autoimmune phenomena may develop, especially in patients who have underlying autoimmune thyroditis may develop in 2.5% – 20% of patients and may not be reversible after treatment has stopped. Although most of these side effects are dose-dependent and reversible, they lead to noncompliance by some patients. The rate of noncompliance has been estimated to be between 5 and 10%. Due to potential adverse effects of interferon treatment, careful screening and monitoring of the patient's condition is needed. Monitoring should

include a complete blood count, serum chemistry panel, and liver function tests performed monthly. The level of thyroid-stimulating hormone should be checked periodically and, for women of childbearing age, a serum pregnancy test performed while the patient is receiving interferon (Zein and Zein, 2002).

Recombinant alpha interferon (IFN) monotherapy was hitherto the only licensed treatment for chronic hepatitis C virus. A proportion of patients show a remarkable response to treatment with rapid normalization of alanine aminotransferase (ALT) and loss of HCV RNA in serum. However, relapse rates limited the efficacy of alpha IFN monotherapy. Given, these earlier responses, the primary objective of treatment remains sustained virological response where HCV RNA remains negative by polymerase chain reaction (PCR) (albeit PCR sensitivity varies) for six months and longer after treatment has been discontinued (Dusheiko *et al,* 2000).

Table 6: Frequency of side effects in patients with chronic viral hepatitis treated with interferon (Zein and Zein, 2002)

Side effect	Patients %
-Flu-like syndrome – fever, headache, chills, myalgia, fatigue	60-80
-Bone marrow hypoplasia – manemia, leucopenia, thrombocytopenia	<5
-Cardiovascular disorders – arrhythmia, cardiomyopathy, hypertension	<5
-Endocrine disorders – exacerbation of diabetes mellitus, thyroid, gyncomastia	<5
-Gastrointestinal disorders – taste alteration, anorexia, diarrhea	15-25
-Liver and biliary – jaundice, liver failure/encephalopathy	<5
-Neuropsychiatric disorders – depression, amnesia, confusion, paresthesia	10-30
-Musculoskeletal disorders – arthritis, leg cramps, muscle weakness	<5
-Reproductive system disorders – amenorrhea, pimportence, uterine bleeing	<5
-Skin disorders – alopecia, pruritis, rash, dry skin	5-15
-Others – respiratory, urinary, vision	<5

3.9. Pegylated interferon

Peg-interferons are produced by the addition of a polyethylene glycol molecule to standard interferon (Dusheiko *et al,* 2000). This addition results in substantial changes in the metabolism of the drug. These drugs were approved in Europe for the treatment of chronic HCV infection before the more recent approval by the United States Food and Drug Administration (FDA). Two companies simultaneously developed peg-interferon forms of their existing non-pegylated interferons. Schering-Plough Pharmaceuticals developed peg-interferon-α-2b (Peg-Intron), and Hoffman La Roche

Pharmaceuticals developed peg-interferons-α-2a (Pegasys). By conjugating the molecule of polyethylene glycol and interferon, the half life of interferon was prolonged substantially because of decreased renal clearance of the new substance.

The rational also for developing antiviral agents with a longer half life for the treatment of chronic HCV infection is based on the dynamics of the viral response to interferon. Because of the prolongation of the half-life of interferon attained with pegylation, only one dose per week is required to maintain effective blood level of the medication which decreases viral replication that occurs on days without treatment during the standard thrice weekly dosage of conventional interferon (Zein and Zein, 2002).

An enhanced IFN molecule produced by the covalent attachment of a branched polyethylene glycol moiety to interferon α-2a exhibits sustained absorption, a restricted volume of distribution, and reduced clearance compared with unmodified IFN α-2a (Roche) (Parkin, 2002) or to interferon α-2b. The pegylation of interferon α-2b produces a molecule with a mean clearance one tenth of a non pegylated IFN α-2b and a sustained maximal serum concentration for 48 to 72 hrs after administration versus eight to twelve hours of IFN α-2b (Glue *et al,* 2000).

3.10. Combination therapy for hepatitis C virus infection

Combination therapy with interferon - α and ribavirin which until recently, was considered the treatment of choice for chronic hepatitis C is relatively ineffective (Poynard *et al,* 1998; McHutchison *et al,* 1998 and Poynard, 1999), 40% of those given this treatment have a durable benefit, and most patients continue to have viraemia after the treatment has been stopped (Zein and Zein, 2002). Also, this combination therapy has numerous and frequent side effects (table 6). Moreover, at the present time, the cost of combination therapy is too great for the large numbers of

patients in Europe and other continents who will require it. The cost of monitoring therapy must be considered. Detection of HCV RNA by PCR is the ~gold standard" and has been recommended to monitor treatment. Genotyping and quantification of viraemia are useful but remain costly. These tests must be made more generally available. The use of other combinations of drugs presently available is unlikely to achieve much better results than the combination of interferon and ribavirin.

Importantly, combination therapy has been shown to double sustained virological response rates in previously untreated patients. Large studies in the USA and Europe indicate that sustained virological response rates of 31% - 35% occur in patients treated with a combination of ribavirin and alpha 2b IFN given for 24 weeks, and in 38% - 43% given for 48 weeks (compared with 13% and 19% for alpha 2b alone given for 48 weeks (Dusheiko *et al,* 2000).

3.11. Ribavirin

The added efficacy of ribavirin is interesting and somewhat surprising given that treatment with ribavirin alone in controlled trials had little antiviral effect (Dusheiko *et al,* 1996). Ribavirin is a purine nucleoside (guanosine) analogue with immunomodulatory effects, increasing the production of type 1 cytokines (interleukin 2 (IL-2) and gamma IFN) and suppressing type 2 (IL-4) cytokines in a dose dependent manner. These shifts to a Th1 profile may be important in reducing the pro-inflammatory response of IFN and possibly reducing bystander damage hence the reduction in ALT in ribavirin treated patients. These changes cannot account for all of the observed effects however. Analysis of the viral kinetics observed after combination therapy with ribavirin and alpha IFN suggests a synergistic action, and a critical block on viral replication and release of virions from infected cell observed in the first phase of viral decline after antiviral treatment. Ribavirin inhibits inosine

monophosphate dehydrogenase and thereby biosynthesis of guanosine triphosphate (GTP) in cells, decreasing the intracellular GTP pool. However, the major antiviral effect may not be related to GTP pool depletion. Ribavirin triphosphate binds to HCV NS 5b polymerase as a nucleotide substrate and is mis-incorporated into nascent RNA (Dusheiko *et al,* 2000).

3.12. Effectiveness and cost effectiveness of treatment

Randomized clinical trials are the traditional approach to addressing questions about the effectineness of treatment. Based on the fact of the prolonged natural history of hepatitis C virus, such trials would require ten to twenty years or more of follow-up and would necessitate a substantial enrollment of patients at considerable expense. Some might even argue the ethics of such a study, because of the known complications resulting from chronic hepatitis C virus and the availability of treatments for it. Moreover the patient recruitment with informed consent might be problematic (Bennett *et al,* 1996 and Wong, 1999). As an alternative decision analysis, computer cohort simulation techniques, and mathematical models are used to estimate the lifelong clinical and economic outcomes resulting from interferon for patients with chronic hepatitis C virus, comparing those results with that expected to occur with conservative care (i.e., no interferon treatment) (Bennett *et al,* 1997 and Wong, 1999). Thus, the current cost and benefit of interferon treatment can be weighed against the economic and health burden of potential future complications. The decision to treat patients with chronic HCV infection should be made after many factors have been considered and each case has been individualized (Zein and Zein, 2002). This study has the aim of investigating this in Egypt.

3.13. Advances and other themes for future therapy

Slower progress has been made in the development of non interferon-based therapies for HCV infection, including protease inhibitors, helicase inhibitors, ribozymes, antisense therapies, cytokine-based therapies, and T-cell based therapeutic vaccines (Zein and Zein, 2002). Anti sense oligonucleotides targeted against the ribosomal binding site of the 5' non translated region of the HCV genome are being investigated. A new ribozyme specific approach to treatment is also under study. Helicase inhibitors and protease inhibitors are not yet available. Overall, advances in the development of therapies for hepatitis C virus have been hindered by the lack of dependable cell cultures systems and an adequate animal model (Zein and Zein, 2002). Furthermore, variation in the response to interferon treatment by different viral genotypes or by differences in the type or vigor of an immune response has been observed and may be another obstacle in the development of uniformly effective therapy or vaccine.

Other themes for the future might include the following: In the field of *diagnosis:* surrogate markers of fibrosis, the role of hepatocellular carcinoma screening, and standardization of HCV testing. In the field of *natural history:* the long term outcome of patients with persistently normal aminotransferase levels, predictors of fibrosis, and predictors of hepatocellular carcinoma. In the field of *virology:* the development of *in vivo* models to assess HCV replication and to assess the effectiveness of the drugs, and the development of alternative animal models to study new antivirals and vaccines. In the field of *therapy:* the benefit of treatment in special groups (acute hepatitis, patients with normal amino transferase, patients with mild disease, extra hepatic syndromes, compensated cirrhosis, non-responders to current therapy patients

with HBV or HIV co-infection), and the benefits of maintenance therapy in non-responders (Zaraski, 1999).

Chapter 4

Hepatitis C Virus in Egypt

Contents of Chapter

4.1. Hepatitis C virus in Egypt

Background, epidemiology and transmission

4.1.1. Egypt's high prevalence

From the literature review it is concluded that hepatitis C virus is a major health problem in Egypt. The population of Egypt has a heavy burden of liver disease mostly due to chronic infection with hepatitis C virus (HCV). Overall prevalence of antibody to HCV in the general population is around 15% - 20% (Angelico *et al,* 1997; Frank *et al,* 2000 and Rao *et al,* 2002). Since its discovery in 1989 (Choo *et al,* 1989), the HCV has been found to cause significant morbidity and mortality in tropical settings (Di Bisceglie, 1998). The prevalence of HCV antibodies (anti-HCV) is reported to be higher in Egypt than in any other country (Arthur *et al,* 1997 and Hepatitis C global prevalence, 1997), with an estimated 8 - 10 million among a population of 68 million having been exposed to the virus and 5 - 7 million active infections. An important cause for the high exposure to HCV was the establishment of a large reservoir of infection as a result of extensive schistosomiasis control programs that used intravenously administered tartar emetic for forty years starting in the 50s to the 80s (Frank *et al,* 2000 and Strickland *et al,* 2002). Blood transfusion and illicit drug use are rare in Egypt. HCV infection is more common among adults, males, those with a history of schistosomiasis, and those living in rural communities of Egypt (Darwish *et al,* 1993 a; Mohamed *et al,* 1996 a and Arthur *et al,* 1997).

Studies of the epidemiology of HCV infections have suggested that the Nile delta region of Egypt has among the highest prevalence rates of HCV in the world (Darwish *et al,* 1993 a and 1996). Blood bank and community-based surveys conducted have reported sero-prevalence rates of HCV to be as high as 40 % in some parts of the country and in villagers over the age of 30 years (Darwish *et al,* 1993 a

and 1996; Arthur *et al,* 1997 and Abdel-Aziz *et al,* 2000). These rates are substantially higher in the Nile Delta region compared with the rest of the country (Frank *et al,* 2000). The prevalence in rural communities in Upper Egypt was approximately 10 %, which was much lower than in inhabitants of villages in Lower Egypt (Abdel-Wahab *et al,* 1994; Darwish *et al,* 1996; Arthur *et al,* 1997 and Frank *et al,* 2000). Among the reasons for this geographic variation in prevalence of HCV infection in Egypt may be the difference in the intensity and duration of intravenous tartar emetic schistosomiasis control programs in Upper and Lower Egypt, with the programs in Lower Egypt affecting a larger proportion of the population over a longer period of time and administering a greater number of doses (Nafeh *et al,* 2000).

The overall anti-HCV prevalence in Egypt was 24.3 % and prevalence was nearly equal among males and females 24.9 % and 23.8 %, respectively (table 7). Anti-HCV prevalence, however, was much higher among individuals older than twenty years of age, with the highest level, 56.7 %, in those over forty years. Among subjects older than twenty years, the small group with at least some university education had a lower prevalence than the remaining subjects. Anti-HCV was found in 12.1 % of primary schoolchildren, 18.1 % of residents of rural villages, and 22.1 % of army recruits, as well as in 31 % of Egyptians applying to work abroad (Mohamed *et al,* 1996 b). In contrast, a high prevalence of antibodies to HCV has been found among apparently healthy Egyptian populations, such as expatriate workers in the Gulf Region (31%)(Mohamed *et al,* 1996 a), blood donors (10 % - 28 %)(Mohamed *et al,* 1996 a and Arthur *et al,* 1997), military recruits (22 % - 33 %)(Farghaly and Barakat, 1993 and Abdel-Wahab *et al,* 1994), rural primary-school children (12 %), and rural village inhabitants (16%-18%) (Farghaly and Barakat, 1993; Abdel Wahab *et al,* 1994 and Kamel *et al,* 1994). In the largest published study, Mohamed *et al,* (1996) assessed

anti HCV in five thousand Egyptians undergoing pre-employment examination, and the prevalence increased with age, peaking at 55 % among those 45 to 49 years old (Mohamed *et al*, 1996 b).

Table 7: Anti-HCV prevalence by age, gender, and education (Habib *et al*, 2001)

	Number	Anti-HCV Positive number (%)
Total	3,999	973 (24.3)
Age (yr)		
0-9	712	50 (7.0)
10-19	1.298	128 (9.9)
20-39	1.142	315 (27.6)
40+	847	480 (50.7)
Gender		
Females	2.172	518 (23.8)
Males	1.827	455 (24.9)
Education (for those >20 years)		
University attendance	67	12 (17.0)
School attendance	678	253 (37.3)
No school attendance	1.244	529 (42.5)

4.1.2. Epidemiology

The epidemiology of, and specific risk factors for, HCV infection in developing areas such as Egypt is quite different from that of the West (Wasley and Alter, 2002), and given the high prevalence of HCV, it is of utmost importance to identify past and current risk factors for infection so that intervention programs may be appropriately focused (Lavanchy, 1999 and Rao *et al*, 2002). Infection with the HCV occurs primarily through percutaneous exposure to contaminated blood or blood products, unlike most other viral hepatitis infections that tend to be acute, hepatitis C virus

infections are often chronic and persist for decades (Yano *et al,* 1996 and Di Bisceglie, 1998). The long-term sequalae of chronic HCV infections include increased risks of liver cirrhosis and hepatocellular carcinoma (Kaklamani *et al,* 1991 and Kuper *et al,* 2000).

Intravenous tartar emetic was used in large campaigns to control schistosomiasis as early as 1921. The Egyptian Ministry of Health and Population during an assessment of the country's health problems in the mid twentieth century, the 1960s, 1970s and early 1980s decided to allocate the resources needed to undertake large mass treatment campaigns in rural communities in which a large proportion of the population were screened for parasites and treated. Mass campaigns were conducted to treat schistosomiasis infections in these areas, during which individuals older than 5 years of age were treated with tartar emetic injections (Maegraith, 1963). The dangers of exposure to human blood were unappreciated at the time, and disposable needles and syringes were unavailable. Those programs were discontinued 20 years ago, but, given the substantial reservoir of infection, it is of utmost importance to identify not only current risk factors for transmission but also those factors that indicate higher risk of past infection. Many people were infected with both hepatitis B virus (HBV) and HCV during these schistosomiasis control campaigns. However, HBV caused chronic infections in only 5 % or less of infected children and adults, whereas HCV infection persisted in 70 % to 80 % (Frank *et al,* 2000). Unlike many Western countries (Alter *et al,* 1999 and Williams, 1999), intravenous drug use (IVDU) is rare in Egypt, especially in rural areas (Darwish *et al,* 2001), making this an unimportant mode of transmission, and exposure via tainted blood products has been minimized after the introduction of screening for anti-HCV (Medhat *et al,* 2002).

Schistosomiasis is a parasitic infection transmitted to humans from snails that harbor the parasite. Most rural and peri-urban areas located in the Nile Delta are in close proximity to the distributaries of the Nile River or irrigation canals drawn from the Nile. These slow flowing waters are infested with snails that serve as the vector for the schistosomal parasite. Schistosomiasis infections, in addition to HCV are hyper endemic in the Nile Delta region (Abdel Wahab *et al,* 2000).

Sero-surveys conducted in the 1990's in Egypt have reported positive associations between HCV infections and a history of schistosomiasis or a history of having received injections for the treatment of schistosomiasis (Darwish *et al,* 1993 a, 1996 and 2001 and Frank *et al,* 2000). Based on this evidence, the studies suggest that inadequately sterilized needles and syringes used during the campaign were probable causes for transmission of HCV in the region (Habib *et al,* 2001). Recently reported data suggests that the very high prevalence of HCV infection in the adult population of rural areas of Egypt, particularly in men living in villages where schistosomiasis is endemic, is at least partially the result of extensive mass-control campaigns using parenteral tartar emetic conducted from the 1950s up until 1982 (Frank *et al,* 2000). Previous studies of hepatitis C viral infection in Egypt have shown a high prevalence of antibody to HCV (anti-HCV) among blood donors (Darwish *et al,* 1992; Kamel *et al,* 1992; Hibbs *et al,* 1993 and Arthur *et al,* 1997) and residents of rural areas endemic for schistosomiasis (Darwish *et al,* 1993 a). It is widely believed that parenteral exposure to the virus is the most important rout for acquiring infection in Egypt (Farghaly and Barakat, 1993 and Mohamed *et al,* 1996 a). Although the prevalence of infection among those too young to be exposed to these mass anti-schistosomiasis injection campaigns is lower than among the older population, infection in this younger cohort indicates that other modes of transmission have

perpetuated the infection in the community. Despite the use of oral drugs for the treatment of schistosomiasis during the past two decades, HCV antibodies were detected in some children below fifteen years of age.

Uncertainty remains regarding the relative importance of various types of parenteral exposures and widely practiced community activities, such as circumcisions, goza (Hookah pipe) smoking in a group, or being shaved at a community barber (Habib *et al,* 2001), in addition to the exposures associated with medical procedures (parenteral medical treatment, blood transfusion, gastrointestinal endoscopy, surgery, hospitalization, dental procedures) that occur in developed countries (Medhat *et al,* 2002). As found in the Delta community (Habib *et al,* 2001), circumcision among male subjects by an informal healthcare provider was associated with HCV infection (Medhat *et al,* 2002). The results of the investigation of Medhat *et al,* (2002) as well as previous reports did not demonstrate other unique community acquired exposures that caused HCV infections (Darwish *et al,* 2001 and Habib *et al,* 2001). Tattooing, hookah pipe smoking, shaving in a community barber were not associated with HCV infection (Medhat *et al,* 2002).

4.1.3. Marital Status and Vertical transmission

There was a significant association between marital status and anti-HCV prevalence (table 8). Those who were or had ever been married had higher anti-HCV prevalence (43.1%) than those who had never been married (13.1%). The association remained significant after adjusting for age among those between fifteen and thirty five years of age, with a Mantel-Haenszel RR of 1.8 (95 % CI: 1.3, 2.6). Age adjustment was limited to this age group because there were very few unmarried individuals older than 35 years (Abdel-Aziz *et al,* 2000).

Interestingly, marriage was found to be a very strong risk for HCV in the logistic-regression model. This association of HCV in spouses could be the result of sexual transmission or to common exposures. Very few researchers have reported that spouses of patients with HCV have an increased risk for acquiring HCV, and this risk increases with age and is proportional to the duration of marriage (Kao *et al,* 1992; Akahane *et al,* 1994; Goto *et al,* 1994 and Magder *et al,* 2005). In addition to potential sexual transmission, married couples share many exposures that could be risks for HCV transmission, both for transmission from a common source (Nafeh *et al,* 2000 and Habib *et al,* 2001). Vertical transmission of HCV from infected mother to infant occurs in approximately 5 % of HCV infected mothers and is reported to increase with increasing viral loads (Zanetti *et al,* 1999).

HCV infections congregated among families, with spouses particularly husbands being at higher risk if their partner was infected with HCV, and children being at increased risk if their parents were infected (Magder *et al,* 2005). Mohamed *et al* (2005), observed that the risk of HCV infection was higher for children when their mothers rather than their fathers were anti-HCV positive and was higher when the parent had circulating HCV-RNA. For instance, he observed that 14% (87/612) of children whose mothers had HCV-RNA were HCV positive, in comparison with 7% (28/401) whose parents only had anti-HCV. Sequencing even showed ten out of eighteen families with both children and parents having HCV-RNA had genetically similar viruses. A prospective study of current risk of infection has shown the strongest predictor of incident HCV was having an infected family member (Mohamed *et al,* 2006). Parenteral exposures increased the risk of HCV but were not statistically significant; 67 % of seroconverters were younger than twenty years old with highest incidence rate in children younger than ten years living with an anti-

HCV positive parent in a Nile Delta village having 24% anti-HCV prevalence (Mohamed *et al,* 2006).

4.1.4. Sero-prevalence by age and gender

The overall anti-HCV prevalence was 24.3% (95% CI: 23.0, 25.7), and the age and gender adjusted prevalence was 23.7% (Saeed *et al,* 1991). Anti-HCV prevalence of males (24.9 %; 95 % CI: 22.9-27.0). However, there was a substantial association between anti-HCV prevalence and age, with a marked rise in the third decade, reaching a peak of over 60% in the fifth decade. Among those older than twenty years of age, males (45.8 %) were more likely to be anti-HCV positive than females (37.6%). However, no gender difference was detected for anti-HCV prevalence among participants twenty years or younger (9.3 % and 9.3 %, respectively) (Abdel-Aziz *et al,* 2000).

Males, who more frequently have schistosomiasis than females (Ghaffar *et al,* 1991; Kamel *et al,* 1994; and El-Khoby *et al,* 2000), and those more than thirty years of age who had risk of exposure to parenteral anti-schistosomal therapy (Frank *et al,* 2000), had much higher anti-HCV infection rates than females and those thirty years of age and younger, respectively.

Table 8: Anti-HCV prevalence by socio-demographic status (Abdel-Aziz *et al*, 2000)

	Total (Number)	Anti-HCV Sero-positive		HCV PCR Sero-positive+
		Number (%)	Probability	Number (%)
All participants	3,999	973 (24.3)		593 (65.5)
Gender			0.5	
Female	2.172			316 (65.4)
Male	1.827			277 (65.7)
Age (yr)			<0.0001	
<20	2.105	196 (9.3)		118 (65.6)
>20	1.897	777 (41.0)		475 (65.6)
Education (>20 yr)*			<0.0001	
None	1.210	524 (43.3)		
School	625	243 (38.9)		
University	59	10 (16.9)		
Marital status				
++(>16 yr)			0.0001	
Never married	625	524 943.3)		
Ever married	1.780	768 (43.1)		
15-20 years old			0.3	
Never married	4398	60 (13.7)		
Ever married	71	13 (18.3)		
20-25 years old			0.001	
Never married	135	13 (9.6)		
Ever married	219	51 (23.3)		
25-30 years old			0.2	
Never married	39	7 (17.9)		
Ever married	262	75 (28.6		
30-35 years old			0.2	
Never married	8	1 (12.8)		
Ever married	281	100 (35.6)		

* Mantel-Haenszel P = 0.4 for education (none compared with school/university) across 10-year age strata, RR = 1.0 (0.9, 1.1)
+ HCV RNA among those who were anti-HCV-sero-positive
++ Mantel-Haenszel P<0.001 for marital status across 5-year strata between 15 and 35 years, RR = 1.8 (95% CI, 1.3, 2.6)

4.1.5. Schistosomiasis and hepatitis C virus infections

Aside from the direct relationship between parenteral treatment of schistosomiasis and the country-wide prevalence of antibodies to hepatitis C virus (anti-HCV), Ghaffar and colleagues reported the relationship between HBV or HCV and hepatosplenic schistosomiasis (Ghaffar *et al,* 1991). The authors proposed that chronic schistosomiasis favored the persistence of the HBV (and non-A, non-B hepatitis)

HCV infections, resulting in splenic enlargement. It is noteworthy that the relationship between HBV and hepatosplenic schistosomiasis was initially reported from Brazil, Egypt, and the Philippines (Lyra *et al*, 1976; Bassily *et al,* 1983; Domingo *et al,* 1983 and Madwar *et al*, 1989).

In addition, Kamal and colleagues reported that Egyptian patients with co-infections have higher HCV-RNA titers, more advanced liver disease, more hepatic complications, and a greater mortality rate than those infected with only HCV (Kamal *et al,* 2000 a). They also noted that patients with co-infections responded poorly to interferon therapy and had a higher relapse rate and higher HCV-RNA titers and more severe hepatic lesions than HCV patients not having concomitant schistosomiasis (Kamal *et al,* 2000 b).

4.2. HCV, cirrhosis and other chronic liver disease implications

Multiple studies have showed the importance of HCV in the causality of chronic liver disease in Egypt. In a study in the NLI, Waked *et al,* pointed out that 73.3 % of 1 023 outpatients had anti-HCV. One hundred patients among them had liver biopsies showing that 89% had chronic hepatitis, cirrhosis, or hepatocellular carcinoma HCC, and 84% of theses had anti-HCV (Waked *et al,* 1995).

Residents of Egypt's Nile river delta have among the world's highest sero-prevalence of HCV infection. The findings are consistent with the increased prevalence and intensity of infection with Schistosoma in the populous Nile delta where exposure to canal water was occurring to several million farmers and their families which resulted in an increase in schistosomal fibrosis. In addition to the hypothesis that past mass parenteral chemotherapy campaigns for schistosomiasis facilitated HCV transmission and furthermore HCV may be a major cause of the high prevalence of liver cirrhosis in Nile Delta villages (Darwish *et al,* 2001). It was reported that only 15-20% of

people infected with HCV have an acute viral hepatitis syndrome, but the majority develop chronic hepatitis that is usually asymptomatic and undetected for many years. Over a course of 20 - 40 years nearly 20 % of those with HCV-caused chronic hepatitis progress to cirrhosis, and a proportion of these (possibly 2 - 3 % per year) die as a result of complications of cirrhosis of hepatocellular carcinoma (Alter *et al,* 1992; Niederau *et al,* 1998; Rodger *et al,* 2000 and Thomas *et al,* 2000). It is unclear what the long-term outcomes of these infections in Egyptians will be, particularly since the predominant HCV genotype in Egypt (type IV) differs from genotypes found in many other parts of the world and since HCV of Egyptians act within a milieu of many other infectious assaults capable of causing chronic liver sequalae, including hepatitis B infection and schistosomiasis (Kamel *et al,* 1994; Angelico *et al,* 1997 and Darwish *et al,* 1996).

Moreover, Darwish *et al,* (2001) demonstrated both an extremely high prevalence of cirrhosis and a notably high fraction of cirrhotic cases potentially attributable to HCV (Darwish *et al,* 2001), but could not project how the burden of HCV related cirrhosis will evolve in the Nile delta during the coming decades. Indeed, chronic liver disease due to HCV is thought to develop at a rather slow pace ordinarily taking decades (Waked *et al,* 1995; Medhat *et al,* 2002; Strickland *et al,* 2002 El-Zayadi *et al,* 2005; Kamal *et al,* 2005; Magder *et al,* 2005 and Mohamed *et al,* 2005) and with no way of dating the onsets of the infections detected in the Egyptian population. Adding to our uncertainties is the fact that little is known about the tendency of genotype IV of HCV, which predominates in Egypt (Angelico *et al,* 1997), to produce chronic liver disease. The pathogenic nature of HCV genotype IV is supported further by the fact that patients infected with genotype 4 show a meager response to alpha-interferon therapy similar to the more pathogenic HCV genotype Ib, and a poor response

compared to patients infected with the less pathogenic HCV genotypes II and III (El-Zayadi *et al,* 1996 and Zylberberg *et al,* 2000). Strickland *et al,* (2002) in a case-control study supported this belief that HCV is the predominant cause of liver disease and that there is a large occult reservoir of HCV induced chronic liver disease in the country. The sum of these findings raise concern that the extraordinarily high sero-prevalence of HCV now observed in the Nile delta may forebode an explosive epidemic of cirrhosis and other manifestations of chronic liver disease in this region (Darwish *et al,* 2001). HCC is now one of the three most frequently diagnosed cancers in Egypt (Abdel-Wahab *et al,* 2000) along with this, the increasing association with HCV, as the greatest risk factor (Hassan *et al,* 2001 and Ezzat *et al,* 2005) just as it is in the United States (Hassan *et al,* 2002). Chronic HCV infection has also been associated with increased risk for B-cell non-Hodgkin's lymphoma NHL. Egyptian NHL patients were 2.3 times more likely to have HCV-RNA in their sera than matched controls (Cowgill *et al,* 2004).

It is noteworthy to mention that the Egyptian Ministry of Health and Population has initiated a country wide program to prevent transmission of HCV and other blood born infections. Health education campaigns and serological screening of all blood transfusion have reduced HCV transmission (Stickland, 2006). In conclusion; the large reservoir of infection in human blood increases the incidence of new HCV infections and should encourage researchers to seek more information on its transmission to assist the Egyptian Ministry of Health and Population and health officials in their preventive efforts. Children with HCV infected parents are at particularly high risk and would benefit from efforts to reduce exposure to HCV contaminated blood and other biological fluids or to become immunized when and if a vaccine becomes available.

4.3. Guidelines in Egypt

4.3.1. Protocol of diagnosis and treatment of HCV, Egypt 2001

The High Authority of Health Insurance in cooperation with the High Laboratory Commission in Egypt in 2001 came up with a very narrow minded limited protocol of treatment for HCV patients. The very fact that it is not used and was extracted from the archives just as reference and was included as part of the study.

First: The dangers of prescribing interferons due to their side effects, added to their lack of effectiveness against genotype IV positive in 90% of HCV cases in Egypt according to acknowledged scientific statistics and finally thin high expense, all lead to following rules and regulations to prescribing interferon.

The choice of a specialized hepatologist responsible for the application of this protocol and diagnosing and treating HCV patients as well as asking and approving the authenticity of the PCR.

The patient's liver enzymes should be more than twice as normal (SGOT >80 units/liter- SGPT >70 units/liter).

Positive HCV antibody testing e.g. ELIZA

The number of white blood cells, platelets and haemoglobin should be normal. Platelets 200.000 – 400.000ML HB; male 14-18 x 100/100 ML; female 12-16 x 1100/ML.

The lack of cirrhosis by ultrasonography

Genotyping the virus as 90% of cases in Egypt is fit for interferon treatment

Presence of HCV in patient's serum after more than 800.000 units

Second: Rules and regulation for PCR testing:

To prove the presence of HCV in patient's serum after more than 800.000 units using PCR

In case of interferon prescription, it is dispensed for one month and response is depicted using PCR, and in case of success it is repeated for another six months then the test is repeated

In case of lack of response, interferon is repeated for another month in combination with ribavirin than PCR is repeated

Thirdly: If the patient did not respond after two months of interferon, it is stopped

Chapter 5

Design and Methodology

Contents of Chapter

The aim of this chapter is to explain in detail the methods used and the methodologies adopted to reach the written objectives of the study. The first section of the chapter starts by reinstating the aim of the research leading to the design and rationale behind the choices made regarding the use of health economics techniques and the choice of HCV as a case study. Subsequent sections examine the collection of data and the extent to which economic evaluations are applied within the constraint of the available data sources and infrastructure. Then, the fieldwork is described within the various medical institutions. The perspective and stages of the analysis are explained up to the stage of the results interpretation.

5.1. Aim

The uniquely high prevalence of HCV in Egypt and the inhibitive cost of available treatment options make it a special political, social and medical situation. Doctors are bound by their oath to advise their patients as to their optimal therapy regardless of the cost. However, the vast majority of the patients are un-insured and cannot afford the financial cost of treatment, which creates a dilemma for physicians.

Moreover, several authors have focused on the high treatment costs of HCV rather than the treatment cost of its complications. However, no authors have studied a complete health economic comparison of the different treatments used in Egypt. This is related to the lack of awareness of the importance and implications of health technology assessment in developing countries in general (Strickland *et al,* 2002; El-Zayadi *et al,* 2005 and Kamal *et al,* 2005).

The economic, the psychological and the physical impacts of HCV are immense. The healthcare system is over-burdened by the high number of patients needing treatment, and hence stretching the scarce resources to a tight string. The government and the

policy makers are overwhelmed by the ever-increasing burden of disease on the healthcare system, especially as the infected population gets older.

The magnitude of the problem and its impact on multiple sectors of the Egyptian population as mentioned above enhanced the importance of this study project. This project aimed to probe the extent to which HTA might yield data that could contribute to the decision-making process relating to healthcare provision and delivery in Egypt, using HCV as a case study. This was attempted through the estimation of the cost of HCV and its implications, the assessment of the effectiveness of the treatment options available in Egypt and the ultimate calculation of the cost effectiveness of those various treatment options in order to assess the burden of HCV care in a low resource society.

5.2. Design and rationale

This research was designed to assess both the cost of HCV disease and the cost of different treatment pathways of HCV, both their effectiveness and cost effectiveness in Egypt. The design was structured as a comparative analysis of alternative courses of action, including anti-viral treatment options as well as no treatment option of the HCV infected patients in Egypt. This was done in terms of their costs and consequences (Drummond *et al,* 1997). The anti-viral treatment options included the combination of conventional interferon (IFN) with ribavirin for one year and the combination of pegylated (PEG) IFN with ribavirin for the same time period for HCV patients with compensated liver disease.

This research as mentioned above took place in Egypt, but the fact that this was held in a leading hospital and the largest of its kind in the Middle East situated in one of the highest populated areas with infected HCV patients in Egypt, contributed to the shaping and evaluation of the study.

The rationale for using HCV as a model derives from the burden that it places on the Egyptian healthcare system, as a result of:

1. The high prevalence for HCV in Egypt, making it the most important public health problem
2. The high cost of treatment for HCV patients
3. The long life cycle of the disease
4. The particularly more aggressive resistance of the Egyptian genotype IV of the virus.
5. The ever present problem of healthcare budget constraints and demands on it. Topped by the extra pressure on the Egyptian Ministry of Health and Population officials and the national health budget expenditure due to the particularly large number of chronic HCV patients.

5.3. Collection of data

A preliminary analysis was first undertaken to verify facts, to determine what the important concepts were, to frame all questions related to the research and to convert the questions into a search strategy. Questions were related to availability of any plans or guidelines for HCV therapy worldwide and in Egypt and were related also to costs of different current treatment strategies within the Egyptian system and within the various categories of medical service institutions in Egypt.

The research started in 2002 at the Bodleian library, Oxford University, where the sources of evidence were identified, and categorized according to their importance. The systematic reviews, as well as the secondary sources of data, were searched and both the extensive hard and comprehensive soft databases were also made use of. The search was initiated electronically using all terms related to hepatitis C virus, pharmacoeconomics, liver disease, health policy, technology assessment and health

economics. Medline and Pubmed were surfed using the following websites: http://www.pubmedcentral.nih.gov and http://www.ncbi.nlm.nih.gov. The keywords: hepatitis C, hepatitis C prevalence, hepatitis C management, hepatitis C treatment, hepatitis C consensus, treatment protocols, hepatitis C cost effectiveness and chronic liver disease were searched. This process lead to countless directly related papers to the research whose references were then used as base to construct a search for authors, books, publications and other online sources.

The most important information reached was concerned with HCV world prevalence data, HCV virology, diagnosis, transmission, and treatment. The parameters of clinical and cost effectiveness were also defined.

The identified parameters of clinical and cost effectiveness included:

- The clinical problem and population demographics
- Disease stages
- Treatment and medical settings providing care for patients with HCV, which were divided into public and private (for profit and non profit) medical institutions
- Alternatives to treatment (comparator)
- Principal health outcome either the cure or the eventual death
- Measures of cost
- Perspective which was the Egyptian healthcare system
- Time horizon over which benefits and costs will be assessed taking into consideration the long life cycle of the disease
- Other considerations related to the patients and their classification
- Special consideration of issues and limitations.

It is noteworthy to mention at this point that even though the study was not part of any formal national or international research group or inter-university channel, there was a "pseudo" assessment group to make sure that the research point was innovative and to fine tune its focus and its boundaries. A panel was interviewed and consulted with the various issues related to the research.

The "pseudo" assessment group consisted of:

1- Dean of the School of Pharmacy. Cairo University, Professor Doctor Nadia Morsi (1998 - 2002)

2- Chairman of the National Pharmaceutical Holding Company, Doctor Galal Ghorab (1994 – 2004)

3- Several pharmaceutical companies' sectors heads

4- Egyptian Minister of Health and Population, Professor Doctor Awad Tag ElDin (2000 – 2005)

5- Head of National Laboratories in the Ministry of Health and Population, Senior Consultant Doctor Magda Rakha (2000 – 2006)

6- Marketing specialists in pharmaceutical companies that manufacture interferon

7- Clinical specialists and commentators in hepatology conferences attended

8- Public health professors and specialists in HCV treatment in Egypt; e.g. Professor Doctor Mostafa Kamal of Ain Shams University, Professor Doctor Thomas Strickland of Maryland University and head of the Wellcome Trust in Egypt

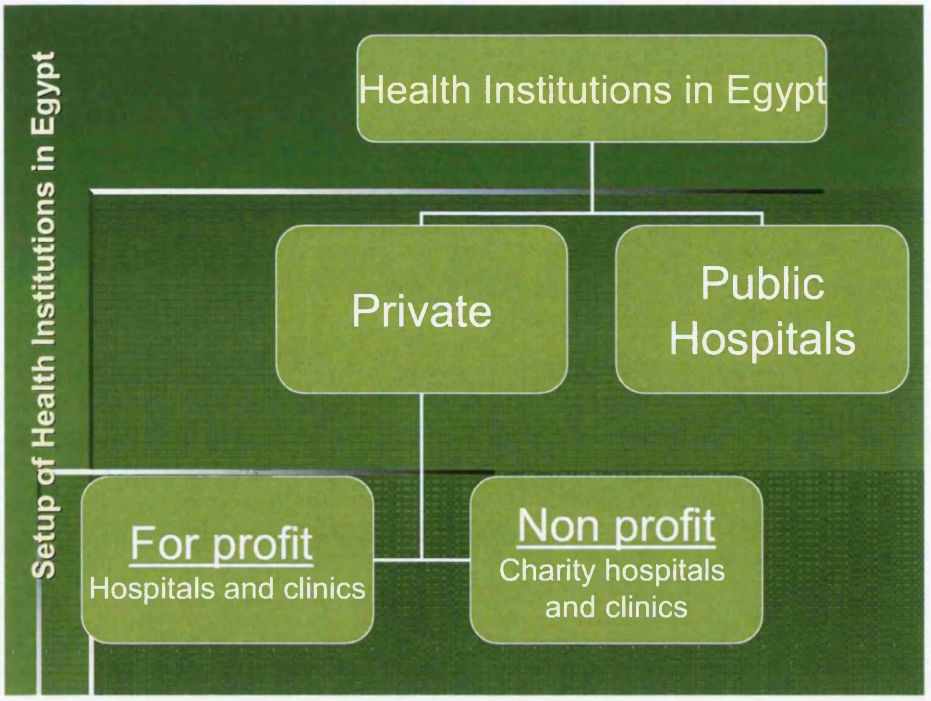
9- Prominent hepatologists and clinicians in Egypt; e.g. Professor Doctor Gamal Shiha of Mansoura University and Professor Doctor Fouad Thakeb,

Professor Doctor Aly Moanes and Professor Doctor Gamal Essmat of Cairo University, last but not least the leader of the clinical part of this research Professor Doctor Imam Waked, Vice Dean of National Liver Institute of Menoufiya University.

Physical data and facts related to Hepatitis C virus were difficult to find, lengthy and effort consuming. The Ministry of Health and Population was visited, as well as the WHO library in Egypt, seminars and conferences about hepatitis C virus attended (National Liver and Kidney Diseases conferences from 2002 to 2005) and various research and teaching centres and universities were also called on and their main faculty members consulted and conferred with such as the Institute for Tropical Diseases.

Field study and visits to the department of pharmacy of the Ministry of Health and Population were undertaken for the verification of treatment protocols and calculation of the cost of drugs. Field visits were then extended to hospitals and other medical institutions for the cost assessment and identification of services given to HCV patients. These visits encompassed public and private medical centres and clinics for review of their patients' data and records. Public medical hospitals and centres included Kasr Al Aini University Hospital, Ain Shams Specialist Hospital, the National Liver Institute in Shebin ElKom and the Institute of Tropical Diseases. Private settings included Dar ElFouad Hospital (private for profit), Yassin Abdel Ghaffar Hospital (private non profit) and prominent clinicians' private clinics (private for profit).

Figure 5: Setup of health institutions in Egypt



The fieldwork in NLI lead towards the realization of the aims of the study, that included the calculation of the various costs of drugs andservices related to the HCV patients' treatment options and the cost of the HCV complications.

This long exhaustive period lead to the decision to use the National Liver Institute in Shebin ElKom, Menoufiya as backbone and main data source of the research. This decision was based on the fact that it was the only accredited specialized centre with high constant patient traffic added to the verity that it was the largest liver patients' referral centre in Egypt and the Middle East, not to mention the latest technologies for the treatment of HCV chronic patients adopted, as well as the liver transplants operations performed there as well. The costs of hospitalizations were estimated and added up. The prospective future costs of hospitalizations were anticipated by reviewing the price fluctuation in the preceding ten years and calculating an annual percent increase to be applied to following years. Markov models from the published literature were followed to help in the cost effectiveness analysis.

The research was constantly re-evaluated for any new or modified theories and facts supporting the emerging results. It was also updated to ensure currency of material and the inclusion of new developments. This is evidenced by the new interferon pricing policies uptaken by the Ministry of Health and Population in Egypt during December 2006 whose effects were incorporated in the results and discussion.

At the time the clinical data collection phase of the research was being conducted, the notion of international guidelines for management of chronic HCV was introduced via expert opinion and they were then searched, accessed and updated. The newer versions of the international guidelines and consensus were reviewed and referred to in the treatment algorithms used in this study. They included:

- Clinical guidelines on the management of HCV, 2001.
- National Institute of Health, Consensus Development Conference Statement, Management of Hepatitis C, 2002.
- Veteran Association (VA) treatment recommendations (Version 5.0). Patients with chronic Hepatitis C, Federal Practitioner, 2003.

5.4. Fieldwork, difficulties and limitations

The researcher was fortunate to receive a permit, which allowed access to all areas of the NLI hospital, its clinics, patients' wards and various administrative departments. The research proposal was first approved by the hepatology department board of the faculty of medicine in Menoufia University to grant access to for the desired premises and then by the NLI hospital board also considered as the ethics committee to validate adoption of required ethical standards. The ethics committee quarterly monitored the progress of the fieldwork. In addition, the researcher ensured that patients' anonymity was maintained throughout the research, with no personal confidential data disclosed.

It is noteworthy to mention that no published Egyptian guidelines were found, and the Ministry of Health and Population in Egypt did not have treatment management protocols. Egyptian physicians simply followed international consensus.

The various treatment alternatives of HCV were found to include treatment with interferon or its pegylated version in combination with ribavirin in varying periods of time and frequency. This was done in alternation with the supportive liver support treatment options, which is in fact a no treatment option.

One of the first limitations in the study was time and concerned the very long life cycle of the disease and the impossibility of tracking the various stages of the disease in any one patient in a prospective longitudinal study. Rather patients were chosen representing the different stages of the disease, which could be considered a representative sample of the natural history. These included outpatients with compensated liver disease (which usually lasts many years), outpatients with decompensated liver disease, and hospitalized patients with different complications representing the major causes of hospital admission that might occur in patients with advanced liver disease due to HCV (ascites, bleeding varices, coma, and liver cancer). This limitation was also overcome with the use of modelling.

The time frame first allocated for this research was three years. This had to be extended due to the lack of structured data and the extremely lengthy time it took to find the NLI as a location that would allow access of its premises for the patient information needed. The outpatient clinics of the NLI were first visited three times weekly from 9:00 am to 1:00 pm to access the raw source of data emanating from the actual patients themselves.

Another major real time consuming issue was seeing each patient with the clinician and interviewing him or her personally after making sure that he/she was HCV

positive. Manual recording of the drugs prescribed, and listing all the tests performed or asked to be performed regularly with a maximum of ten patients per visit. This was needed because there were no records of any prescriptions issued per patient; simply records of quantities of drugs dispensed per day, prescriptions are issued on the spot, given to the patient, who then goes to the hospital pharmacy, where records of all the drugs given per day were kept but not per patient.

A list of all drugs prescribed to the entire patient group and their dose was compiled (it was compiled into a list of fifty three drugs). The list was then classified into ten drug categories for ease of manipulation and calculation. The price of each drug prescribed and the number of units in each pack was checked and reviewed from the market. The price per unit was calculated and the total cost of the treatment term (following international consensus) computed. This process was performed for all one hundred and twenty nine patients in the outpatient clinics and a similar process was followed for the inpatients, taking into consideration that one hundred and sixty-five patients were researched and they were found to be prescribed one hundred and sixty five drugs which were then classified into fifteen categories.

For research time restrictions and privacy limitations in private medical institutions, the figures and numbers gathered in the NLI were verified against corresponding patients' situations in each institution via interviews, consultations and expert discussions.

The problems encountered in the handling of this case study involved the highly sensitive political aspect of the subject matter and the scarcity of relevant information in Egypt.

Other limitations related to system constraints concerned with cost data breakdown availability and accessibility necessary for its calculation. In the NLI, it was more a

question of availability than accessibility. However, in the private sector, limitations were more due to the accessibility of patient data and the classified financial records of profits and actual costs breakdown in the various private institutions.

Not only was cost classification in the NLI different from the internationally recognized formats and terminology but it was also unsystematically available, handled or saved in a manner to allow a more detailed standardized classification. This was overcome with the creation of constant cost categorization, later explained (section 5.7.1 & 2).

Cost assessment limitation in the private sector was overcome by constructing a model of categorized costs from the NLI and performing a comparative study of corresponding categories. This was done by comparing each cost category to that in the private sector, and that patients in the private sector actually pay hospitalization and consultation fees that covers their cost and may or may not lead to a profit in private for profit or non profit institutions respectively. That led to a cost increment factor calculation for each cost category in the private institution relative to that same category in the NLI. This estimated comparative factor made the cost calculation for the various treatment pathways as well as the cost of disease assessment possible in the chosen medical settings, which in turn led to a more comprehensive research.

The other difficulties encountered were divided into two categories:

1. Personal difficulties
2. System difficulties

They both covered the following:

- General lack of data and the shortage of comprehensive database and information sources
- Lack of support from government or research centres in Egypt
- Public hospitals setup
- Private clinics confidentiality policies and incomplete and deficient data
- Inadaptability of data in Egypt to international methodologies and standards
- Politicians' concepts of healthcare and its policies
- Official medical body of the government regarding HCV as a very politically sensitive issue and personal hindrances from top officials to the research
- No peer discussions identifying key difficulties in order to define relative solutions or alternatives to the clinical problems
- Logistics: Menoufiya, Swansea, Cairo
- No standardized format for troubleshooting
- Finding an Egyptian clinician who was aware of the concepts of HTA and willing to help in the research

5.5. The medical settings of the study and patient classification

Five medical non-university centres, in addition to the NLI were chosen to give a more comprehensive assessment of the disease in Egypt.

- The first, the NLI, is a private non-profit hospital dedicated solely for patients with liver related diseases in Cairo.

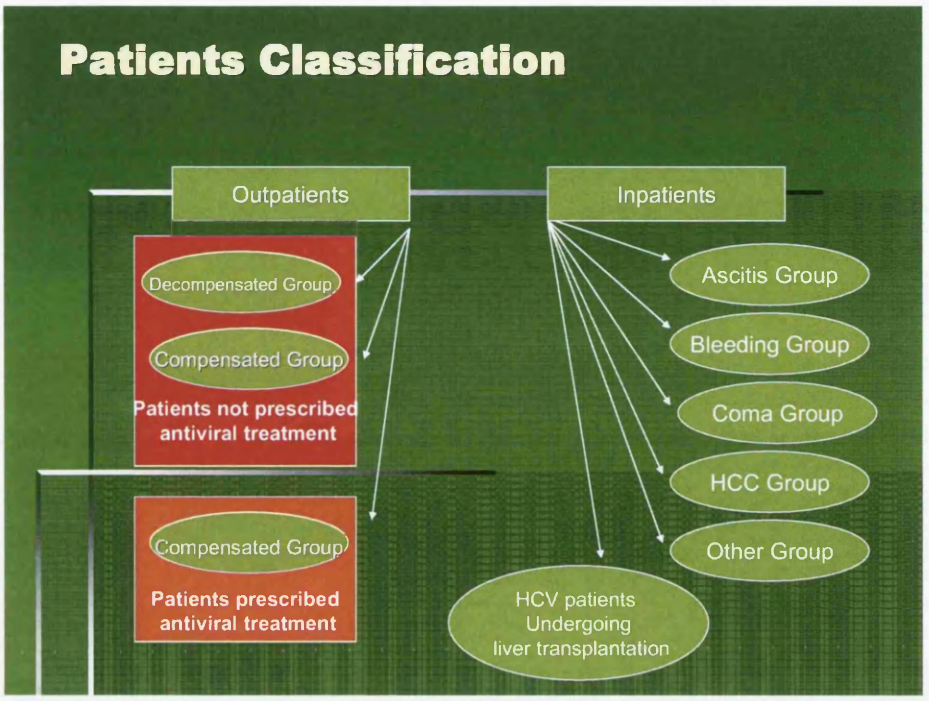
- The second, a private for-profit hospital that has a large liver practice and has the largest liver transplantation program in Egypt.
- The remaining three were private hepatology clinics to compare with the outpatient clinics of both NLI and private non-profit hospital.

It should be noted that there is no difference in patients' medical profiles between the various institutions (only variations in their social or financial status), nor are there any difference in treatment patterns. Not only do all Egyptian doctors and clinicians follow international treatment recommendations, but also mostly they have more than one practice, one private and the other either public or non-profit.

Prices of similar interventions and diagnostics were collected from both hospitals (private for profit and non profit) to calculate the cost of care of HCV patients in each; this was done by comparing the same evaluated categorised item from the NLI outpatients' clinics and inpatients' wards to their respective private settings such as the consultation fees, the imaging, the laboratory costs and the hospital stay. This comparison led to the final HCV patient cost of treatment estimation in the various medical settings of Egypt via a factor calculated for each chosen setting.

Liver diseased patients with HCV were classified in this research into three main classes based on their treatment guidelines for ease of cost calculation. Patients come to the NLI at different stages of the natural history of their liver disease, and receive management and treatments accordingly. Basically they are either outpatients not requiring hospitalization, or inpatients with advanced liver disease and different emergencies requiring hospitalization, each with subgroups ensuing different management decisions and cost implications as seen in the following figure.

Figure 6: HCV Patient classification



I. HCV outpatients who don't require hospitalization, which were then collectively categorized according to the stage of liver cirrhosis into three groups:

1. Patients with compensated liver disease prescribed supportive liver treatment (not being under antiviral prescription)

2. Patients with decompensated liver disease prescribed supportive liver treatment (not being under antiviral prescription)

3. Patients with compensated liver disease with antiviral prescriptions

II. HCV inpatients that need to be hospitalized. The patients were categorized according to the reason of their hospitalization into five groups:

1. Patients hospitalized for the management of refractory ascites that complicates liver cirrhosis (ascites group).

2. Patients hospitalized for bleeding varices in the oesophagus and stomach due to portal hypertension secondary to liver cirrhosis (bleeding group)

3. Patients hospitalized for hepatic coma due to advanced liver disease (coma group)

4. Patients hospitalized for liver malignancy and hepatocellular carcinoma (HCC group).

5. Patients hospitalized for other complications due to liver cirrhosis (others group).

III. HCV patients undergoing liver transplantation

5.6. The perspective and the measurement of costing used

The evaluation is undertaken from a healthcare and a societal perspective, it incorporates drug- and disease-related costs but does not include patient or unpaid caregiver time; thus the costs of treatment are assessed and the benefits weighed but the production losses are not included in the study (Gerard and Mooney, 1993 and Drummond *et al,* 2001). This is due to not only the difficulties involved in acquiring relevant data and the ever-present time constraint factor, but also to the actual availability of such data in the first place in an organized accredited format in the Ministry of Health and Population or any other governmental or private accredited institution in Egypt.

This research went through all three stages involved in the process of costing healthcare interventions (McPake *et al,* 2002) starting with identification of costs, their measurement and their translation into a monetary value (Phillips, 2005).

The identification of costs stage involved listing the resource effect of the treatment of HCV patients, based on the societal perspective considered. There were first the direct

costs, which were subdivided into medication costs and direct non-medication costs. The indirect costs and the intangibles associated with healthcare and productivity costs were not considered in the study. The constant costs, a study specific cost category was used to depict all costs incurred due to the patient's treatment in a public hospital and not *directly* paid by the patient or his Healthcare payer (this is the value of government subsidy to the treatment of HCV patients).

The measurement of costs stage involved the quantification of the resources used in the treatment of HCV patients, and deciding which interventions and services' costs were available to measure. This stage was performed through a collective appraisal of all services given to the outpatients and inpatients and processing the data to reach the most pertinent values. The collective appraisal was first done to the services given to outpatients then to inpatients via direct review of their hospital records.

Finally the valuation of costs and its translation into monetary value stage was done by means of assigning prices to the categories chosen via micro costing or bottom-up approach (Raftery, 2000 and Brouwer *et al,* 2001). Micro-costing was the method of choice for costing in the research, where each component of resource used is estimated and a unit cost derived. It is noteworthy to point out that this method leads to the most precise estimates of costing (Drummond *et al,* 2001) however; it is never possible to do a perfect job.

5.7. The stages of the analysis undertaken and the specifications of the courses of actions

Initially, time was spent in the outpatient clinics of NLI, Menoufiya to personally and individually investigate HCV positive patients with either compensated or decompensated liver disease prescribed supportive liver treatment. Patients with compensated liver disease with antiviral prescriptions were also investigated at this

first stage and were included in the research. The medical outcome of each treatment option, as well as its effectiveness, were also taken into consideration, their values were retrieved from the literature and from the NLI unpublished data.

The second stage was spent investigating the cost of treatment of hospitalized HCV patients in the NLI. This phase extended over the second and third year of the fieldwork; it served to identify, measure and value costs related to treatment of HCV patients in the NLI. The last of the field work stages was spent investigating private medical settings.

5.7.1. Stage one (outpatients' investigations)

Outpatients' data was collected in the NLI, Menoufiya from one hundred and twenty nine outpatients attending the clinics for their routine examination checkups with either compensated or decompensated liver disease prescribed supportive liver treatment not requiring hospitalization. **The cost of caring of each outpatient** was evaluated. It was divided into three main components in this study;

1. The medication cost (the cost of drugs prescribed to the patient)
2. The direct non-medication costs (clinic admittance fee, laboratory tests and diagnostic investigations)
3. The constant costs directly and indirectly incurred by patients per visit (in this case subsidized government costs calculated from classified hospital records including the salaries and staff, water, electricity, etc....) (NLI is a subsidized public medical institution)

The identification of cost components was followed by the measurement of frequency and quantity related to that component and ended by the valuation of the cost component then summing them up to reach the total cost for drugs and services rendered to the HCV patient. In both patient groups the monthly costs of drug

treatment (medication cost), of investigations and of follow up were assessed (direct non medication cost).

This breakdown was done in order to highlight the cost weight or percentage that each of these cost components contributes to the total cost and to evaluate effectively the actual impact it has on the treatment effectiveness in general. The cost breakdown was also used to compare the cost of each disease stage across the various medical settings; university versus private profit and non-profit hospitals.

Data was collected, checked, revised and tabulated in excel sheets (Microsoft Excel; Version 2003). Duplicate data entry was performed to ensure quality control.

The cost of antiviral therapy and its outcome were obtained via the calculation of the medication costs of treatment of two groups of patients in the NLI each prescribed one form of interferon combination therapy.

Cost categories were divided into the same previously mentioned three segments. However the medication cost in that case included the antiviral drug combination cost.

- Two hundred and twenty outpatients in the NLI were prescribed conventional IFN 3 million units 3 times weekly for one year in combination with ribavirin 1200 mg per day (Zaraski, 1999; Dusheiko *et al*, 2000; Buti *et al,* 2002; Dusheiko, 2002 and Davis *et al,* 2003), with a sustained virological response (SVR) of 15.9 % (NLI unpublished data).

- Another one hundred patients were prescribed pegylated IFN 180 micrograms once a week for one year in combination with ribavirin 1200mg per day (Zaraski, 1999; Dusheiko *et al,* 2000; Buti *et al*, 2002; Dusheiko, 2002 and Davis *et al,* 2003) with an SVR of 54% (NLI unpublished data). The sustained viral response rate to pegylated interferon and ribavirin in Egyptians infected with HCV genotype IV

(causing approximately 90% of infections in the country), ranges between 29% and 69%, with the higher value in those treated 36 weeks or longer (El-Zayadi *et al,* 2005 and Kamal *et al,* 2005).

Two important issues should be stressed at this stage: the first is that that the Ministry of Health and Population of Egypt mandates very rigid drugs' pricing policies and regulations in all Egyptian medical institutions and centres whether they are public or private. The second is that the prices of medical services and testing given and performed in the NLI are actually the price of that service in Egypt, this is due to the fact that the medical services' pricing are also constant throughout all government, public and university settings in the country and only varies in private settings.

5.7.2. Stage two (inpatients' investigations)

Time was then spent in the NLI, Menoufiya inpatients wards and patient data archiving departments to investigate different causes of hospitalization and costs of treatment of HCV inpatients.

The inpatients' data was collected in the NLI, Menoufiya from one hundred and eighty three patients and their records during hospitalization and from the records of twenty patients who underwent liver transplantation. The cost of caring for each patient by reason of hospitalization was assessed and the total cost of hospitalization was evaluated. Cost categories were divided into the following four main segments;

1. The medication cost
2. The direct non medication costs
3. The blood costs (included separately, as the blood costs were found prominently substantial from the hospital records and were unevenly distributed over the various studied groups).

4. The constant costs (in this case subsidized government costs calculated from classified hospital records per patient per bed per day).

The direct non medication costs included all the services specially offered to each particular patient during hospitalization including the hospital stay in its subsidized value, operations, laboratories, injections, disposables, imaging, endoscopy and endoscopic injection sclerotherapy for bleeding varices.

The constant costs included besides electricity, water food, etc... the physicians and nurses salaries which were considered, and calculated from classified hospital records and budgets as an overhead per bed per day. This classification is different from the internationally recognized classification and terminology as the study was performed in a government-subsidized hospital. It should be noted that total constant costs are actually reached from the hospital classified records; this number was then broken-down to the number of beds in inpatient wards or number of visits in outpatient clinics and named as constant cost per patient in public settings. This directly relates to the fact that for the private institutions the actual cost could not be reached; as this was too private cost benefit information for any researcher to know and we had to make do with price comparisons in each cost component that produced factors; these factors help us to reaching the final calculations needed.

The total cost of hospitalization was then calculated, based on actual directly incurred inpatient costs calculated from the hospital classified records (not prices as they are all subsidized, lowest cost with no profit). Again, medication costs were available, direct non-medication costs, blood transfusion costs were also incorporated separately and finally constant costs for the whole of inpatient wards broken-down to cost per bed per day (which include medical staff, light, electricity ....).

Data was collected, checked, revised and tabulated in excel sheets (Microsoft Excel; Version 2003). Duplicate data entry was performed to ensure quality control.

5.7.3. Stage three (private settings' investigations)

Field visits and general assessments were conducted in private non-profit and private for profit **clinics** to evaluate both the supportive treatment costs and antiviral treatment costs for HCV outpatients with compensated and decompensated cirrhosis. Cost categories were divided into the following three main segments; as also seen in the outpatients' investigations:

1. The medication cost (antiviral drug combination or supportive treatment cost)
2. The direct non-medication costs (tests and consultation fees according to the standardized norms)
3. The constant costs (none in the private clinics' case)

An estimated factor was worked out for the comparison of the direct non-medication costs segments in the private non-profit and the private for-profit clinics in relation to that of the NLI and was found to be 1.7 and 2.5 times that of the NLI fees respectively.

Similarly, field visits and general assessments were conducted in private non profit and private for profit hospitals to evaluate the hospitalization costs (medication costs, direct non medication costs, constant costs and blood transfusion) of the two medical settings chosen for comparison were assessed for each cost category by direct comparison to the public NLI setting and calculated for both the private for-profit and non-profit hospitals.

Cost categories were divided into the following four main segments; as also seen in the NLI inpatients investigations:

1. The medication cost

2. The direct non-medication costs (tests and consultation fees according to the standardized norms)

3. The blood costs (included separately, due to the uneven distribution of blood costs over the various studied groups).

4. The constant costs (none in the private clinics case)

The data collected was used to obtain the annual cost of caring of patients with hepatitis C virus prescribed liver support treatment, first only as outpatients with compensated liver disease then with decompensated liver disease but still not needing hospitalization. The outcome of antiviral therapy and its cost were also obtained and compared with the supportive treatment's data collected and finally various indications of hospitalization costs of HCV inpatients were also processed and assessed.

5.8. Analysis and interpretation of data

A Markov model reflects the progression of the disease through different states. In each state costs are associated, which enables resources utilized at each stage of progression to be computed (Bender, 2000). It is thus possible to consider the impact of treatment on patient progression and resource utilization. Furthermore, Markov models provide a way to assess effectiveness, as the treatment creates a different set of probabilities of a patient moving from one stage to the next.

In this research, a model was constructed to aid the calculation of the cost of disease over the life cycle of the patients with hepatitis C virus following the Markov model of hepatitis C virus according to D'Amico *et al,* (1986), Arroyo *et al,* (1999) and Wong *et al,* (2000). The cost of each treatment plan was calculated from the data collected.

The quality of the model should not be in question because of the internationally recognized structure of the model used for the life cycle of the disease (Wong *et al,* 2000). Moreover the data used for the study was personally collected by the investigator directly from its original sources in the largest hepatology centres in Egypt dealing with HCV with a totally unbiased aspect (there was no reason or pressure for any bias).

The Markov model (Figure 4) of the disease life cycle over twenty years after the diagnosis was as follows: Patients with compensated liver disease will remain compensated for fifteen years following diagnosis. **Sixty percent** of patients will remain compensated for another five years (D'Amico *et al,* 1986; Arroyo *et al,* 1999 and Wong *et al,* 2000). Alternatively, the remaining **forty percent** will develop decompensated cirrhosis for five years and get hospitalized for the various reasons of hospitalizations on average four times in the last two two years before either death or the eligibility of a liver transplantation (nearly one third of the patients with decompensated liver disease, NLI unpublished data). Patients who receive antiviral therapy and achieve a sustained virological response (SVR) will be considered cured and are excluded from further calculations (15 % for standard IFN and 55 % for PEG-IFN). The remaining 85 % and 45 % respectively will continue in the calculation of the cost as the previously described natural history model.

Nine flow charts were developed, three for each medical institution setting; one for the supportive liver disease treatment pathway without antiviral treatment, the second for the standard IFN treatment pathway and the third for the PEG-IFN treatment pathway; for each of the NLI, the private non-profit, and the private for-profit medical setting.

Costs of disease of HCV patients were calculated and compared with the aid of the abovementioned flow charts and Markov models, using computer cohorts of one hundred patients under the three different scenarios and computed and statistically analysed; the supportive liver disease treatment pathway, the standard IFN treatment pathway and the PEG-IFN treatment pathway in each of the studied settings. Data was entered into a Microsoft Excel (Version 2003). Duplicate data entry was performed to ensure quality control. Data was first entered concerning each group of interviewed patients from the hard copies compiled in NLI then each data entry was revised a second time by direct comparison of both hard and soft copies. The cost of each scenario was computed and compared among the three different settings. Data analysis was performed with a statistical package for personal computer and presented in tabular and graphical forms using SPSS version 12 for windows (SPSS, Inc., Chicago, IL).

Costs of the numerous treatment pathways calculated at the earlier phases of the research were integrated in these models assuming a conservative 5 % annual increase based on the fact that the rate of inflation in Egypt is 6 % and the interest rate is 8.5-9% according to the Central Bank of Egypt data, 2006. The chosen 5 % value is low because the Egyptian government has strong regulations on the pricing of drugs and medical services (Prices of medication and healthcare increased only 50 % or more in the last 10 years!).

Other facts considered while processing the calculated values in this disease calculation is the long life cycle of the hepatitis C virus. This led to the subjection of the future costs and benefits to discounting, to bring them into line with present values. Discounting at the recommended 3% annual rate was also integrated into the

final figures calculated for money spent over the twenty year period of the cycle of the disease (Drummond *et al,* 2001 and Wong, 2006).

Cost effectiveness analysis (CEA) was adopted as a form of economic evaluation where both the costs and consequences of health treatments or programs are examined; it was based on existing medical evidence and literature of effectiveness (Gold *et al,* 1996 and McCombs, 1998). The costs incurred from each adopted substitute treatment pathway was broken down into several components and calculated. The benefits in terms of patient lives saved were also determined. The measure of effectiveness chosen is the lives saved by the health program selected, this gives a clear dimension to the objective of the intervention.

5.9. Summary

In Chapter two, the healthcare and economics relationship was explained along with the role of health technology assessment and the various procedures of economic evaluation. Chapter three was all about hepatitis C, its history, its infection and its treatments. Chapter four drew attention to the special problem of HCV in Egypt. In this chapter, the need to more practical prevailed, and the methodologies used to reach the objectives of the study were explained and the choices made have been advocated. All the data collected and the field work described and performed lead to many outputs and results that will be explained in the coming chapter before being discussed in the one following that.

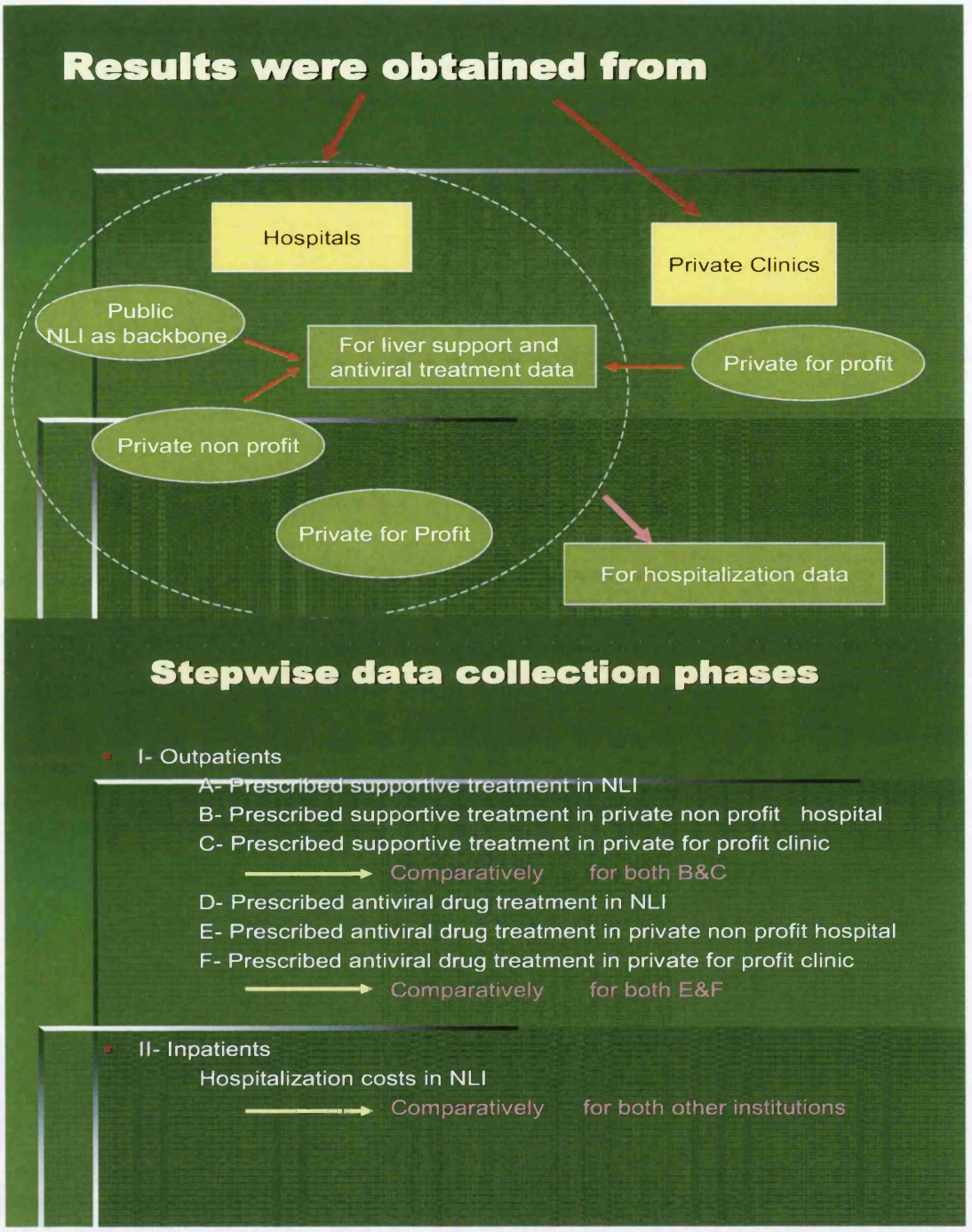
Chapter 6

Results

Contents of Chapter

The research was conducted in the National Liver Institute (NLI) Menoufia, Egypt; a specialized tertiary referral hospital. Access was granted via an acceptance letter from the hospital board, allowing presence in the staff resticted areas, in the outpatients' clinics and in the inpatients wards. Patient confidentiality was respected throughout the research, the cases were treated as anonymous cases to adhere to the ethically approved procedures of anonumity required by the NLI board considerd as the ethical committee for the hospital. The NLI is a governmental subsidized hospital. It is appendaged to the Medical School of Menoufia University. It is the only specialized center solely dedicated to liver disease. NLI has one hundred and twenty beds, it also has the busiest outpatient clinics with 100 000 (one hundred thousand) visits per year where patients are referred from all over Egypt, starting from Alexandria in the north to Assiut in the south. It is also noteworthy to mention that it was the first hospital in Egypt to initiate a liver transplant program. In addition to the NLI, specialized private hospitals were investigated for data comparaison; the first, a private non profit hospital dedicated solely for liver disease having both inpatients's wards and outpatients' clinics, the second, a private for profit hospital, chosen particularly because it is the only private hospital that performs liver transplants in Egypt; data concerning its inpatients was accessed. Data and costs about outpatients frequenting private for profit clinics were collected from three specialized and prominent outpatient centers.

Figure 7: Schematic representation of the institutions under study and the stepwise data collection from each



6.1 Outpatient Data

6.1.1. Cost of outpatients' treatment prescribed supportive treatment in the NLI

Data was collected from patients attending the clinics for their monthly examination routine checkups in the NLI. One hundred and twenty nine patients with positive HCV were examined, 75 of whom were males (p=0.39) and 54 were females. Those outpatients were divided according to the stage of liver disease into two main groups: patients with compensated liver cirrhosis and patients with decompensated liver cirrhosis prescribed supportive treatment.There was no significant difference in the gender distribution between the two groups (table 9).

The cost of treatment incurred by each patient was evaluated by dividing it into three main segments; medication costs, direct non medication costs and constant costs.

Table 9: Gender distribution for patients grouped by severity of liver cirrhosis

	Males	Females	Total	X^2	P
Compensated	43 (55%)	35 (45%)	78	0.735	0.391
Decompensated	32 (63%)	19 (37%)	51		
Total	75 (58%)	54 (42%)	129		

The medication costs are those of the drugs prescribed. The direct non medication costs are those incurred due to the direct monthly clinic admittance fee per patient and all the tests and the diagnostics which are shown in the following table.

Table 10: Direct non medication cost breakdown and frequency for outpatients prescribed supportive treatment

Expense	Cost	Frequency
Clinic admittance fee	5 LE	every one month
Ultrasound	40 LE	every three months
Blood picture	10 LE	every three months
Liver tests	40 LE	every three months
Alfa feto protein	50 LE	every six months
Total	**520 LE**	**For one whole year**

The constant costs are those paid by the hospital and/or subsidized by the government as a total overhead directly injected into the hospital and calculated from its budget and its classified records to be 35 LE per patient per visit.

The mean total annual cost per patient per year grouped by severity of liver cirrhosis (values in Egyptian pounds) in table 11 shows that the medication cost of the decompensated group at 1 675 LE is significantly higher than the 1 306 LE of the compensated group at $p<0.05$ (table 11). Those values constitute 58% and 64% of the mean annual cost for the compensated and decompensated groups respectively. This value is shown to decrease slightly in the private non profit hospital (53.3% for compensated patients and 59.4% for decompensated patients) and is nearly halved for private for profit hospitals, with values 32 % and 37.8 % respectively (Table 16 and 17).

Table 11: Means of annual cost per patient per year grouped by severity of liver cirrhosis in the NLI (Values in Egyptian Pounds)

	Compensated	Decompensated
Constant**	420 (35*12)	420 (35*12)
Direct non medication	520	520
Medication	1,306	1,675*
Mean total annual cost	**2,246**	**2,615***

* Significant at the 0.05 level using t-test
**The Constant costs are those subsidized by the government as total overhead calculated from the hospital classified records as 35 LE per patient per visit.

All patients were prescribed variable combinations of 53 drugs (table 12). For statistical analysis similar drugs were then grouped in 10 categories as follows; lactulose, hepamerz & neomycin drug category, liver support category, vitamins category, diuretics category, propranolol & mononitrate (B blockers category), acid suppressants category, antidiabetics, antihypertensives, antispasmodics and others' category (table 13).

Table 14 shows the breakdown of the means of annual medication costs per patient per year grouped by severity of liver cirrhosis. The table shows the significantly higher value of liver support drug category for the decompensated patient group 956 LE versus that of the compensated patient group 533 LE ($p<0.05$). However, the significantly lower value of acid suppressants drug category for the same patient group ($p< 0.05$) is also seen. The values are evenly distributed over the remaining 8 drug categories with the propranolol & mononitrate category noticeably lower than the other categories (82 LE and 72 LE for both patient groups) while the lactulose, hepamerz & neomycin category especially higher than the other categories (1,231 LE and 916 LE for both patient groups).

Table 12: List of drugs prescribed to HCV outpatients

1	Legalon	15	Aldactone 100	29	Ranitidin 300mg	43	Ultraproct supp
2	Vit E 100	16	K viton	30	Ranitidol 150 mg	44	Omipac 10mg
3	Vit E400(Pharco)	17	K viton	31	Ranitak 150mg	45	Omipac 20mg
4	Vit E400(Mepaco)	18	E viton	32	Ranitak 300mg	46	Dactarine
5	Vit B Complex	19	Dipovit amp.	33	Monomac 20	47	Ventoline
6	Colospasmin	20	Neomycin	34	Amaryl 1g	48	Captopil
7	Antox	21	Hepamerz	35	Amaryl 2g	49	Diflucan
8	Farcovit	22	Multivitoplex	36	Amaryl 3g	50	Insulin
9	Zantac	23	Motinorm	37	Burinex	51	Mixtard
10	Spasmo digestin	24	Amrizol 500mg	38	Burinex	52	Migracid
11	Tri – B	25	Copoten	39	Citrocid	53	Edimex
12	Indral	26	Konakion 300mg	40	Domperidone		
13	Ursofalk	27	Lactulose	41	Epimag Eff		
14	Heamaton	28	Ranitidin150mg	42	Capoten 25mg		

Table 13: Drug categories prescribed to HCV outpatients

1	Lactulose, Hepamerz & Neomycin
2	Liver Support
3	Vitamins
4	Diuretics
5	Propranolol & Mononitrate
6	Acid Suppressants
7	Antidiabetics
8	Antihypertensives
9	Antispasmodics
10	Others

Table 14: Mean annual medication costs per patient grouped by severity of liver cirrhosis (Values in Egyptian Pounds)

Drug categories	Compensated	Decompensated
Lactulose, Hepamerz & Neomycin	916	1,231
Liver Support	533	956*
Vitamins	165	141
Diuretics	299	420
Propranolol & Mononitrate	82	72
Acid Suppressants	677	501*
Antidiabetics	545	576
Antihypertensives	360	504
Antispasmodics	257	230
Others	177	200

* Significant at the 0.05 level using t-test

Figure 8 illustrates the percentages of the mean annual medication costs per patient per year grouped by severity of liver cirrhosis in a relative pie chart with the decompensated group larger than its counterpart. This figure shows that the acid suppressants and liver supports drug categories are significantly larger ($p<0.05$) in the decompensated group. Table 15 and figure 8, emphasizes the difference in values and percentages respectively along with highlighting a difference in the antispasmodics category values for both groups which was not otherwise apparent.

Figure 8: Percentages of means of annual medication costs per patient per year grouped by severity of liver cirrhosis (Values in Egyptian Pounds)

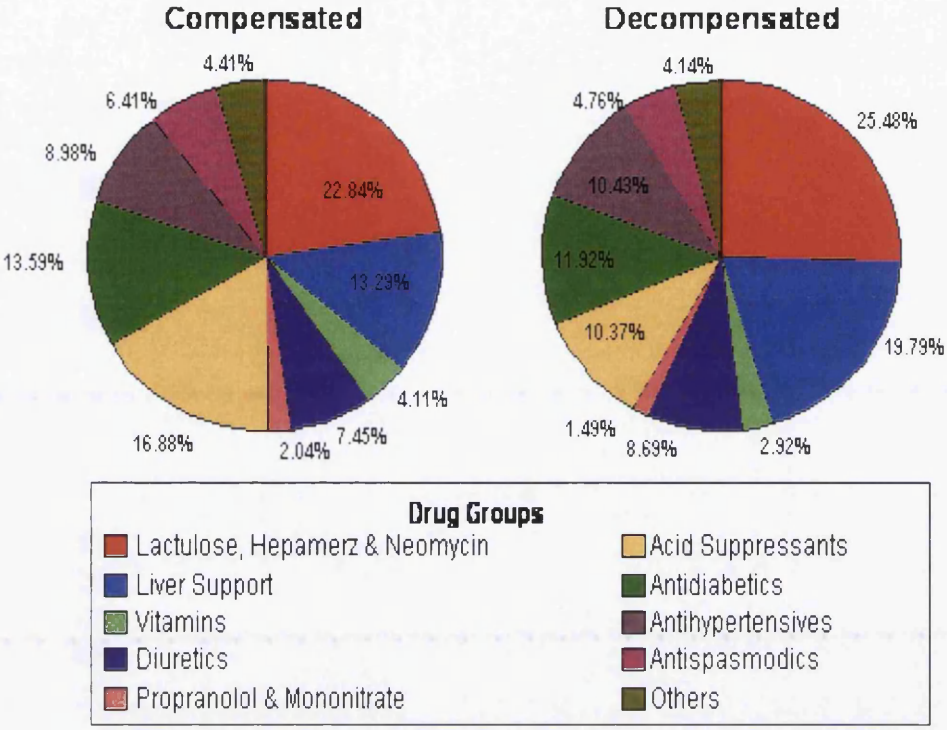
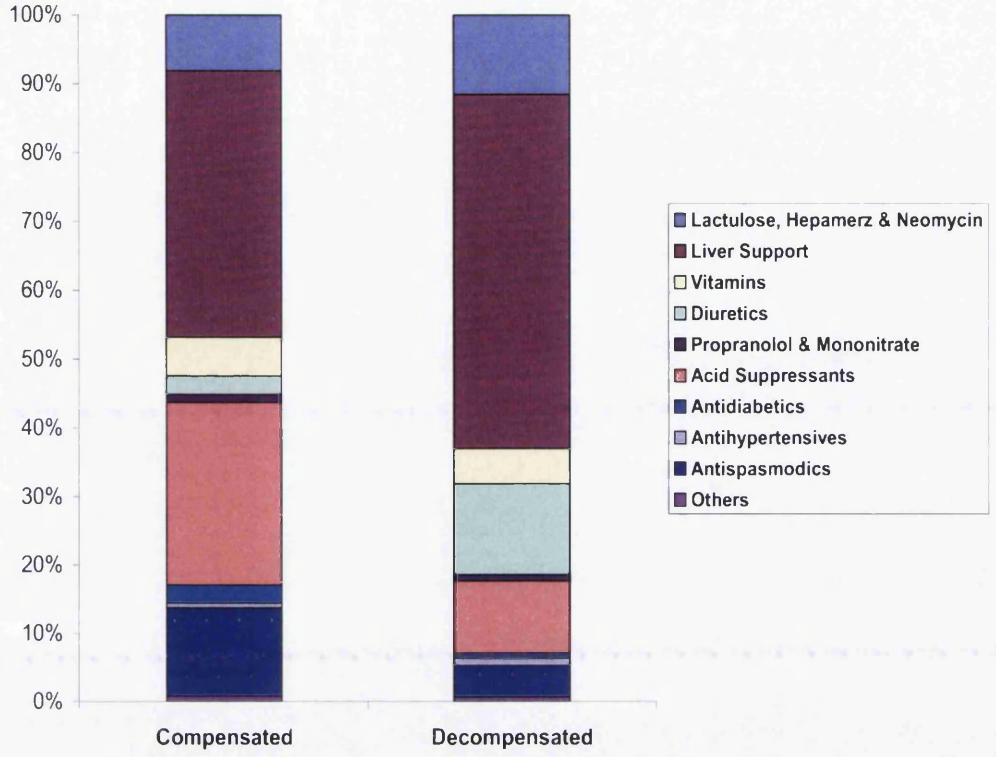


Table 15: Total annual medication costs in each drug category grouped by severity of liver cirrhosis (Values in Egyptian Pounds) and means of annual Drug categories costs' <u>percentages</u> per patient group

Drug categories	Compensated		Decompensated	
Lactulose, Hepamerz & Neomycin	8248	8.1 %	9851	11.53 %
Liver Support	39444	38.73 %	43989	51.48 %
Vitamins	5774	5.67 %	4357	5.1 %
Diuretics	2688	2.64 %	11344	13.28 %
Propranolol & Mononitrate	1148	1.13 %	792	0.93 %
Acid Suppressants	27099	26.61 %	9018	10.55 %
Antidiabetics	2726	2.68 %	576	0.67 %
Antihypertensives	720	0.71 %	1008	1.18 %
Antispasmodics	13122	12.88 %	3906	4.57 %
Others	884	0.87%	600	0.70 %
Total	101854	100 %	85441	100 %

Table 15 shows the total annual medication costs in each drug category grouped by severity of liver cirrhosis for all 129 patients, the liver supports are understandably the highest costing category; they are then followed by the acid suppressants and the diuretics in the compensated and decompensated groups respectively. The breakdown of the means of annual medication costs percentages' per patient per year grouped by severity of liver cirrhosis (table 15) shows the higher value of liver support in addition to lactulose, hepamerz & neomycin drug categories on the weight of the total medication cost (46.8%) for the compensated drug group versus (63.1%) the decompensated patient group. However, vitamins drug category values are nearly 5 % in both patients groups. Figure 9 colourfully illustrates the relative weight of the various drug categories on the total cost of treatment in each patient group as percentages. The lactulose, hepamerz & neomycin and liver support drug categories are prominent in both patient groups, and acid suppressants stand out in the compensated group, while diuretics do so in the decompensated patients's prescriptions. Following the line of prescription analysis figure 9 also shows the parallelism of values in the liver support, Lactulose; Hepamerz & Neomycin and vitamins drug categories while diuretics and acid suppressants alternate by being weightlier in the decompensated and compensated patients' groups respectively.

Figure 9: Medication costs (% of total) in each drug category grouped by severity of liver cirrhosis



6.1.2. Cost of outpatients' treatment prescribed supportive treatment in private clinics

Field visits and general surveys were conducted in private non profit and private profit clinics to assess the supportive treatment costs for HCV patients with compensated and decompensated cirrhosis. The medication costs in both private settings are similar to those of the NLI due to the mandatory regulations of the Ministry of Health and Population standardizing the price of drugs throughout all medical institutions and outlets in the country. It is vital to point out that there are no constant fees in the private medical settings as they are financially independent non subsidized medical entities.The direct non medication costs were calculated by comparing the values of the consultation fees, and medical tests: ultrasound, blood picture, liver tests, alfa feto protein, and working out a factor in relation to the direct

non medication costs for the outpatients in NLI. This factor was calculated to be 1.7 and 2.5 times of the non medication direct costs of the NLI for the private non profit and the private for profit clinics respectively (Tables 16 & 17).

Table 16: Means of annual cost per patient per year grouped by severity of liver cirrhosis in private non profit hospital

	Compensated	Decompensated
Medication	1,306	1,675
Direct non medication	1142	1142
Constant	NA	NA
Total	**2,448**	**2,817**

The direct non medication cost is 1.7 times that of the NLI. The cost of consultation is 30 LE.

Table 17: Means of annual cost per patient per year grouped by severity of liver cirrhosis in private for profit clinics

	Compensated	Decompensated
Medication	1,306	1,675
Direct non medication	2,750	2,750
Constant	NA	NA
Total	**4,056**	**4,425**

The direct non medication cost is 2.5 times that of the NLI. The cost of consultation is the average of 80LE, 120LE and 300LE.

6.1.3. Cost of outpatients' treatment prescribed antiviral drug treatment

- In NLI

Patients with compensated liver disease, visiting the outclinics of the NLI, who were prescribed ribavirin and interferon (IFN) or pegylated interferon combination therapy were investigated and included in the research.

The antiviral combination treatment course included: conventional IFN injections three million units three times weekly and 1200 mg ribavirin daily, for one year (Zaraski, 1999; Dusheiko *et al,* 2000; Buti *et al,* 2002; Dusheiko, 2002 and Davis *et*

al, 2003), or pegylated IFN injections three million units once weekly and 1200 mg ribavirin daily for one year (Zaraski, 1999; Dusheiko *et al,* 2000 and 2002; Buti *et al,* 2002 and Davis *et al,* 2003).

Patients were given the antiviral medication and the viral load was monitored for the first three months, when the responders and the non responders were indentified. The non responders were given the supportive treatment alternative and were excluded from this study group. While responding patients, those with a decreased viral count, continued to take the medication for the remainder of the 12 months.The success of the treatment was assessed by the sustained virological response (SVR) six months after cessation of treatment.

Two hundred and twenty patients were treated with conventional IFN injections in combination with ribavirin, they had viral count laboratory testing (PCR) performed 3 months after initiating the treatment, 12 months and finally 18 months later to determine the SVR which turned out to be 15.9%; i.e 35 patients were cured from 229 patients.

Another group of one hundred patients were treated with pegylated IFN injections in combination with ribavirin, they had viral count laboratory testing (PCR) performed; 3 months after the beginning of the treatment, 12 months and finally 18 months later to determine the SVR which was calculated to be 54%; i.e 54 patients were cured from 100 patients.

The direct non medication costs are those incurred due to the clinic admittance or consultation fee totalling 30 LE in 18 months and all the laboratory testing which were performed during the whole treatment period; according to the following table.

Table 18: Direct non medication cost breakdown and frequency for NLI outpatients prescribed antiviral treatment

Expense	Cost	Frequency
Blood picture	10 LE	every one month
Liver function tests	40 LE	every one month
Polymerase chain reaction (PCR)	500 LE	every three months
Consultation fee	5 LE	every two months
Total direct non medication cost	**2630 LE**	**For one whole year**

The constant costs are those paid by the hospital or subsidized by the government as a total overhead cost, directly injected in the hospital and calculated from its budget and its classified records. Its value was calculated to be 210 LE per patient in 18 months.The clinic admittance or consultation fee, the laboratory testing costs and the constant costs are grouped together in table 19 and added to have total non medication cost (2,840 LE) grouped seperatly in this case of total antiviral treatment costing for ease of calculation.

The medication costs are assessed by summing the drugs prices of the combination therapy prescribed and calculated as follows:

A. The standard interferon injection costs 45 LE, amounting to 135 LE for three times per week and the pegylated form costs 485 LE and is given once weekly. The total interferon and pegylated interferon treatment one year course costs **6 480LE** and **23 280 LE** respectively.

B. Ribavirin dose is 1200mg/ day and 12 capsules 400mg cost 72 LE, totaling **6 570 LE** per patient per year.

From A & B: The medication costs for a patient treated with of interferon - ribavirin combination would be 13 050LE which is the sum of both interferon 6 480LE, and ribavirin 6 570 LE.

The total treatment cost for the same patient treated with interferon combination therapy is the sum of the antiviral medication cost and the total non medication cost (*clinic admittance or consultation fee, the laboratory testing costs and the constant costs*) as per the frequency of the table 19 would be 15 890 LE (table 20).

From A & B: The medication costs for a patient treated with pegylated interferon - ribavirin combination would be 29 850 LE which is the sum of both interferon 23 280LE and ribavirin 6 570 LE.

The total treatment cost for the same patient treated with the pegylated interferon combination therapy is the sum of the antiviral medication cost and the total non medication cost (*clinic admittance or consultation fee, the laboratory testing costs and the constant costs*) as per the frequency of the table 19 would be 32 690LE (table 21).

The difference in the cure rate is a little more than tripled (15.9% versus 54%) and the difference in the price of the interferon / pegylated interferon weekly dose is a little less than quadrupled (6 480:23 280) but the final comparison of the total treatment cost of both alternatives is more than doubled (15 890:32 690).

- In private medical settings

The same calculations were done for the two other private medical settings, namely the private for profit and the private non profit clinics that were chosen for the study.

The total non medication costs (*clinic admittance or consultation fee, the laboratory testing costs and the constant costs*) as per the frequency of the table 19 for the private non profit hospital and the private clinics was determined to be 4 780LE and 8 100LE

respectively. It is important to point out that there are no constant fees in the private medical settings as they are financially independent non subsidized medical entities.

The total treatment cost for a patient treated with the interferon combination therapy would be 17 830LE and 21 150LE in the privat non profit hospital and the private clinics respectively (Table 20). While the total treatment cost for a patient treated with the pegylated interferon combination therapy would be 34 630LE and 37 950LE in the private non profit hospital and the private clinics respectively (Table 21).

A very important detail was observed from tables 20 and 21; the total cost of the cured patient (integration of both the cure rate and the total treatment cost) treated with the seemingly more expensive pegylated interferon combination therapy **is less** than the standard interferon alternative in *all* three medical settings.

Table 19: Comparison of total non medication cost/year in the NLI, the private non profit hospital and the three private clinics

Name of medical institution / Name and frequency of test	**Menoufiya NLI** /Year	**Private non profit hospital** /year	**Private clinics** /Year
Monthly blood picture	120 LE	204 LE	300 LE
Monthly liver function tests	480 LE	816 LE	1200 LE
Quarterly PCR	2000 LE	3400 LE	5000 LE
Consultation fee (6times/year)	30 LE	360 LE	1600 LE
Constant cost **	**210 LE**	**0 LE**	**0 LE**
Total cost	**2 840 LE**	**4 780 LE**	**8 100 LE**

**The Constant costs are those subsidized by the government as total overhead calculated from the hospital classified records.

Table 20: Total cost of treatment of each cured patient treated with interferon and ribavirin combination in the three medical settings

	Menoufiya NLI	Private non profit hospital	Private for profit clinics
Cost of each pt of the 220 pts	13 050+2 840 = 15 890 LE	13 050+4 780 = 17 830 LE	13 050+ 8 100 = 21 150 LE
Cost per cured pt (n=35) *	99 880 LE	112 074.28 LE	132 942.85 LE

* is the number of cured patients

Table 21: Total cost of treatment of each cured patient treated with pegylated interferon and ribavirin combination in the three medical settings

	Menoufiya NLI	Private non profit hospital	Private for profit clinics
Cost per patient (100pts)	29 850+2 840 = 32 690 LE	29 850+4 780 = 34 630 LE	29 850+8 100 = 37 950 LE
Cost per cured patient (n=54) *	60 537.03 LE	64 129.62 LE	70 277.77 LE

* is the number of cured patients

6.2. Inpatient Data

One hundred and eighty three positive HCV hospitalized patients' records were examined in the NLI; nearly 10% of the total number of patients in 2003; 165 patients were males and 18 patients were females. Table 22 shows that patients were mostly males in all subgroups and there was no statistical significance in the gender distribution of the different groups (p =0.699).

Table 22: Gender distribution for patients grouped by reason of hospitalization

	Males	Females	Total	X^2	P
Ascites	25 (96%)	1 (4%)	26	2.201	0.699
Bleeding	65 (89%)	8 (11%)	73		
Coma	44 (90%)	5 (10%)	49		
HCC	3 (75%)	1 (25%)	4		
Others	28 (90%)	3 (10%)	31		
Total	**165 (90%)**	**18 (10%)**	**183**		

The patients were then arranged according to the reason of their hospitalization, into five groups as follows:

- **Group 1**: Patients hospitalized for the management of refractory ascites that complicates liver cirrhosis (**ascites group**).
- **Group 2**: Patients hospitalized for bleeding varices in the esophagus and stomach due to portal hypertension secondary to liver cirrhosis (**bleeding group**)
- **Group 3**: Patients hospitalized for hepatic coma due to advanced liver disease (**Coma group**)
- **Group 4**: Patients hospitalized for liver malignancy and hepatocellular carcinoma (**HCC group**).
- **Group 5**: Patients hospitalized for other complications due to liver cirrhosis (**others group**).

The cost of care given to each patient was evaluated starting with categorizing it into four main segments;

1. the medication cost
2. the direct non medication costs
3. the blood costs
4. the constant costs (as labelled in this study)

The medication costs (medication costs) are the costs of drugs given to the patient during hospitalization. **The direct non medication costs** include all the needs and services offered to the patient during hospitalization including the hospital stay, operations, laboratories, injections, disposables, imaging, endoscopy and endoscopic injection sclerotherapy for bleeding varices. **The blood costs** are those incurred by blood transfusion and were separately included due to the uneven distribution of blood over the various studied groups. **The constant costs** are those directly paid by the Ministry of Health and Population in the form of subsidy to the NLI and including the physicians' and nurses salaries, electricity, water, food, etc as calculated from

classified hospital records as an overhead per bed per day. This is based on the fact that this study was mainly performed in the NLI, a public hospital, and that the government of Egypt subsidizes the medical services given in all public medical institutions.

This is different from the internationally standardized terminology since the breakdown of the hospital budget was not laid out to complement the data needed for the international format and only included costs paid by patients or institutional payer and then there was the government subsidy to the hospital which was then processed to a value per patient per bed. The data lacked the indirect cost seperatly categorized as is the norm.

The breakdown of the means of costs of caring per patient grouped by reason of hospitalization as shown in table 23, highlighted that blood transfusion cost was significant in patients hospitalized for bleeding and ascites compared to the other groups ($p>0.05$). Table 23 also shows that ascites patients have the highest constant costs' values versus the bleeding patients who had the lowest values though non significantly so ($p>0.05$). This could be related to the mean length of hospital stay shown in figure 12. The mean total cost is high for the group of patients labelled others and HCC patients (5 481 LE and 4 670 LE respectively), which is very apparent in figure 13. However, the significantly high medication costs for bleeding patients 1 038 LE at $p<0.05$ affected the mean total costs of 3 713 LE but not enough to overcome the mean total costs of the ascites group 4 019 LE which comes third in decreasing order of the means of the total costs that ends with 3 477 LE for the coma patients. On the other hand, the direct non medication costs' values were greatest for the patients labelled others group and least for the bleeding group but still non significantly so ($p>0.05$). The medication and blood costs were found significantly

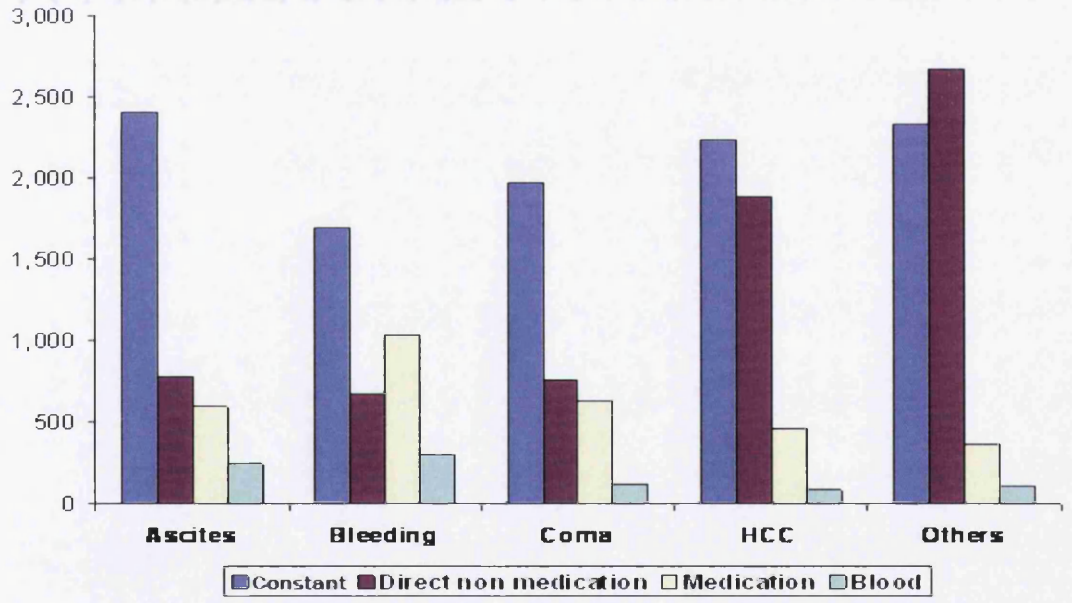
higher for the bleeding patients. This is graphically represented by a bar chart in figure 11.

Table 23: Means of costs per patient grouped by reason of hospitalization (Values in Egyptian Pounds)

	Ascites	Bleeding	Coma	HCC	Others
Medication	594	1,038*	632	460	362
Direct non medication	776	676	753	1,890	2,677
Blood	242**	302**	117	85	109
Constant	2,407	1,697	1,975	2,236	2,333
Total	4 019	3 713	3 477	4 670	5 481

* Significant when compared to groups: ascites, coma and others
** Significant when compared to groups: coma and others

Figure 11: Breakdown of the means of costs per patient grouped by reason of hospitalization (Values in Egyptian Pounds)



The bar chart (figure 12) illustrates the mean length of hospital stay per patient group grouped by reason of hospitalization (values in days). The ascites patients come first with 9.2 days, followed by the others, HCC and coma patients with values of 8.9, 8.5 and 7.5 days respectively, bleeding patients tail the groups with a value of 6.5 days.

Figure 12: Mean length of hospital stay per patient grouped by reason of hospitalization (Values in days)

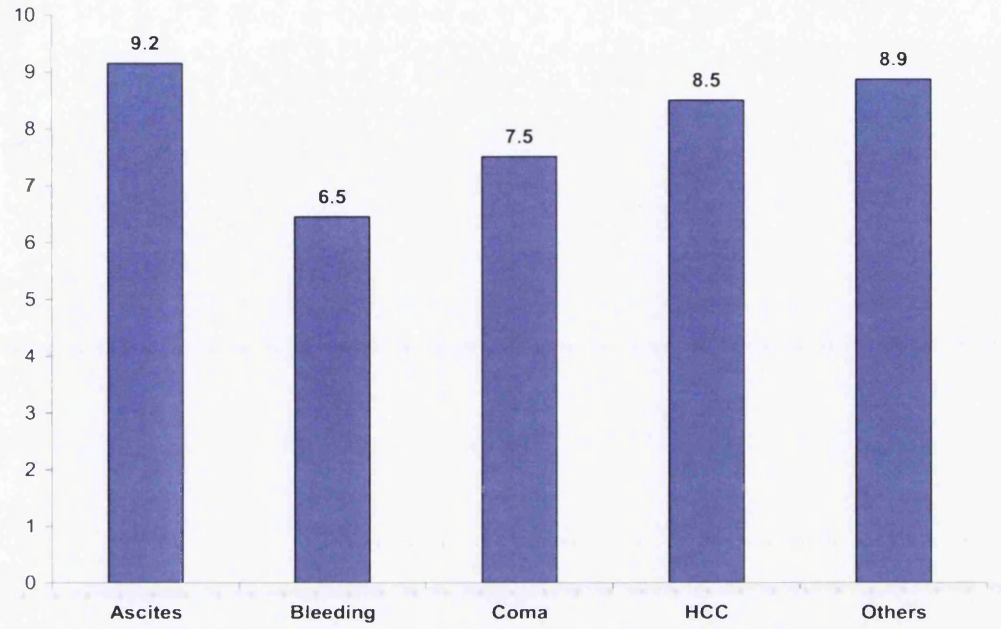
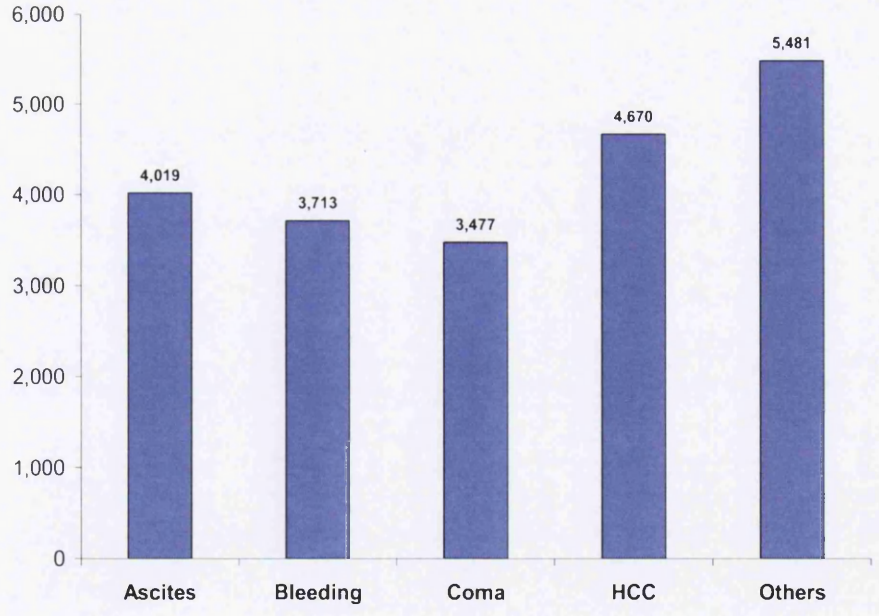


Figure 13: Mean total costs per patient grouped by reason of hospitalization (Values in Egyptian Pounds)



All patients were prescribed variable combinations of 154 drugs shown in table 24. For statistical analysis similar drugs and drugs used for similar conditions were then grouped in 15 categories as follows; lactulose, hepamerz & neomycin drug category,

mononitrate (B blockers category), acid suppressants category, antidiabetics category, antihypertensives category, antispasmodics category, vasopressors category, analgesics category, fluid replacements, immunosuppressants, antibiotics and others' category shown in table 25.

Table 26 shows the breakdown of the mean cost of medication per patient for each drug group grouped by reason of hospitalization (values in Egyptian Pounds). The highest mean cost is the fluid replacements category followed by antihypertensives and antibiotics. All three categories' values were evenly distributed among the various patient groups. However the vasopressor category was significantly higher for the bleeding group 578.7 LE compared to the ascites 212 LE, coma 211.8 LE and others group 98 LE, while the diuretics category was significantly lower for the same group 1.7 LE compared to the ascites 6.1 LE and coma 4.4 LE groups. The others drug category was noticed to be 79.3 LE for HCC patients, significantly higher compared to all other groups at $p < 0.05$.

Figure 14 is a relative pie chart representating the means of totals of medication costs per patient in each drug group, it points to the discernible impact of vasopressors (578.7 LE) cost on the total cost of the bleeding patients (1037.8 LE), while the fluid replacements drug category is noticeable in both the ascites and HCC patient groups (449.8 LE of 593.7 LE) and (277 LE of 460 LE) respectively, finally, the antibiotics drug category (241.1 LE) cut a sizeable chunk of the HCC group pie (460 LE).

Table 24: List of drugs given to inpatients for all reasons of hospitalization

1	1 Alfa amino	53	Cyclocabron	104	Lignocain Oint
2	Acupan	54	Cyclocortiv	105	Losec
3	Adrenalin	55	Dactarin gel	106	Markin Vial
4	Adrenaline amp	56	Depotrex	107	Maxim Vial
5	Airocsol oint	57	Diamicron	108	Mediatic
6	Albumin	58	Dicinone	109	Metomycin
7	Aldacton	59	Dipovit Amp	110	Micazol oint
8	Aldacton cap	60	Dopamin	111	Minophillin
9	Amarol	61	Dormicam	112	Minophillin Surup
10	Amax Tab	62	Dysflatyl	113	Mitophillin
11	Aminophillin	63	E Viton	114	Morphin amp
12	Aminophillin Syp	64	Edimex	115	Motillium
13	Aminovit amp	65	Emox	116	Mucopect syrup
14	Amoran Tab	66	Epideron	117	Muril Amp
15	Amoxil	67	Epilat	118	Neomycin
16	Amoxillin	68	Ethanol	119	Novalgin
17	Amprexol syrup	69	Ethanol amine	120	Omipac amp 10ml
18	Amricol Syrp	70	Evox	121	Omipac amp 20ml
19	Amrizol	71	Evox 20ml	122	Osipect syrup
20	Anital	72	Farcoline	123	Paramol
21	Antox	73	Filden gel	124	Paramol Syrp
22	Apidram Vial	74	Flagyll	125	Pecidin
23	Atropin	75	Fortum	126	Pecidin
24	Augmentin	76	Frutal	127	Penicillin 40 unit
25	Avil	77	Garamycin	128	Penicillin 80 unit
26	Avrin Amp	78	Garamysin oint	129	Phenytoin gel
27	Biomex 500-bedamex	79	Gastrovit	130	Potassium Chloride
28	Bisolvan	80	Geramysin oint	131	Potassium Syp
29	Bisolvan amp	81	Glycerin	132	Primpran
30	Bronchofen	82	Glyopressin	133	Prisanine
31	Buscopan	83	Hepamyrs	134	Salperazone
32	Calcimat	84	Heparin	135	Sandostatin
33	Calcimat amp	85	Histoacryl	136	Sodium bicarbonate
34	Calcium	86	Histryl	137	Solukortif
35	Calma Tab	87	Ibrazol	138	Spasmodigestin tab
36	Capiton	88	Ibrazol tab	139	Tavanic
37	Capoten	89	Indral	140	Tavanic Vial
38	Capotril	90	Insulin	141	Teramycin
39	Cedofaxin amp	91	K Viton	142	Theragran
40	Cefopid	92	Kantolock	143	Tramal
41	Cefotax	93	Klaforan	144	TriB amp
42	Cifarol	94	Klosram	145	Unasyn Vial
43	Cilimarin	95	Konakion	146	Ursocol
44	Cipro	96	Konakion tab	147	Ursofalk
45	Cipro vial	97	Kostram	148	Valium syrup
46	Cital	98	Kupect	149	Ventanyl amp
47	Cital tab	99	Lactulose	150	Zantac
48	Claritine	100	Lanoxin	151	Zantac Tab
49	Clixan 20ml	101	Lasix	152	Zestrel
50	Clixan 40ml	102	Legalon tab	153	Zylocain
51	Colimex syrup	103	Levanox	154	Saline for dehydration

Table 25: Drug categories given to inpatients for all reasons of hospitalization

1	Lactulose, Hepamerz & Neomycin
2	Liver Support
3	Vitamins
4	Diuretics
5	Propranolol & Mononitrate
6	Acid Suppressants
7	Antidiabetics
8	Antihypertensives
9	Antispasmodics
10	Vasopressors
11	Analgesics
12	Fluid Replacements
13	Immunosuppressants
14	Antibiotics
15	Others

Table 26: Mean cost of medication per patient for each drug group grouped by reason of hospitalization (values in Egyptian Pounds)

Drug categories	Ascites	Bleeding	Coma	HCC	Others
Lactulose, Hepamerz & Neomycin	22.3	17.5	59.5	7.9	24.7
Liver Support	18.7	7.3	25.3	-	16.5
Vitamins	4.9	3.8	6.9	3	4.7
Diuretics	6.1	1.7*	4.4	6.1	4.4
Propranolol & Mononitrate	0.6	0.3	0.3	-	0.6
Acid Suppressants	18	20.5	21.9	39.8	25
Antidiabetics	16.3	26.2	18	-	93
Antihypertensives	280.1	275.1	282.1	-	165.1
Antispasmodics	2.4	1.4	0.9	-	2.3
Vasopressors	212	578.7**	211.8	22.6	98
Analgesics	3.4	1.7	1.7	3.5	2.2
Fluid Replacements	449.8	74.3	506.7	277	157.9
Immunosuppressants	4.4	7.4	10	5.8	3.8
Antibiotics	246.9	196.4	227.2	241.1	216.8
Others	9.7	7.8	8.4	79.3***	13.1

* Significant when compared to groups: ascites and coma at $p < 0.05$.
** Significant when compared to groups: ascites, coma and others at $p < 0.05$.
*** Significant when compared to all other groups at $p < 0.05$.

Figure 14: Mean medication costs per patient in each drug group grouped by reason of hospitalization (values in Egyptian Pounds)

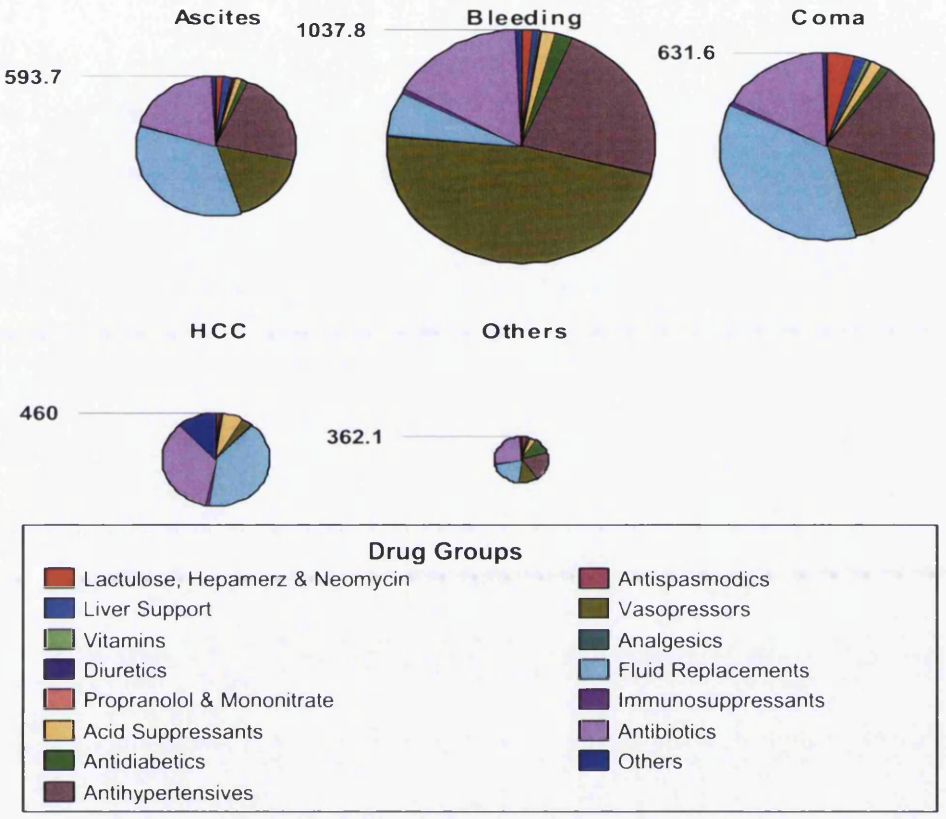


Figure 14 shows the effect of the cost weight of the antibiotics and vasopressors drug categories on the grand total and each drug group total, the antihypertensives and fluid replacements are also emphasized throughout the groups. Figures 14 equally illustrate the weight of each drug category in each patient group, emphasizing the perceptible cost effect of the antihypertensives and the vasopressors drug categories on all but the HCC patient group while the fluid replacement drug category cost is more evident in that group. Figure 15 illustrates also the percentage of each drug category on the total medication costs for each group of inpatients.

Figure 15: Medication costs of inpatients (% of total)

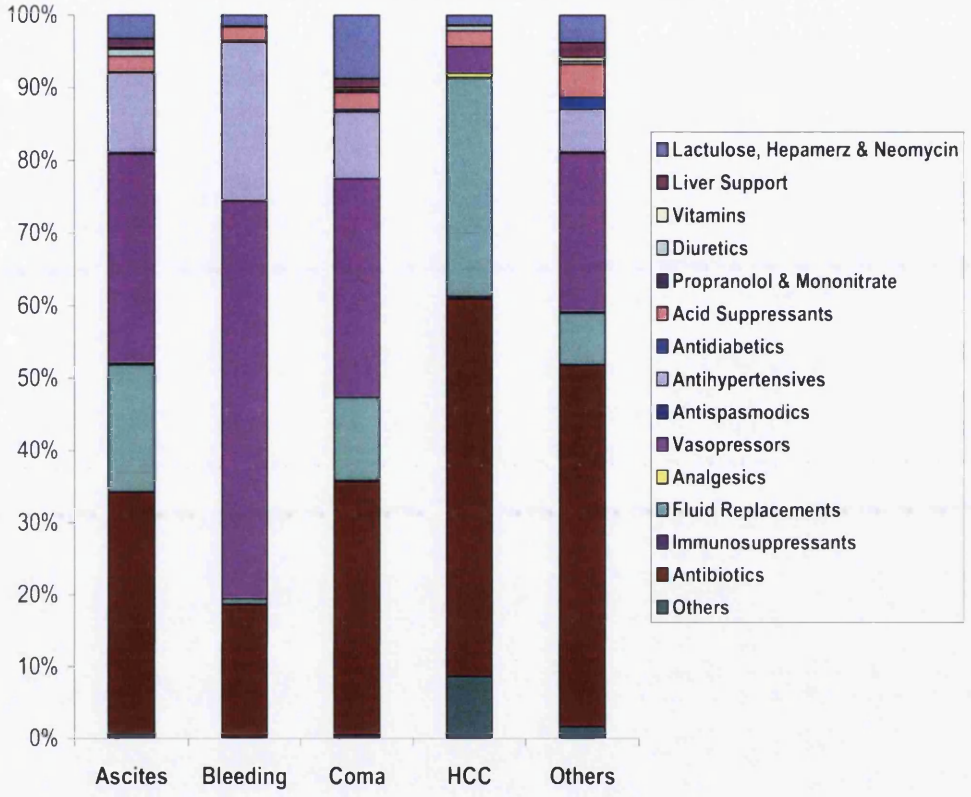


Table 27 shows the means of costs per patient *per day* grouped by reason of hospitalization (values in Egyptian Pounds). It shows the significantly higher values of both the medication (193 LE) and blood costs (52 LE) for the bleeding patients compared to all groups ($p<0.05$). The table also shows the constant value of 263 LE of the constant costs for all groups. It was calculated from hospital records as a value per bed per day.

Finally there was no significant difference in the values of the direct non medication costs throughout the groups with the others group having the highest value of 484 LE per day and the ascites group having the lowest with 88 LE.

Table 27: Means of costs per patient *per day* grouped by reason of hospitalization (Values in Egyptian Pounds)

	Ascites	Bleeding	Coma	HCC	Others
Medication	64	193*	89	61	49
Direct non medication	88	117	126	183	484
Blood	29	52*	20	8	12
Constant	263	263	263	263	263
Total	444	625	498	516	809

- Significant when compared to all other groups

Figure 16 shows the mean total costs per patient *per day* grouped by reason of hospitalization (values in Egyptian Pounds). The mean is high for the others patients' group (809 LE) followed by the bleeding patients' group with 625 LE per day, while the mean becomes low for the coma patients' group (498 LE per day) and lowest for the group of ascites (444 LE).

Figure 16: Means of costs per patient *per day* grouped by reason of hospitalization (Values in Egyptian Pounds)

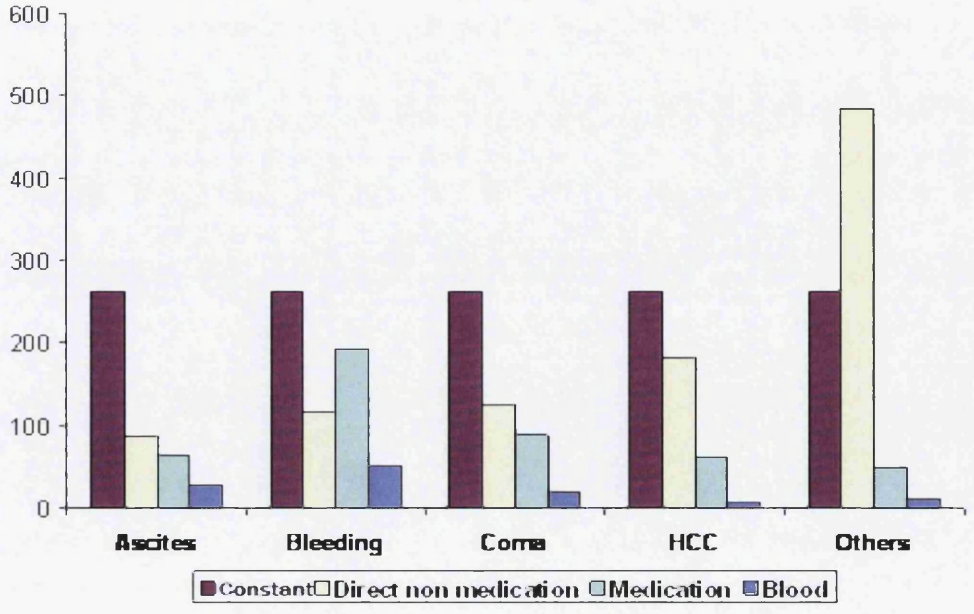


Figure 17: Means of total costs per patient *per day* grouped by reason of hospitalization (Values in Egyptian Pounds)

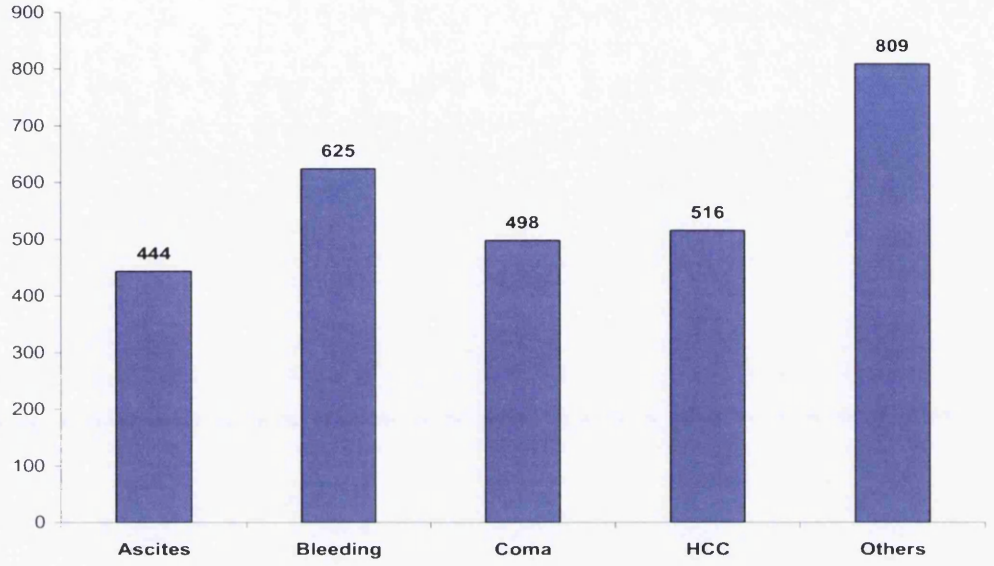


Table 28: Means of costs per patient grouped by reason of hospitalization in private non profit hospital (Values in Egyptian Pounds)

	Ascites	Bleeding	Coma	HCC	Others
Medication	594	1,038	632	460	362
Direct non medication (*the old values have hospital stay included)*	1368	1222	1356	3610	5176
Hospital Stay	690	488	563	638	668
Medical Supervision	1104	780	900	1020	1068
Blood	242	302	117	85	109
Total	3 998	3 829.5	3 567.5	5 812.5	7 382.5

The cost of direct non medication treatment is two and a half times that of the NLI. The cost of consultation is the average of 80LE, 120LE

Table 29: Means of costs per patient *per day* grouped by reason of hospitalization in private non profit hospital (Values in Egyptian Pounds)

	Ascites	Bleeding	Coma	HCC	Others
Medication	64	193	89	61	49
Direct non medication (*the old values have hospital stay included*)	156	214	232	346	948
Hospital Stay	75	75	75	75	75
Medical supervision	120	120	120	120	120
Blood	29	52	20	8	12
Total	444	654	536	610	1 204

The cost of direct non medication treatment is twice that of the NLI. The cost of medical supervision is 120LE. The cost of hospital stay is 75 LE.

Table 30: Breakdown of the means of costs per patient grouped by reason of hospitalization in a private for profit hospital (Values in Egyptian Pounds)

	Ascites	Bleeding	Coma	HCC	Others
Medication	594	1,038	632	460	362
Direct non medication (*the old values have hospital stay included)*	6 840	6 110	6 780	18 050	25 880
Hospital Stay	3 680	2 600	3 000	3 400	3 560
Medical Supervision	2760	1950	2250	2550	2670
Blood	242	302	117	85	109
Total	14 116	12 000	12 779	24 545	32 581

Table 31: Means of costs per patient *per day* grouped by reason of hospitalization in a private for profit hospital (Values in Egyptian Pounds)

	Ascites	Bleeding	Coma	HCC	Others
Medication	64	193	89	61	49
Direct non medication (*the old values have hospital stay included)*	780	1 070	1 160	1 730	4 740
Hospital Stay	400	400	400	400	400
Medical supervision	300	300	300	300	300
Blood	29	52	20	8	12
Total	1 573	2 015	1 969	2 499	5 501

The cost of direct medication treatment is ten times that of the NLI. The cost of medical supervision is 300LE. The cost of hospital stay is 400LE.

6.3. Cost of disease and cost effectiveness of antiviral treatment

6.3.1. Computed cost of disease

The aforementioned calculated data and figures, collected from the NLI, used as backbone model for the study and from the private settings (both for profit and non-profit), used as comparative models for a more comprehensive study, were entered into a Microsoft Excel (Version 2003). Duplicate data entry was performed to ensure quality control. The data was assessed using SPSS according to a computer cohorts of 100 patients constructed based on the Markov models adopted from the literature (D'Amico *et al,* 1986; Arroyo *et al,* 1999 and Wong *et al,* 2000). It is noteworthy to mention that the hepatitis C virus disease costs are incurred constantly over the life cycle of the disease, assuming a twenty year follow-up period. Data analysis was performed with a statistical package for personal computer SPSS (version 9; SPSS, Inc., Chicago, IL) to calculate the cost of each year of the disease for a full cycle. Because the time horizon for development of complications from HCV infection may be twenty years, Markov computer models have been developed to simulate the likely outcomes with a cohort of 100 patients for the three treatment scenarios studied; the

supportive treatment alternative pathway and both antiviral treatment alternatives; the interferon ribavirin combination pathway and the peginterferon ribavirin combination pathway.

The official inflation rate in Egypt is 11.8 % and the mid Central Bank interest rate corridor is 9.75 % (CBE, 2006), incorporating this data with the fact that due to the government regulations and control on the pricing of drugs and medical services, the prices of drugs increased nearly 50 % over the last ten years, lead to the incorporation of a 5 % annual increase over the projected twenty years of the study, this over a twenty year period would lead to an increase of 110 % on any sum spent today. With all considerations of virus developments, inflation and discounting as well as liver transplantation costs were integrated into the final results; estimating the cost of disease, the cost of treatment and the number of lives saved by each of the treatment pathways chosen in each of the three medical settings under study; the National Liver Institute, the private non profit and for profit hospitals.

Processing and calculating the total costs of the disease and the treatment for the one hundred patients over a twenty year period is as follows: In the absence of antiviral treatment, the lifetime *undiscounted* costs of disease via the supportive treatment pathway including the cost of treatment and of complications, particularly decompensated cirrhosis and liver transplantation as computed in this study amounts to: 144 872 LE, 187 373 LE and 339 041 LE per patient in each of the medical settings included; namely the National Liver Institute, the private non-profit and the private for profit hospitals respectively. In the presence of the antiviral treatment, the lifetime *undiscounted* costs of disease via the standard interferon treatment pathway amounts to: 92 155.61 LE, 111 807.58 LE and 196 054.74 LE per patient in each of the medical settings included; namely the National Liver Institute, the private non-

profit and the private for profit hospitals respectively, while the lifetime *undiscounted* costs of disease via the pegylated interferon treatment pathway amounts to: 75 704.6 LE, 89 179.5 LE and 142 573.5 LE per patient in each of the medical settings included; namely the National Liver Institute, the private non-profit and the private for profit hospitals respectively (Table 32).

Table 32: Undiscounted cost of the disease according to the various treatment pathways per patient in 20 years in each of the chosen medical settings

	Pathway	Menoufiya NLI	Private non profit hospital	Private for profit hospital
Cost / patient in 20 years	Supportive treatment	144 872.23 LE	187 373.83 LE	339 041.37 LE
Cost / patient in 20 years	Interferon treatment	92 155.61 LE	111 807.58 LE	196 054.74 LE
Cost / patient in 20 years	Pegylated interferon treatment	75 704.61 LE	89 179.5 LE	142 573.49 LE

Table 33: Total cost of disease and treatment and mortality over 20 years of all one hundred patients according to the various treatment options available in each of the chosen medical settings using SPSS computer software

Pathway	Menoufiya NLI cost	Mortality over 20 years	Private non profit hospital cost	Mortality over 20 years	Private for profit hospital cost	Mortality over 20 years
Supportive treatment	14 487 223 LE	20	18 737 383 LE	20	33 904 137 LE	20
Interferon treatment	9 215 561 LE	10	11 180 758 LE	10	19 605 474 LE	10
Pegylated interferon treatment	7 570 461 LE	6	8 917 950 LE	6	14 257 349 LE	6

Taking into consideration that hepatitis C virus disease cycle extends over a twenty year period and this study considers money expenditure; money spent today is not like

money spent years later so a discount factor of the standard 3% was used as well as inflation and interest rates on the costs was incorporated into the cost calculations using SPSS computer software.

It is important to mention that the above calculated values were undiscounted so the same calculations were repeated after discounting all future costs from the cost of the disease and cost of treatment in the various pathways chosen to further emphasize the effectiveness of one route versus the others and adjust to the long term life cycle of the disease. This was performed by substracting the immediate costs (first year costs) (Tables 34-36) from the total costs of disease and treatment over the 20 years cycle.

Table 34: Total discounted cost of disease and treatment over 20 years of the one hundred patients according to the various treatment options available with its breakdown to the first year immediate costs and all future costs in *the National Liver Institute* using SPSS computer software

Pathway	NLI total 20 year cost (Table 33)	Immediate costs	Future costs	Discounted Future costs values	Totals
Supportive treatment	14 487223 LE	None incurred	14 487 22 LE	8 021 575.38 LE	8 021 575.38 LE
Interferon treatment	9 215 561 LE	960 353 LE	8 255 208 LE	4 570 908.67 LE	5 531 261.67 LE
Pegylated interferon treatment	7 570 461 LE	2 378 140 LE	5 192 321 LE	2 874 988.138LE	5 253 128.14 LE

In the absence of antiviral treatment, the lifetime *discounted* costs of disease via the supportive treatment pathway including the cost of treatment and of complications, particularly decompensated cirrhosis and liver transplantation as computed in this study amounts to: 80 215.8 LE, 103 748.9 LE and 187 727.2 LE per patient in each of the medical settings included; namely the National Liver Institute, the private non-profit and the private for profit hospitals respectively. In the presence of the antiviral

treatment, the lifetime *discounted* costs of disease via the standard interferon treatment pathway amounts to: 55 312.6 LE, 66 696.24 LE and 114 569.7 LE per patient in each of the medical settings included; namely the National Liver Institute, the private non-profit and the private for profit hospitals respectively. While the lifetime *discounted* costs of disease via the pegylated interferon treatment pathway amounts to: 52 531.3 LE, 60 634.46 LE and 91 523 LE per patient in each of the medical settings included; namely the National Liver Institute, the private non-profit and the private for profit hospitals respectively (Tables 34-36).

Table 35: Total discounted cost of disease and treatment over 20 years of the one hundred patients according to the various treatment options available with its breakdown to the first year immediate costs and all future costs in the *Non profit private hospital* using SPSS computer software

Pathway	Non profit private hospital total 20 year cost (Table 33)	Immediate costs	Future costs	Discounted Future costs values	Totals
Supportive treatment	18 737 383 LE	None incurred	18 737 38 LE	10 374 888.97 LE	10 374 888.97 LE
Interferon treatment	11 180 758 LE	1 072 91LE	10 107 85LE	5 596 716.545 LE	6 669 624.545 LE
Pegylated interferon treatment	8 917 950 LE	2 522 02LE	6 395 93 LE	3 541 426.441 LE	6 063 446.441 LE

Not only is the pegylated interferon combination antiviral therapy route for hepatitis C by far the cheapest alternative in terms of total lifetime disease discounted costs for patients admitted in the three medical settings included in the study when compared with both the supportive treatment and the standard interferon treatment pathways (Tables 35 - 37), it also saves more lives as compared to the other alternatives. Only 6 lives are lost in the pegylated interferon route while 20 lives are lost in the supportive treatment route and 10 in the interferon treatment pathway alternative (Table 34).

Then comes the interferon treatment pathway alternative in terms of total lifetime disease discounted costs when compared to the supportive treatment pathway alternative in all three medical settings.

Table 36: Total discounted cost of disease and treatment over 20 years of the one hundred patients according to the various treatment options available with its breakdown to the first year immediate costs and all future costs in the *private for profit hospital* using SPSS computer software

Pathway	Private hospital total 20 year cost (Table 33)	Immediate costs	Future costs	Discounted Future costs values	Totals
Supportive treatment	33 904 137 LE	None incurred	33 904 137 LE	18 772 720.66 LE	18 772 720.66 LE
Interferon treatment	19 605 474 LE	1 347 578 LE	18 257 896 LE	10 109 397.02 LE	11 456 975.02 LE
Pegylated interferon treatment	14 257 349 LE	2 818 740 LE	11 438 609 LE	6 333 557.803 LE	9 152 297.803 LE

Both the undiscounted and discounted cost effectiveness computed figures and values in this study strengthen the previous undiscounted cost of disease data in general, they show that the antiviral treatment is a better choice in terms of numbers of lives saved (table 39) and in terms of cost in the long run along with cost effectiveness values (table 36-41). The number of lives saved by each treatment alternative is a key factor in the cost effectiveness calculation, it is considered as the effectiveness endpoint of the interventions (treatment options) under study. It was estimated from the Markov models for each alternative allowing for the very pertiment fact that the 5 years survival rate of the decompensated patients is 30-40% (60-70% 5 year mortality) (D'Amico *et al,* 1986 and Arroyo *et al,* 1999). The following calculated cost effectiveness values, first, emphasized the pegylated interferon combination antiviral therapy treatment alternative for hepatitis C as the cheapest alternative in terms of

total lifetime disease discounted costs for patients admitted in the three medical settings included in the study against the other alternatives available, and second, shedded more light on the effectiveness of this treatment pathway of choice when compared with both the supportive treatment and the standard interferon treatment pathways. This was put into view via the negative values displayed for the antiviral standard interferon and ribavirin combination treatment pathway versus the supportive treatment pathway in all three medical settings, the same goes for the case of the antiviral pegylated interferon and ribavirin combination treatment pathway versus the standard interferon and ribavirin combination treatment pathway. Finally the negative values of cost effectiveness of the antiviral pegylated interferon and ribavirin combination treatment pathway against the supportive treatment pathway option was also hightlighted in all three medical settings namely: the National Liver Institute, the non-profit private hospital and the for profit private hospital settings.

Table 37: Comparative values of number of lives saved per treatment pathway in the three chosen medical settings

Number of lives saved / Treatment pathway	Menoufiya NLI	Private non profit hospital	Private for profit hospital
Supportive treatment	20	20	20
Interferon treatment	10	10	10
Pegylated interferon treatment	6	6	6

Table 38: Cost effectiveness of the total undiscounted cost values in *the National Liver Institute* according to the constructed Markov model of the 100 patients' computer cohort

Pathway	NLI total 20 year cost (Table 33)	Deaths/ 100 pts	Cost comparison	Lives saved/ 100 pts	C/E ratio (cost / life saved)
Supportive treatment	14 487 223 LE	20			
Interferon / Supportive	9 215 561 LE	10	-5 271 662 LE	10	<0
Pegylated interferon / Supportive	7 570 461 LE	6	-6 916 762 LE	14	<0
Pegylated interferon / Interferon			-1 645 100 LE	4	<0

Table 39: Cost effectiveness of the total discounted cost values in *the National Liver Institute* according to the constructed Markov model of the 100 patients' computer cohort

Pathway	NLI total 20 year cost (Table 34)	Deaths/ 100 pts	Cost comparison	Lives saved/ 100 pts	C/E ratio (cost / life saved)
Supportive treatment	8 021 575.375 LE	20			
Interferon / Supportive	5 531 261.67 LE	10	-2 490 313.705 LE	10	<0
Pegylated interferon / Supportive	5 253 128.138 LE	6	-2 768 447.237 LE	14	<0
Pegylated interferon / Interferon			-278 133.532 LE	4	<0

Table 40: Cost effectiveness of the total undiscounted cost values in the *Non profit private hospital* according to the constructed Markov model of the 100 patients' computer cohort

Pathway	Non profit private hospital total 20 year cost (Table 33)	Deaths/ 100 pts	Cost comparison	Lives saved/ 100 pts	C/E ratio (cost / life saved)
Supportive treatment	18 7373 83 LE	20			
Interferon / Supportive	11 180 758 LE	10	-7 556 625 LE	10	<0
Pegylated interferon / Supportive	8 917 950 LE	6	-9 819 433 LE	14	<0
Pegylated interferon / Interferon			2 262 808 LE	4	<0

Table 41: Cost effectiveness of the total discounted cost values in the *Non profit private hospital* according to the constructed Markov model of the 100 patients' computer cohort

Pathway	Non profit private hospital total 20 year cost (Table 35)	Deaths/ 100 pts	Cost comparison	Lives saved/ 100 pts	C/E ratio (cost / life saved)
Supportive treatment	10 374 888.97 LE	20			
Interferon / Supportive	6 669 624.545 LE	10	-3 705 264.425 LE	10	<0
Pegylated interferon / Supportive	6 063 446.441 LE	6	-4 311 442.529 LE	14	<0
Pegylated interferon / Interferon			-606 178.104 LE	4	<0

Table 42: Cost effectiveness of the total undiscounted cost values in the private *for profit hospital* according to the constructed Markov model of the 100 patients' computer cohort

Pathway	Private hospital total 20 year cost (Table 33)	Deaths/ 100 pts	Cost comparison	Lives saved/ 100 pts	C/E ratio (cost / life saved)
Supportive treatment	33 904 137 LE	20			
Interferon / Supportive	19 605 474 LE	10	-14 298 663 LE	10	<0
Pegylated interferon / Supportive	14 257 349 LE	6	-19 646 788 LE	14	<0
Pegylated interferon / Interferon			-5 348 125 LE	4	<0

Table 43: Cost effectiveness of the total discounted cost values in the private *for profit hospital* according to the constructed Markov model of the 100 patients' computer cohort

Pathway	Private hospital total 20 year cost (Table 36)	Deaths/ 100 pts	Cost comparison	Lives saved/ 100 pts	C/E ratio (cost / life saved)
Supportive treatment	18 772 720.66 LE	20			
Interferon / Supportive	11 456 975.02 LE	10	-7 315 745.64 LE	10	<0
Pegylated interferon / Supportive	9 152 297.803 LE	6	-9 620 422.857 LE	14	<0
Pegylated interferon / Interferon			-2 304 677.217 LE	4	<0

Table 44: The comparative constructed Markov model over 20 years of the 100 patients' computer cohort according to the various treatment options available in each of the chosen medical settings

Standard INF			Peg INF			Supportive ttt	
R	NR		R	NR	Comp		Decomp
35	65		60	40	60		40
	3 months only			3 months only			
Comp 70%		Decomp 30%	Comp 70%		Decomp 30%		
45		20	28		12		
Comp for 15 years				Comp for 15 years		Comp for 15 years	
Comp 5 years		Decomp 5 years	Comp 5 years		Decomp 5 years	Comp 5 years	Decomp 5 years
		LTx			LTx		LTx
		6			4		13

R: response NR: no response LTx: liver transplantation ttt: Treatment Comp: Compensated decomp: Decompensated

Chapter 7

Discussion

Contents of Chapter

7.1. Introduction

This study documents the feasibility of health technology assessment and health economic techniques within the Egyptian healthcare system. The importance of economic research is explicitly emphasized in the course of this study for both the welfare of Egyptian patients, for the healthcare budget and for the society at large.

The antiviral treatments' options for hepatitis C virus (HCV) and their outcomes' data for the full twenty year cycle of the disease were investigated. Their costs, their effectiveness and cost effectiveness were also measured. The outcomes of the supportive treatment (no treatment) option were also documented and their costs assessed; including cost of hospitalization, physician fees, hospital charges and hospitalization days. This was done principally in the Menoufiya National Liver Institute (NLI), the largest liver tertiary referral centre in the Middle East. The resultant data of the NLI was then compared with two other private institutions; the first a non profit private hospital and the second a for profit institution.

The study revealed that the cost of pegylated interferon combination therapy for NLI patients over the full cycle of the disease was the most cost effective alternative amounting to 75 704.61LE per patient versus 92 155.61LE and 144 872.23LE for the standard interferon and the supportive treatment (no treatment) pathways respectively and thus the cost effectiveness values of the pegylated interferon alternative were negative compared to the other pathways. The same results were found to be true for patients attending private for profit and non profit medical settings. Thus the early intervention with pegylated interferon treatment proved to be the most appropriate route from a social aspect, the cheapest alternative to the healthcare budget and consequently the best choice

to aspiring policy makers and healthcare reformers. This was different than the initial predictions of this study, since the supportive treatment option was seemingly a lot cheaper than the much more expensive antiviral option.

This Egyptian study thus adds to the growing international recognition that the HTA process must be scientifically sound, consistent across applications, transparent and of practical use in both policy-making and health-care practice (Jonnson, 2002 and Zentner *et al,* 2005). Further, more countries are placing greater emphasis on ensuring that the results of HTA are considered in key decision-making processes (Sorenson *et al,* 2008).

7.2. Importance of technology health assessment

In Europe, HTA provides important benefits by empowering governments to make value-driven decisions, supporting innovation and providing patients and physicians with the information for making the best treatment choices (Sorenson *et al,* 2008). In Egypt, governments are still unaware of the benefits of such a tool, and this study was an opportunity to emphasize the importance of HTA to the Egyptian clinicians and policy and decision makers through a high impact example such as HCV treatment alternatives assessment.

Countries employ a wide array of approaches to control the costs of health technology and support the optimal use of new treatments and HTA has assumed an increasing role in national priority-setting, decision making and health-policy processes. In recent years, various European States have developed systems to evaluate innovations and treatments determining their relative value for investment and mechanisms for equitable and accessible treatment provision (Sorenson *et al,* 2008). Alternatively, this assessment is

the first to be used in Egypt for optimal treatment support with no official system determining values for treatment provision accessibility.

Sorenson, Drummond and Kanavos (2008) thought that decision-makers are more likely to utilize HTA if there are established policy instruments (e.g. reports, practice guidelines) and commitments to use them effectively. Furthermore, they thought that patient demand and the cost effectiveness of a technology can change so it is important to review HTA recommendations on a consistent basis (Sorenson *et al,* 2008). This is thought to be also true for Egypt and would thus require greater participation and collaboration among stakeholders particularly HTA personnel, government officials, the industry, health providers and patients. Without adequate input and understanding of the HTA process, stakeholders may mistrust the evidence and subsequent recommendations.

Moreover, HTA's effectiveness rests on accurate assessments and the appropriate implementation and use of subsequent recommendations. HTA can encourage a particular treatment if assessments of that treatment alternative are performed properly and consider a wide range of long term associated costs and benefits rather than focusing solely on short term costs. This study showed that, HCV pegylated interferon combination therapy long term costs and benefit were far less costly than the seemingly short term cheaper alternatives.

However, HTA's value in encouraging innovation and value-added healthcare also depends on the assessment process; including when and how the review was performed and the resulting decision-making procedures (Busse *et al*, 2002; Anell, 2004; Zentner *et al*, 2005 and Drummond, 2006).

This health technology assessment of HCV treatment alternatives is among the first of such assessments to the author's knowledge to be performed in Egypt. This Egyptian HTA typically entailed: 1) identifying the policy question; what is the best treatment option for HCV in Egypt? 2) systematic retrieval of scientific and non-scientific evidence, and analysis, from the NLI and the other chosen medical settings and 3) appraisal of evidence, including judgments regarding the meaning of the evidence and its applications to inform the decision-making process (Sorenson *et al,* 2008).

The scope of this study was wide enough to encompass many issues of interest surrounding the methodology itself and the HCV as a subject of study. The assessment phase included the systemic review of evidence, which was then followed by the economic evaluation. The study ended with an appraisal and an interpretation of the outputs of the assessment.

7.2.1. Policy implications

Economic evaluation's and HTA's role and usefulness in the future depend on how they were developed as practical aids to decision-making (Gilbody and Petticrew, 1999). Economic evaluation should be used as an "aid to thought"; through the systemic collection of evidence and classification of choices, it offers a powerful tool to the organization of evidence and rational decision making (Gilbody and Petticrew, 1999). Australia, Canada, Finland, New Zealand, Norway and others have made submission of economic evaluations an official mandatory requirement for placement of medication on their national formulary (Hoffman and Graf von der Schulenburg, 2000), then Denmark and France have started to encourage such submissions (Hoffman and Graf von der Schulenburg, 2000). The National Institute for Health and Clinical Excellence (NICE) of

the UK expects companies to submit a dossier of evidence of clinical and cost effectiveness relating to the product, the treatment or the particular technology when an assessment is being undertaken.

Clearly, evidence from economic evaluation is just one input contributing to a complex decision making process. For HTA to be of optimal benefit, the assessment process needs to be linked with innovation and other aspects of policy-making, recognizing the complexities of decision-making that require consideration of subjective and normative concerns. Without these links, HTA may have limited power to inform the policy process and facilitate access to new and effective treatments (Sorenson *et al,* 2008). This is particularly true for healthcare decision-makers in the Egyptian Ministry of Health and Population.

However, some impediments to HTA's optimal benefit and use in Egypt, as deduced from this research, include "communication" between health economists and decision-makers, as well as clinical imperatives, availability of data or rather unavailability of data and appropriate management systems and finally, the lack of knowledge and expertise in economic evaluation.

The lack of expertise and knowledge in economic evaluation and HTA shades all sectors of the healthcare system in Egypt; including clinicians, policy makers, health workers and medical institution managers, as well as the scarcity of trained health economists. The appropriate management systems include the decision making system itself where decisions are often made quickly mostly to serve political imperatives. The lack of data was also a key issue as there is often insufficient well structured evidenced-based data available on which to build the evaluation.

Finally, the ever present strife between clinicians and healthcare personnel on one hand and health economists on the other, is also emphasized when it comes to evaluating clinical outcomes and health expenditures, considering that effective implementation of HTA requires the involvement of key stakeholders. A recent OECD study found stakeholder acceptance to be one of the key determinants of whether decisions are actually put into practice within health systems (OECD, 2005). Those are all assumptions based on problems met in the course of this research and the survey of historical reviews and papers concerned with implementation and application of health economics in other countries (Ross, 1995 and Sorenson *et al,* 2008).

Economics and health assessment will only be used to any great extent in healthcare when efficiency becomes a key day to day objective of healthcare services. Mooney, (1999) reported that the average doctor frequently has little incentive to try to pursue efficiency and this is believed to be true for the average doctor in Egypt as well. Mooney also adds that the lead has to come from the top, especially from politicians prepared to be answerable to their electorate for the sensible stewardship of healthcare funds and not to the emotionalism that so often surrounds healthcare decision-making at the political level (Mooney, 1999). Moreover, Berg *et al,* (2004) suggest that the lack of integration between HTA evidence and guideline development may be attributable to a number of factors including a disconnect between the requirements of clinical practice and data generated by HTA and the medical profession's aversion to combining economics and health (Berg *et al*, 2004). What is rather depressing in Egypt is the relatively poor quality of some of the strategic decision-making that emanates from the Ministry of Health and Population and its departments. Policy-makers as they are everywhere, although they

seek to save the public's interest have one severe restriction to overcome: their positions (Gyldmark and Morrisson, 1993; Mueller, 1997 and Sauerland, 1999).

That means if research comes up with results in policy advising, that are scientifically reasonable but politically unpopular, there is a great chance that those suggestions will not be implemented. Politicians often look for short-term solutions (that come up with short-term benefits and long-term costs) rather than performing real reform projects (that will have high costs in the short-term and positive effects only in the long run) (Sauerland, 1999), and this is typically the case of HCV management in Egypt. Obviously, we have to look for institutions that provide politicians with incentives to look for long term policies (Buchanan, 1993).

7.2.2. Cost effectiveness as an assessment tool

Cost effectiveness or cost-utility analyses are most often considered appropriate analytical designs, particularly when the proposed product has significant clinical advantages over the comparator and relative benefits need to be considered against costs (Sorenson *et al,* 2008).

The cost effectiveness method was used in this research project because of the measurable health benefits and measurable cure via the blood viral load. The cost is also measurable in monetary form. It was also used because it is an assessment tool for efficiency (Williams, 1974) and it involves the same disease, same outcome and same area of medicine. Ultimately, there were no norms or benchmarks needed for this study due to the negative values for the effectiveness of the treatment with pegylated interferon option, a surprise to all.

The study approach was direct and repetitive throughout and the extrapolation of events over time and the health outcomes follows literature, as well as all criteria of generalizability, transferability, accessibility and quality was there in the analysis (Maxwell, 1984), which made the sensitivity of analysis not needed.

7.3. Hepatitis C virus as a case study for economic evaluation

The high prevalence of HCV and its expensive long term repercussions have prioritized the need for informed policy-makers, not only for allocating sufficient resources to cover the treatment costs for those most in need but also for selecting those best able to benefit, and selecting and adopting the treatment of choice according to standardized methodologies. Furthermore, the urgency also arises due to the fact that HCV is frequently asymptomatic until liver cirrhosis develops, at which time treatment is less effective and not always successful and thus creating a huge health burden as Wong and co-workers reported (Wong *et al,* 2000). This was also found to be true in Egypt in addition to the decreased effectiveness of the antiviral treatment on the Egyptian strain of the virus (type IV) in comparison to strain types I II and III (Waked *et al,* 1995 and Strickland, 2006). Despite HCV latency, given prevalence ranging from 0.1% to 5% in different countries worldwide and the staggering 15-20% in Egypt (Angelico *et al*, 1997; Frank *et al*, 2000 and Rao *et al*, 2002). Chronic HCV infection has become the leading cause of chronic liver disease and liver transplantation, and has also led to rising rates of hepatocellular carcinoma in Egypt (Hassan *et al,* 2001 and 2002 and Ezzat *et al*, 2005).

Adding to the high cost of treatment, the cost of the long term effects of untreated patients, makes hepatitis C virus a perfect example both to emphasize the importance of

economic evaluation and to enhance the efficiency of the financial resources of healthcare.

7.3.1. Public health and individual implications

In a molecular evolutionary analysis of the HCV genetics, Tanaka and his co workers traced the Japanese HCV epidemic back to the 1930-40s and traced the US epidemic to the late 1960s, while the Egyptian epidemic was traced to the mass parenteral anti-schistosomal therapy in the 60s (Tanaka *et al,* 2002). These analyses suggest that the HCV epidemic in the US and Egypt may be twenty to thirty years behind that in Japan, and thus HCC morbidity and mortality may rise. Supporting this hypothesis, El-Serag and Masson found a rising HCC incidence within the US-based Surveillance, Epidemiology, and End Results (SEER) database over the past two decades with a progressive shift to younger individuals (El-Serag and Masson, 1999). Because of the high prevalence of infections with HCV in Egypt, it has become the greatest risk factor for HCC (Hassan *et al,* 2001 and Ezzat *et al*, 2005). Similarly to what is happening in the United States prevalence of HCC is increasing in Egypt as well, along with its increasing association with HCV (Hassan *et al,* 2001 and Ezzat *et al*, 2005). HCC is now one of the three most frequently diagnosed cancers in Egypt as reported by Abdel-Wahab *et al,* (2000) and by the National Cancer Institute (NCI) age adjusted death rate data (Abdel-Wahab *et al,* 2000).

Despite the decline in HCV incidence in the late 1980s, projections by the US Centre for Disease Control and Prevention suggest that the number of patients infected with HCV in the coming decade will continue to increase, perhaps quadrupling from 750 000 in 1990 to 3 million in 2015, because of the high incidence in the 1970s and early 1980s and the

persistent HCV latency (Armstrong *et al*, 2000 and Kim *et al*, 2002). Numerous mathematical predictive and Markov models project that annual HCV related mortality may double or triple over the next 10-20 years for France, Switzerland, Canada, Australia and the US (Deuffic *et al*, 1999; Wong *et al,* 2000; Zou *et al*, 2000; Hepatitis C Australian council, 2002; Sagmeister *et al,* 2002 and Davis *et al,* 2003). An analysis comparing the HCV and HIV epidemics in France suggests that HIV mortality is likely to be falling while that from HCV infection will likely rise to exceed that from HIV infection (Deuffic-Burban *et al,* 2004). There is no study to the author's knowledge that predicts the HCV-related mortality and the direction of the HCV epidemic in Egypt.

7.4. Hindrances and obstacles

In finding the evidence, in converting the search question into a strategy and in identifying the sources of evidence many hindrances were encountered by the researcher. The first obstacle was met with at the start of the fieldwork; as much as the clinical expert opinions were important in shaping the course of this study, the political experts were very ungenerous with their knowledge due to the very sensitive political impact of HCV treatment in Egypt. The Minister of Health and Population, at the time, even advised towards the abortion of the project.

The second limitation was related to the secondary sources of information in the Egyptian healthcare system and the unavailability and accessibility of reviews relating to the treatment and the prevalence data in Egypt. However a comprehensive search of all relevant studies that were both consistent clinically and statistically was still performed via a strenuous effort to locate original reports by means of hand searching, reference lists and expert data.

A major obstacle in this study was met within the period of preparation of the economic evaluation, when it was discovered that no historical data was available in the medical institutions visited. No information was kept, especially for outpatients, no records about the prescriptions, the tests performed, nor was there even a written protocol of treatment followed, just an unwritten oral know-how passed on from one clinician to the other. This fact necessitated a personal interview with patients and the physical presence of the researcher during the routine clinical examination process. This hindrance was compounded in the private sector fieldwork phase, as no private clinic would allow an external researcher to be present during the medical examination and compromise its reputation and the privacy of its patients. This problem was solved in using the NLI as backbone of data and reference benchmark to the research.

A permit was granted from the NLI, after the studying of the research protocol to allow the researcher access to its outpatient clinics and inpatient wards as well as its accountancy classified records. This permit was a rebirth to the study and an acknowledgment to its important objectives. The fact that NLI was a university hospital made the researcher presence around the patient totally acceptable and in many cases patients were happy to help and very generous with their time and in sharing their experience.

To help formulate clear and equitable decisions, economic evaluation of healthcare interventions must be based on good quality information. Ideally, good quality data should be available on the importance of the topic, the effects (effectiveness and safety) of interventions that are available either at present or in the future and, naturally, on the economic consequences of their adoption. Unfortunately, good quality, multi-

dimensional information is seldom available in an easily accessible format particularly in Egypt. Economic evaluation is sometimes based on either incomplete data or partial already-available data (Sauerland, 1999) and this study practically showcased this fact not only regarding all the missing information about HCV and its economic implications in Egypt but also regarding the entire missing data infrastructure that would contain such information.

A major stumbling block in the course of this study was the international classification of cost sectors' inadaptability in the research. The indirect costs components could not be measured, calculated or reached in the course of this analysis for neither the public NLI setting nor the private settings. NLI actually lacked the data and the private settings would not impart with such classified financial information. A research inherent constant cost component was thus introduced to cover both part of the internationally known indirect cost and the government subsidy to healthcare in its public institutions.

Other hindrances met were more personal than so far mentioned. The stretched distances and locations of the research; Menoufiya, Cairo and Swansea were also taxing and time consuming but the exposure was very enriching towards the end result.

The lack of relation to a structured research body, government or research centre in Egypt; to support through clinical and academic problems and to guide through a standardized format of trouble shooting was also problematic. This turned out to be a positive aspect though in appraising the evidence and relevance of the data and the results. This was because there was no conflict of role in question or bias towards any end result in particular. The facts that all stages of the investigation were valid and open

to external scrutiny, that patients were randomly included and blinded as well as P values calculated were a standpoint that added strength to the final results.

7.5. Results and their implication

The results reached were important in terms of both their individual values and their collective ones in that they represented unbiased data from randomized blinded patients. They quantify the cost of treatment of hepatitis C virus patients and the cost of the disease for the first time in Egypt.

The quantitative products of the results are also crucial in showing the prescription patterns for the patients with inclusion of significance measures.

7.5.1. Outpatient Data

I- Cost of outpatients prescribed supportive treatment in Egypt

The cost evaluation of the supportive treatment was not an easy process, it started with visiting many of Egypt's prominent clinicians, private centres and hospitals both private and public. The lack of any sort of records and the lack of a standard written treatment protocol and prescription format was a great obstacle in knowing factually what was being done and to what extend was it repeated. Even though the NLI in Menoufiya was no different in the sense that no written protocols were mandated and no records kept, the high HCV patient traffic made the reaching of the information feasible yet strenuous. Each patient visiting the clinics was examined, his or her condition and the drugs prescribed recorded. The handling and computing of the data was then performed and the pattern deduced and proven. This was the stage where the cost of the drugs prescribed was calculated per unit per patient then collectively per group per patient condition. The same was done for all other direct non medication procedures costs. The results showed

the patterns followed, and ultimately the efficiency of the unwritten treatment protocols from a medical point of view. The numbers reached should be looked at closely by healthcare policy and decision makers to increase effective delivery of appropriate healthcare and expenditure decisions in Egypt.

The data of outpatients with positive HCV showed that the decompensated patient yearly medication cost values are expectedly and significantly higher at 1 675 LE than the 1 306 LE of the compensated group at $p<0.05$. These two figures are constant throughout the three chosen medical settings due to mandatory drug pricing policies by the Egyptian Ministry of Health and Population. The numbers of mean total cost of treatment in the result section (2 246 LE, 2 448 LE and 4 056 LE per year per compensated patient treated in the NLI private non profit and private for profit institutions) show that the cost of the quality medical service provided in the medical private sector far outweighs (nearly double) the cost of treatment, taking into consideration that the consultation fees in the NLI and the private non profit hospital clinics are 5 LE and 30 LE respectively which jumps to a staggering 200 LE per visit in the private for profit setting. Therefore, a revised rational prescription policy would only have a great impact on the mean total cost in the former two settings while it would not greatly affect the mean total cost of treatment in the latter setting.

The breakdown of the means of annual medication costs per patient per year grouped by severity of liver cirrhosis shows the significantly higher value of liver support and acid suppressants drug categories on the weight of the total medication cost (38.73 % - 26.61% respectively) for the compensated drug group versus (51.48 % - 10.55 % respectively) for the decompensated patient group. However, diuretics drug category cost

percentage reaches 13.28% of the total amount for decompensated cirrhosis cases spent while it barely exceeds 2 % for compensated cirrhosis patients. Vitamins drug categories on the other hand collects nearly 5 % of the cost of drugs for both types of patients but have no real treatment value to the patient and can be easily removed from prescriptions and thus decreasing costs of medication by that 5%. This and other similar calculations will lead to the improvement of prescribing policies, to the increased awareness of physicians to this evidence based data to promote the decrease in the cost of medications for outpatients of HCV and the decreased treatment burden of HCV patients in both non profit and public hospital and thus maximizing the economic efficiency of resources used.

A prescription audit data body for assessing drug trends and compiling annual spending on prescriptions must be made available in order to accomplish a satisfactory informative system and consequently better future studies.

The lack of proper breakdown of expenditures leads to a discrepancy in usage of standardized and internationally recognized cost nomenclature and ultimately in resource allocation. This issue was addressed in this study by the usage of direct and constant costs of HCV and its treatment instead of direct and indirect costs (*constant costing directly relates to the subsidized cost incurred by HCV throughout its cycle as shown in the Markov model adopted*).

The constant costs as defined in this study are the costs paid by the NLI as an overhead calculated from the hospital classified budget as 35 LE per outpatient per visit and those figures could be in a way considered as the subsidized cost sponsored by the Egyptian Ministry of Health and Population for each patient admitted to the hospital along with the

cost of the medication prescribed to each; this constant cost amounts to 18.7% and 16% (compensated and decompensated patient groups respectively) from the mean annual cost per patient per year grouped by severity of liver cirrhosis. These subsidized costs could be greatly reduced if the patients visit the hospital fewer times, meaning every two or three months to perform the testing needed since the most frequent test is a quarterly one, instead of the monthly visit routine adopted. This would mean providing the patients with quarterly prescriptions thus lessening the burden in terms of clinic admittance and constant cost. Furthermore, it might have a positive effect on patients' moral and that of their families, to decrease frequency of hospital visits. The costs decrease would amount to 14.2% if patients visit the hospital every three months (quarterly) for prescription filling, laboratory testing and ultrasound, provided that prescription's refills are for the full three months period. It should be mentioned that the patients are not only examined in hospital's outpatient clinics for disease progression but they are given their medication as well under the rules of the national healthcare system in Egypt.

In conclusion, to decrease the mean annual cost of supportive treatment for HCV patients, it is worthwhile for the governmental and non governmental medical institutions to reconsider the prescribing policies or write up a prescribing protocol to reduce waste of economic resources on drugs of no medical value to the patient. In addition, the government and any medical care payer body or institution, should also reconsider or design the protocols of treatment with lesser physician consultation frequencies to cut off a major chunk of direct non medication costs incurred by such patients' visits, this should be done after studying the cost effectiveness of the effect of such visits on patients morale, and psychological health state.

II- Outcome and costs of anti-viral treatment

All randomized controlled drug trials have focused on short-term outcomes such as normalization of transaminases, improved liver histology or treatment-induced viral negativity. Peginterferon plus ribavirin yield sustained viral negative responses (persistent loss of viraemia six months after discontinuation of antiviral treatment) in 45% - 61% of patients (Manns *et al,* 2001 and Fried *et al,* 2002). Response rates are higher in patients who are younger, have genotype II or III (as high as 88%), and those without bridging fibrosis or cirrhosis (as high as 61%) (Manns *et al,* 2001 and Fried *et al,* 2002). Likewise in NLI trials, the effectiveness of viral treatment neared 60% (54%) in the peginterferon plus ribavirin combination case in genotype IV while it was only 35% in case of interferon plus ribavirin (this according to the unpublished data of the NLI).

The cost effectiveness ratio of the anti-viral treatment option in relation to the supportive alternative was negative in value in addition to the lives saved via the antiviral treatment; therefore, the use of antiviral treatment was good to both healthcare budget and to the patient's welfare. Randomized drug trials demonstrated that sustained viral responses result in improved survival and decreased liver complications though long-term follow-up of patients are lacking. Despite some controversy and some negative results (Harper and Dienstag, 1996; Koretz, 1996 and Poynard and Opolon, 1998) increasing numbers of non-randomized clinical studies suggest that viral eradication improves liver histology, decreases the risk for HCC or cirrhosis and decompensation and perhaps improves survival (Kuwana *et al,* 1997; Schalm *et al,* 1997; Benvegnu *et al,* 1998; Niederau *et al,* 1998; and Serfaty *et al,* 1998). Treatment-induced viral eradication also restores impaired QOL measures in those with chronic HCV infection (Foster *et al,* 1998; Bonkovsky and

Woolley, 1999; Foster, 1999; Ware *et al,* 1999 and Hassoun *et al,* 2002). One recent study suggests that, even in the absence of viral eradication, antiviral treatment improves QOL as measured with the Medical Outcomes Study 36-items Short Form survey instrument (SF-36) (Wright *et al,* 2005). Similarly, even in the absence of viral eradication, a study suggests that treatment may decrease the rate of fibrosis progression (Sobesky *et al*, 1999), perhaps forestalling the development of advanced liver disease and permitting the development of further therapeutic advances. Other studies suggest that treatment-induced normalization of transaminases in the absence of viral eradication may decrease the future risk of HCC (Imai *et al,* 1998; Ikeda *et al,* 1999; Yoshida *et al,* 1999 and Shiratori *et al,* 2005).

A well informed evidence-based account submitted to healthcare officials and policy makers enhances their ability in the decision making process and strengthens their perception regarding the importance of pharmacoeconomics as a tool of efficiency and effective resource allocation to the various alternatives, thus improving overall societal healthcare benefits. In this case study, a well informed evidence-based account leads to the saving of costs of treatments of complications and enhancing the recourses utilized by HCV patients according to data discussed later.

A- Costs of standard interferon anti-viral treatment

This study was designed as an attempt to answer some of the questions that physicians need to address and patients need to consider and decision and policy makers need to confront when undertaking treatment of HCV infection. It was also performed to highlight any other additional issues that need be addressed, amended and/or altered when undertaking treatment decisions regarding HCV.

Cost estimates used in pharmacoeconomic analyses for standard interferon treatment in Egypt 45 LE (AWP) assuming full dose and compliance, the AWP of 52 weeks of ribavirin 1200 mg daily for patients <75kg, and 3 million units of interferon three times a week, is 13 050 LE (2006 values). When considering monitoring costs, follow-up and average wholesale drug costs in Egypt, in the various medical institutions chosen (2006 values), estimates ranged from 15 890 LE to 21 150 LE in the NLI and the private for profit hospital respectively for 48 weeks of ribavirin and interferon administered as above. Comparatively interferon treatment in the US have ranged from $US 2300 AWP to $US 2150 AWP to $US 2511 including drug-induced costs for six months and $US 3800 AWP for 12 months (Bennett *et al,* 1997 and Kim *et al,* 1997) (1$ US converts to nearly 5.1 LE). An Australian publication estimated the net cost of six months of interferon treatment (treatment costs minus conventional management) to be $US 1098 (based on the Australian healthcare system price using the same conversion rate) (Shiell *et al*, 1994). In a US veterans Administration study, ribavirin and interferon pharmacy costs alone were reported to be $US 5100 and $US 10 200 for 24 and 48 weeks (Inadomi and Sonnenberg, 1999).

Antiviral treatment for genotype IV in Egypt is usually for 48 weeks. An evaluation for viral response typically occurs at week twelve, and those who are viral positive with a less than 2-log drop in viral load may discontinue therapy because the likelihood of a sustained viral response is low (Davis, 2002). Subsequent analyses of viral monitoring during therapy suggests that antiviral therapy should be discontinued among patients not becoming viral negative or not achieving a 2-log viral load drop by week twelve (Davis *et al,* 2003). With this stopping rule, the implementation of a twelve week evaluation of

treatment response lowered antiviral drug costs compared with full dose treatment for 48 weeks.

B- Cost range of cured patients using standard interferon in various medical institutions

The estimated costs' range for standard interferon treatment combination therapy was 99 880 LE and 132 942.85 LE (2006 values) for 48 weeks of combination therapy administered as above depending on weight for the NLI and the private for profit hospital respectively, when accounting for the cost per cured patient according to the 15.9 % cure rate and when accounting for discontinuation of therapy for twelve week non-responders and when combining actual dosages received after adjusting for drug discontinuation, but adding office visits, and laboratory tests.

C- Cost range of cured patients using pegylated interferon in various medical institutions

In addition, cost estimate of a complete 48-week course of parenteral pegylated interferon administered at 1.5 μg/kg per week in combination to ribavirin with fixed administration at 1200 mg per day is 29 850 LE (2006 values). When considering monitoring costs, follow-up and average wholesale drug costs in Egypt, in the various medical institutions chosen (2006 values), estimates ranged from 32 690 LE to 37 950 LE in the NLI and the private for profit hospital. Because of dose reductions, discontinuations for the absence of a viral response after twelve weeks, at an efficiency of 54% as calculated in the NLI during the course of the research. Using Egyptian AWAPs in 2006, these numbers are readjusted to range from 60 129.62 LE to 70 277.77 LE for the same medical institutions. Less recently in Europe, a complete 48-week course of pegylated

interferon administered at 1.5 μg/kg per week plus ribavirin with fixed administration at 800 mg per day or weight-based administration >10.6 mg per kg per day or weight-based administration, including monitoring costs and follow-up was initially estimated to cost Euro 21 601 per fixed and Euro 23 716 for weight-based administration of ribavirin plus pegylated interferon, but actual costs would be 33% lower at Euro 13 085 and Euro 14 480 respectively (using German AWAPs in 2000), because of dose reductions, discontinuations for adverse effects as occurred in the trial or for the absence of a viral response after 24 weeks (Siebert *et al,* 2003).

It should be noted that such therapy is expensive and HCV infection usually progresses slowly, raising questions about the value or cost versus the effectiveness of treatment (Liang, 1998). However, this research tried to answer this question within the boundaries of the Egyptian situation. Multiple other pharmacoeconomic studies have been performed and suggest that antiviral combination therapy should be cost effective (Buti *et al,* 2002; Siebert *et al,* 2003; Wong *et al*, 2003; Sullivan *et al,* 2004 a and Shepherd *et al,* 2005) and one analysis found pegylated interferon plus ribavirin to be cost saving versus interferon plus ribavirin (Sullivan *et al,* 2004 b).

7.5.2. Inpatient Data

I- Cost of inpatients with HCV complications

Although Egyptian clinicians were familiar with the reasons for hospitalization of HCV patients from both the international Markov models and their practical experience, the cost of hospitalization of each reason was not known, nor was the average length of hospital stay, neither the types of drugs prescribed nor their cost in relation to their medical importance. Thereby this phase of the research albeit monotonous in its

collection stage, became very illuminative in its analytical stage and as a quantitative product.

Breakdown of the means of costs per patient grouped by reason of hospitalization (values in Egyptian pounds), mean length of hospital stay per patient grouped by reason of hospitalization (values in days), mean total costs per patient grouped by reason of hospitalization (values in Egyptian pounds) and mean cost of medication per patient for each drug group grouped by reason of hospitalization are all steps in the path of assessing the cost of HCV treatment and their cost effectiveness in Egypt. They are all also tools to evaluate the effectiveness of treatment strategies while adopting evidence based methodologies. These calculations may also be considered as quantitative guidelines to maximize effective healthcare delivery by adopting health technology assessment techniques. Furthermore these figures inform doctors and clinicians about the economical impact of their medical decision in explicit numbers. This will prompt them to consider all aspects of their treatment decisions on patients, on medical institutions and ultimately on the whole community.

Nearly 10 % (183 patients) of the total number of patients admitted in the NLI during 2003 were studied. The costs of caring for HCV patients hospitalized for the various complications of decompensated liver cirrhosis in the NLI and the private non profit hospital are nearly the same, with the private non profit 14 % higher in cost average than the NLI; this is very little difference considering that the NLI is being subsidized by the government. The fact that its costs are nearing those of a private hospital means the management need to consider the high constant costs that it incurs per patient that ranges from 43 % to 60 % in the total cost of hospitalization. Those figures should be a warning

bell to the management so as to reduce costs or restructure the administrative and the management systems, this would lead to decrease their constant costs and to maximize the use of their resources. On the other hand, this small difference in hospitalization cost in the private non profit institution in relation to the NLI also leads us to credit the private non profit hospital for an efficient and economical management.

Direct costs for HCV infection in the US were estimated to exceed $US 1 billion in 1998 (Kim, 2002 and Grant *et al,* 2005).Those figures place antiviral treatment costs which appear to be relatively expensive, in context. In the 187 patients examined in this study and diagnosed with end-stage liver disease between 2003 and 2006, the mean hospital charges and costs including laboratory tests, medications ranging from 3 477 LE to 5 481 LE per patient per hospitalization time in a public hospital NLI, 3 567.5 LE to 7 382.5 LE in a private non profit hospital and in a private for profit setting these figures multiply to reach 12 000 LE to 32 581 LE. The charge data included laboratory tests and medications but did not include terminal care support.

In 153 patients with end-stage liver disease between 1991 and 1995, Wong and co-workers, found mean hospital charges (not costs) ranging from $US 39 235 to $US 222 968 *(227 563 LE to 1 293 214 LE*) per patient (Wong *et al*, 1997). The charge data did not include outpatient visits, laboratory tests, home support services, medications or terminal care support, so the costs for treating end-stage liver disease are likely to far exceed those for antiviral treatment.

In this study it was shown that all patients were prescribed variable combinations of 154 drugs. Similar drugs and drugs used for similar conditions were then grouped in fifteen categories as shown in results. This was done for the convenience of statistical analysis,

at the same time; it highlighted the patterns for prescriptions and the cost of each drug category. The parallelism of rational prescribing patterns of physicians to the cases and medical situations was thus emphasized. If this research was done as a form of random medical prescriptions assurance, the results are clear as to the type of medical treatment the patients get in the NLI. The cost of each drug group, show the patterns and recurrence of drugs used and the complementary relationship they have with the various conditions under study but no economizations are evident for the inpatients' costs as all the medications prescribed are well rationed and pertinent to the condition of the patients. This study revealed that the lack of adoption of evidence-based perspectives caused the discrepancies of high cost and inefficient resource allocation in the healthcare system as evidenced from the length of hospital impact on inpatient costing in HCV patients. It is noteworthy to mention that the length of hospital stay affects the final cost of treatment. This; combined with the fact that the indirect costs are too large in terms of their effect on the final cost and that they depend directly on the length of hospital stay, should be taken into consideration with each admittance and exit permit written. The release order responsibility should be well regarded as it is not just another day but a major chunk of money that could be better spent on patients elsewhere!

7.5.3. Treatment pathways' choices

Technological advancements, developments in medical science and increasing expectations of communities from healthcare providers continue to focus attention on the healthcare dilemma. There is great concern, on an international level, that healthcare costs continue to rise, while evidence of improved patient wellbeing is difficult to find in many areas. Similarly, anti-HCV treatment appears to be expensive particularly when it comes to a

developing country like Egypt. Therefore the costs of treatment must be weighed against the cost of illness and the benefits of viral eradication. Simple comparisons of drug and disease costs do not account for drug effectiveness, so these kinds of analyses in isolation do not characterize the 'value' of a drug. Since, pharmacoeconomic analyses consider not only treatment costs but also disease costs, the present study measured for the first time the efficiency of response, the probability of progressive liver disease, and the costs of antiviral treatment. This measurement took into consideration the disease itself and the end-stage liver disease in Egypt as others did elsewhere in the world (Davis *et al,* 1998; Sinha and Das, 2000; Buti *et al,* 2002; Sullivan *et al,* 2004 a & b and Grieve *et al,* 2006). Even though not all patients develop liver complications, numerous economic evaluation of HCV infection suggest that, in the absence of antiviral treatment, costs of supportive treatment, costs of complications, particularly liver transplantation and decompensated cirrhosis, lead to lifetime undiscounted disease costs which were computed in this study to be 144 872 LE, 187 373 LE and 339 041 LE per patient in each of the centres included namely the NLI, private non profit and for profit hospitals respectively (Kim *et al,* 1997 and Younossi *et al,* 1999). These figures were discounted to be 80 215.75 LE, 103 748.88 LE and 187 727.20 LE respectively, and could be used to compare with those in the literature for the US and Germany; the lifetime discounted disease costs ranging from $US 24 600 to $US 38 700 (1995 and 1998 values respectively) for cohorts with a range of histological stages (Kim *et al,* 1997; Kim, 2002 and Younossi *et al,* 1999). Comparing the Egyptian values with the German numbers taking into consideration that one US $ equals 5.1 Egyptian pounds, the numbers are quite close indicating the extremely high cost of the disease in Egypt; bearing in mind that it is a developing country and

consequently this burden is magnified compared to other more developed rich countries. This study thus allows decision makers to reassess the clinical implications of the disease and to reconsider the treatment options and maybe even to develop a mandatory protocol of treatment that might be beneficial to all stakeholders involved, namely; the patients, the government and its politicians and its policy makers and ultimately the whole society. Not only is the pegylated interferon treatment route for HCV by far the cheapest alternative in terms of lifetime costs for patients admitted to the three centres included in the study when compared with both the supportive and the interferon treatment pathways, it is also the treatment alternative that saves the most lives as compared to the other two pathways. This is further clarified and emphasized when a cost effectiveness calculation is performed. It is noteworthy to mention that another international analysis found peginterferon and ribavirin to be cost-saving versus interferon plus ribavirin (Sullivan *et al,* 2004 b).

Importantly, cost-effectiveness analyses typically discount costs and outcome projections to reflect the higher present value of money. Discounting is particularly relevant to analyses of the cost of HCV because anti-HCV infection treatment costs occur now, and the costs of potential end-stage liver disease occur in the future. Integrating the currently recommended 3 % annual discount rate in the cost evaluations (Sagmeister *et al,* 2001; Sennfält *et al,* 2001; Buti *et al,* 2002; Grieve and Roberts, 2002; Salomon *et al*, 2003; Stein *et al,* 2002 and Sullivan *et al,* 2004a & b). In two recent studies discounting at the recommended 3 % annual rate reduces HCV costs in the absence of antiviral treatment $US 33 404 to $US 18 301 and from Euro 25 500 to Euro 14 100 (Siebert *et al,* 2003 and Wong *et al,* 2003), while in NLI it decreased from 144 872.23 LE to 80 215.75 LE and in

the presence of antiviral treatment it decreased from 75 704.61 LE to 52 531.28 LE less than $US 10 000.

In Egypt there is no threshold, below which a therapy may be considered to be "cost effective". Thus $US 10 000 cost of pegylated interferon combination treatment may not be within the range of other widely accepted or mandated medical interventions such as treating hypertension, coronary artery by-pass surgery, haemodialysis or screening for colorectal or breast cancer; but it is definitely less than what the same disease would cost if otherwise treated and the disease is an inescapable fact in the country of the pyramids.

Although the Egyptian HCV epidemic ended twenty five years ago, the very high "silent" reservoir of infection makes HCV, instead of schistosomiasis, Egypt's most important public health problem. It is important to mention though that current antiviral treatment regimens will have little impact on the HCV reservoir of infection (Strickland, 2006). Clinical management of the estimated five to seven million Egyptians with chronic HCV infection is also a national problem that will not be resolved until more effective, less toxic, and less expensive chemotherapeutic agents become available. As only a fraction of HCV infected Egyptians can pay for, or have insurance that covers, treatment with the currently available antiviral regimens. However, the Egyptian Ministry of Health and Population could reassess the use of its available, though insufficient resources, to provide a more adequately managed treatment option-based-evidence based methodologies of economics and health assessment. In this case, provide treatment at an early stage of chronic infection rather than wait for the full cycle of the disease with all its costly repercussions; consequently a larger segment of the population would benefit from therapy (Grieve *et al*, 2006).

Robinson, (1993 a) gave a simple definition or raison d'être to economic evaluation as a technique that was developed by economists to assist decision making when choices have to be made between several courses of action. In essence, it entails drawing up a balance sheet of the advantages (benefits) and disadvantages (costs) associated with each option so that choices can be made. Although the precise forms of economic evaluation may vary, the "cost-benefit" framework is common to all of them. This research was no exception to that framework, as the benefit of using antiviral combination therapy for HCV was calculated against the cost of not treating patients.

This research proved that economic evaluation and technology assessment are feasible techniques within the Egyptian healthcare system and showed their direct relevance to health service decision making. It identified routes to overcome the implications and barriers of their incorporation in the process of medical decision making in the country. It further proved that better healthcare does not necessarily always require additional resources; the same resources could have enhanced results if invested more prudently in the appropriate time and adequate treatment option. There is ample evidence handled in the results and discussion to demonstrate that informed policy decisions can have a positive effect on the health budget and consequently on the health status of Egyptian communities.

Chapter 8

Summary

Contents of Chapter

8.1. Introduction

The aim of this project was to explore the feasibility of incorporating health technology methodologies within clinical decision making and medical policy making in Egypt using treatment of hepatitis C virus (HCV) as a case study.

The study data was collected primarily in the National Liver Institute (NLI) in Menoufiya (a tertiary referral university hospital) during the period of 2003-2004. The results were then compared with corresponding data from two non university settings: the first a private non profit hospital dedicated to liver disease in Cairo, and the second, a private for profit hospital; the only private setting in Egypt that performs liver transplants.

The data collected in this study was used to calculate the cost of caring for patients during different stages of liver disease benchmarked by an internationally recognized Markov model illustrating the extended life cycle of the disease which was calculated to be 144 872.23 LE for the NLI and 187 373.83 LE for the private non profit hospital and 339 041.37 LE for the private for profit hospital over twenty years. Those figures were found to be higher when compared to the cost of interferon and ribavirin combination therapy; 92 155.61 LE for the NLI and 111 807.58 LE for the private non profit hospital and 196 054.74 LE for the private for profit hospital. The lowest treatment pathway cost in twenty years time was found to be the pegylated interferon and the ribavirin combination therapy; 75 704.61 LE for the NLI and 89 179.5 LE for the private non profit hospital and 142 573.49 LE for the private for profit hospital. This is totally surprising because the cost of treatment for one patient per year prescribed the supportive treatment was calculated to be 2 840 LE for the NLI and 4 780 LE for the private non profit hospital and 8 100 LE for the private for profit hospital while the cost for treating one patient per year with the pegylated interferon and the ribavirin combination therapy

was calculated to be 60 537.03 LE for the NLI and 64 129.62 LE for the private non profit hospital and 70 277.77 LE for the private for profit hospital.

8.2. The outcomes of the study

The results, in terms of cost effectiveness of the treatments options, impacted the whole society. It was more cost effective to use antiviral therapy in relation to the cheaper supportive option where not only cost effectiveness ratio was negative for both the regular interferon and the pegylated interferon alternatives but also 10 % and 14 % of lives were saved respectively. Moreover, among both antiviral treatments studied pegylated interferon option was more cost effective and saved 4 % more lives. Antiviral treatment costs have been shown for the first time to the author's knowledge, to be nearly completely offset by the prevention of future liver-related complications. Peginterferon plus ribavirin, or the interferon combination options were quantitatively shown to reduce future morbidity from liver complications, to improve survival and to be cost effective. This fact was accentuated by the initiation and the implementation of the national new mandatory HCV antiviral treatment centres throughout the country by decree of the Minister of Health and Population in January 2008.

The main policy implication deduced from this work is that health economics and health technology assessment methods should form a main tool for policy developers and clinicians. This is because in my opinion, those methods are optimum for developing clinical decisions that include consideration of multiple dimensions of evidence (effectiveness, costs) of the various treatment alternatives.

Because better healthcare does not always require additional resources, there is sufficient quantitative evidence in the results to demonstrate that altered policy decisions can have a profound effect on the health status of communities in Egypt. This research has sought to emphasize as Coast (2004) did, the need for whole systems thinking, based on good

quality evidence, and a broader long term perspective. This might of course involve an investment of resources at early stages in the healthcare spectrum, dealing with problems in their very early stages, with the aim of removing people from the healthcare system rather than 'moving them on' to a more complex and expensive part of the system.

Effectiveness data and data describing cost issues can successfully be calculated as part of a profile of treatment attributes and decision criteria. It is also clear that, when used appropriately; health technology assessment processes can provide valuable input into decision making, policy making processes and rational therapy promoting.

8.3. Proposed suggestions

While working on this case study a range of unanswered questions were identified, some of which are directly related to the consideration of costs and their calculation within the Egyptian healthcare system and some of which relate to practical implementation of health economics more generally.

Despite the emphasis on evidence relating to both effectiveness and cost-effectiveness in policy documentation, the fruit of applicability and birth of health economic evaluations and HTA in Egypt are related to the development of guidelines and adequate databases for the conduct, design and methodology of such studies (Hoffman and Graf von der Schulenburg, 2000). This would lead economic evaluations to become part of normal practice and organizational environments. This is important as HTAs are useful only if they are expected to contribute to the decision-making process. Moreover, if the necessary data and resources are insufficient or lacking, the assessment will not be helpful and may even delay access to treatments (Sorenson *et al,* 2008). This would first have an impact on the healthcare budgetary system and general population benefit and also would hinder matching world trends in innovative economic health technologies.

Given the complexity and scale of the healthcare problems in Egypt, hospitals, laboratories, doctors and clinics need to be connected. The current situation is just too fragmented for any long term effective solutions. Together, health economists and decision makers share the responsibility of education; the first should provide materials for teaching and the latter should encourage and fund it. Fundamental educational and professional training is highly recommended to the current decision making personal in addition to the next generation of healthcare and policy makers. This would lead to a systematic involvement in the medical decision making and in the provision of policy advice as economic evaluation and HTA would be directly linked to both cost reductions and increase efficiency of the policy and decision making process. It would also pave the way to the development of evidence-based practice, heading into implementation and practical realization of the need for fairness in resource allocation and service provision, are major steps along the road to providing prosperity to the community as an interlinked entity. This should be done in parallel with a total cultural change throughout all the echelons of providers, decision makers, suppliers, professionals and workers in the health care and medical fields.

To overcome the barriers to the use of economic evaluation, the need to balance evidence, economics equity and patient empowerment within a system of multiple constraints and limited manoeuvrability. Furthermore, to make health assessment fit with decision making imperatives; action falls on the health economists and the decision makers, each on their own or together. Overall, greater stakeholder involvement is needed to improve the implementation of decision and policy and manage uncertainty while simultaneously allowing access to safe technologies.

Health economists should get a better understanding of the needs and constraints under which decision makers work if pharmacoeconomics is to be applied in a useful way to

them. They should look at the practical approach and understand the internal issues, pressures and political problems as analytical and predictive power often comes from standing back and taking a broader view.

Decision makers should improve the system by enhancing data collection and processing of both costs and outcomes of treatments and medical services as well as reassessing the guidelines for data availability and accessibility particularly beyond the high administrative personnel and government officials.

A clear and well-communicated decision-making process must be in place before HTA's recommendations can be implemented. Lack of a defined process can create doubts about the legitimacy of decisions and make them less likely to be supported by stakeholders (Neumann, 2004 and Drummond, 2006).

Other points to be considered to promote research in the field of health economics and implementation of HTA in the future are:

- Fair access to services and health information
- Setting national standards and service models to increase efficiency of the healthcare system
- Address the organizational issues and cultures
- Initiate consensus and protocols for treatment and prescription
- Audit treatment programs
- Computerizing the system and initiate national security number relation to healthcare
- Studying hospital stay impact effect on health budget

All this should be done taking into consideration that the multi-faceted intricacies of organizational cultures and politics added to the differences in personalities combine to produce a spectrum of outcomes, ranging from utter failures to highly successful

programs and policies. More work is needed to assess the effectiveness of intra-organizational, inter-organizational, inter-professional, and collaborative approaches to the organization and delivery of services (El Ansari *et al,* 2001 and El Ansari and Phillips, 2001) in order to accompany the effectiveness and efficiency research and analysis.

In conclusion, the study showed that economic analysis and HTA in Egypt founded on a sound understanding of current practice, effectiveness and cost effectiveness data can actually and practically change and improve clinical practice and healthcare decisions and increase the efficiency of a wonderfully altruistic medical system but an unfortunately economically failing one.

Chapter 9

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