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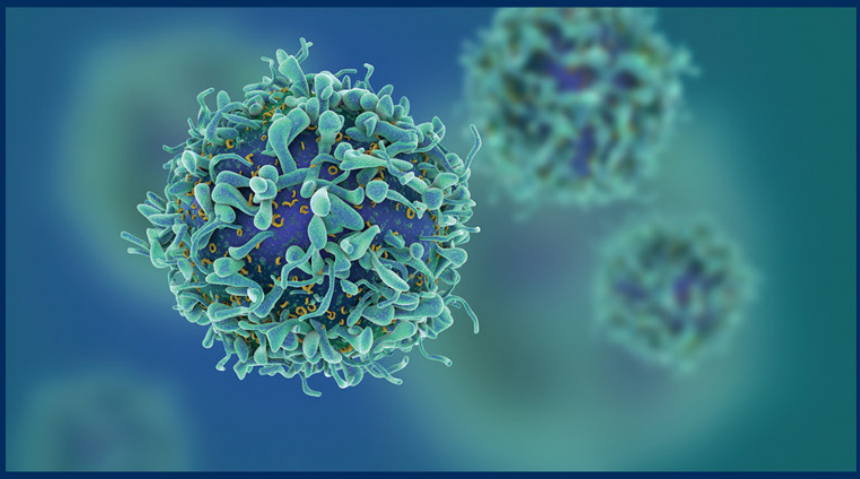
Economic Evaluation of Cancer Drugs

Using Clinical Trial and Real-World Data



Iftekhar Khan
Ralph Crott
Zahid Bashir

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These are our works, these works our souls display

Behold our works, when we have passed away

For Suhailah, Yohanis, Hanzalah, my father, and all those affected by cancer

For Jon and Fiona, my children

For Saima, Hassan, and Hibba

Contents

Preface

The cost of cancer care has increased hugely and put pressure on healthcare systems around the world. An important part of this cost is the cost of cancer medicines. Economic evaluation of cancer drugs is an extremely important area that affects health policy and access to cancer treatment. The economic evaluation of cancer drugs can involve careful trial design, robust economic modeling, and sound statistical analysis and research methodology, drawing together the disciplines of medical statistics, clinical research, and economics.

Several books already exist that address theoretical or practical aspects of cost-effectiveness analysis. However, no unified text on the cost-effectiveness of cancer medicines is currently available. This book attempts to deal with the matter within a practical framework, focusing on key concepts and drawing on the experiences of health technology appraisals (HTA) of cancer drugs – either approved or rejected by government reimbursement agencies (the payers). This book also offers an insight into how health economic evaluation of cancer interventions has been carried out in practice, with many examples throughout, where data are collected in clinical trials or in real-world settings.

This book is not just about performing cost-effectiveness analyses of cancer drugs using clinical trial and real-world data, but also emphasizes the strategic importance of economic evaluation through the drug development process. It also offers guidance and advice on the complex factors at play before, during, and after an economic evaluation for a cancer intervention. In addition, this book bridges the gap between industry (pharmaceutical) applications of economic evaluation and what students may learn on university courses. The book is suitable for statisticians, health economists, cancer researchers, oncologists, and anyone with an interest in the cost-effectiveness of interventions for cancer using clinical trial and/or real-world data. It would also be a valuable book for a postgraduate course in health economics.

We candidly admit that our objectives have been set high when structuring this book. Economic evaluation covers several disciplines and addressing all of these has been challenging. We hope that the material in this book is suitable for a range of researchers of varying abilities, so that some will find the entire book useful whereas, for others, particular chapters will be

useful. As a student textbook, this book can be complemented by additional reading material suggested in the bibliography.

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Acknowledgments

We would like to gratefully acknowledge helpful reviews by Dr. Noan-Min Chau from the Licensing Division of UK Medicines and Health Regulator Agency (MHRA) and also Tarita Murray-Thomas from the Clinical Practice Research Data Link (CPRD) within the MHRA. Their comments have resulted in a much-improved text. We also acknowledge the reviews by Dr. Suhailah Khan and Uzma Ikramullah for proofreading parts of the text. We graciously acknowledge the National Institute for Health and Care Excellence (NICE), which has made available to the public such excellent material, as demonstrated in this book. Finally, we would like to thank the anonymous reviewers of earlier chapters. Their comments have been extremely helpful enabling us to deliver a much-improved text.

About the Authors

Dr. Iftekhar Khan is a medical statistician and health economist by qualification and training. Dr. Khan has extensive experience in cancer trials in industry, academia, and regulatory environments, spanning over 18 years. He was formerly associate professor in Medical Statistics and Methodology at King's College, London, and lead statistician at UCL CRUK Cancer Trials Centre and Oxford University's Center for Statistics in Medicine. Professor Khan is also a Senior Research Fellow in Health Economics at the University of Warwick and a Senior Statistical Assessor within the Licensing Division of the UK Medicine and Health Regulation Agency where he regularly evaluates oncologic and other drugs and devices for licensing.

Dr. Ralph Crott is a former professor in Pharmacoeconomics at the University of Montreal in Quebec, Canada and former head of the EORTC Health Economics Unit (Brussels, Belgium) and former senior health economist at the Belgian HTA organization (KCE). Dr. Crott has been active in economic evaluation of new medical technology since 1984. He also held research and/or teaching positions at York University in the United Kingdom and the Catholic University of Louvain, Belgium. He received his PhD in applied economics at the Catholic University of Louvain (UCL, Belgium) and holds additional masters degrees in econometrics (Flemish University of Brussels (VUB, Belgium), biostatistics (Limburg University, Belgium), public health with a major in clinical research (Catholic University of Louvain, Belgium), and technology assessment (Aston University, United Kingdom).

Dr. Zahid Bashir has over twelve years of experience working in the pharmaceutical industry, specifically in medical affairs and oncology drug development, where he is involved in the design and execution of oncological clinical trials and development of reimbursement dossiers for HTA submission. Dr. Bashir also has extensive clinical experience in teaching oncology and haematology in the UK NHS hospital.

Acronyms and Abbreviations

ACD	advanced consultation document
AE	adverse events
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AFT	accelerated failure time
AHRQ	Agency for Healthcare Research and Quality
AIC	Akaike Information Criterion
ALK	anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
ASMR	medical improvement score
ATC	average total cost
AUC	area under the curve
BB	beta binomial
BEV	bevacizumab
BIM	budget impact model
BNF	British National Formulary
BRCA	breast cancer gene
BSC	best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CAP	chemotherapy for advanced prostate cancer
CCG	clinical commissioning group
CCyR	complete cytogenic response
CDF	Cancer Drug Fund
CDR	Common Drug Review
CE	cost-effectiveness
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CEESP	Commission d'Évaluation Économique et de Santé Publique
CESP	Comité Economique des Produits de Santé
CHEERS	Consolidated Health Economic Evaluation Reporting
chemo-RT	chemoradiotherapy
CI	confidence interval
CMA	cost minimization analysis
CML	chronic myeloid leukemia
CMS	Center for Medicare Services
CPRD	Clinical Practice Research Datalink
CPT	current procedural terminology
CR	complete response
CRA	clinical research associate
CRC	colorectal cancer

CRF	case report form
CRUK	Cancer Research UK
CSM	condition-specific measures
CSRI	client services receipt inventory
CT	computed (axial) tomography
CUA	cost-utility analysis
CV	cabozanitib and vandetanib
DALY	disability-adjusted life-years
DAPA	dementia and physical activity
DCF	data collection form
DES	discrete event simulation
DFS	disease-free survival
DICE	discretely integrated condition event
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
DoR	duration of response
DRG	diagnostic-related group
EAMS	early access to medicine
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form (CRF)
EFS	event-free survival
EGFR	epidermal growth factor receptor
EHR	electronic health records
EINB	expected incremental net benefit
EMA	European Medicines Agency
ENB	expected net benefit
ENMB	expected net monetary benefit
ENBS	expected net benefit of sampling
EoL	end-of-life
EORTC	European Organization for Research and Treatment of Cancer
ERG	evidence review group
ESMO	European Society of Medical Oncology
EUnetHTA	European Network of Health Technology assessment
EVPI	expected value of perfect information
EVPPI	expected value of partially perfect information
EVSI	expected value of sample information
FACT	Functional Assessment of Cancer Therapy
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act
FDG-PET	2-fluoro-2-deoxyglucose positron emission tomography
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GDP	gross domestic product
GDPR	General Data Protection Regulation

GLM	general / generalized linear model
GLOBOCAN	Global Cancer Observatory Database
HAS	Haute Autorité de Santé
HCCor	half-cycle correction
HCC	hepatocellular carcinoma
HEAP	health economic analysis plan
HES	Hospital Episode Statistics
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
HUI	health utility index
ICD	international classification of diseases
ICD-O	international classification of diseases for oncology
ICER	incremental cost-effectiveness ratio
ICERev	Institute for Clinical and Economic Review
IDMC	independent data monitoring committee
INB	incremental net benefit
INFORMED	Information Exchange and Data Transformation
INMB	incremental net monetary benefit
IPCW	inverse probability-of-censoring weighting
IQWiG	Institute for Quality and Efficiency
irRC	immune-related response criteria
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	instrumental variable
IV	intravenous
KM	Kaplan-Meier
LCS	lung cancer scale
LMG	life-month gained (as unit)
LOCF	last observation carried forward
LSmean	least squares mean
LT	liver transplantation
LYG	life-years gained
MAMS	multi-arm, multi-stage
MAR	missing at random
MCAR	missing completely at random
MCID	minimum clinical important difference
MCO	managed care organization
MDS	myelodysplastic syndrome
MDT	multidisciplinary team
MED	minimum effective dose
MHRA	Medicines and Healthcare products Regulatory Agency
MI	multiple imputation

mITT	modified ITT
MLM	multilevel models
MM	multiple myeloma
MMR	major molecular response
MNAR	missing not at random
MPFS	Medicare Physician Fee Schedule
MRD	minimal residual disease
MSM	marginal structural model
MTA	multiple technology appraisal
MTC	mixed treatment comparison
MTD	maximum tolerated dose
NBM	negative binomial model
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCLA	National Lung Cancer Audit
NCR	National Cancer Registry
NCRS	National Cancer Registration Service
NHB	net health benefit
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIHR	National Institute for Health Research
NMA	network meta-analysis
NMB	net monetary benefit
NPV	net present value
NSCLC	non-small-cell lung cancer/carcinoma
OCS	ovarian cancer-specific
QD	once daily
OLE	open label extension
OLS	ordinary least square
ORR	objective response rate
ORR	overall response rate
OS	overall survival
PAE	potential adverse event
PAS	patient-access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PBM	preference-based measures
PBS	Pharmaceutical Benefits Scheme
pCODR	pan-Canadian Oncology Drug Review
pCR	pathological complete response
PCS	prostate cancer subscale
PD	progressive disease
PFS	progression-free survival
PFS1	progression-free survival 1
PH	proportional hazards
PIM	promising innovative medicine

PP	post-progression
PP	per protocol
PRCT	pragmatic RCT
PPRS	Pharmaceutical Price Regulation Scheme
PPS	post-progression survival
PR	partial response
PS	propensity score
PSA	probabilistic sensitivity analysis
PSM	propensity score model
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QLQ	Quality of Life Questionnaire
QoL	quality of life
QTWiST	Quality of Time Spent Without Symptoms of Disease and Toxicity
RBRVS	resource-based relative value system
RCC	renal cell cancer
RCT	random clinical trial
REC	research ethics committees
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation
RP	Royston-Parmar
RPSFTM	rank-preserving structural failure time model
RT	radiotherapy (see chemo-RT)
RWD	real-world data
RWE	real-world evidence
SACT	systemic anti-cancer therapy
SAPs	statistical analysis plan
SBRT	stereotactic body radiation therapy
SD	stable disease
STDev	standard deviation
SDiff	standardized difference
SE	standard error
SG	standard gamble
SMC	Scottish Medicines Consortium
SNM	structural nested model
SNNM	structural nested mean model
SNS	Sistema Nacional de Salud
SR	surgical resection
STA	single technology appraisal
TA	technology appraisal
TACE	transarterial chemoembolization
TEAE	treatment emergent adverse events
THIN	The Health Improvement Network
TKI	tyrosine kinase inhibitor

TOI	Trial Outcome Index
TPS	tumor proportion score
TSD	technical support document
TTBT	time to next treatment
TTF	time-to-treatment failure
TTO	time trade-off
TTP	time to progression
UCLH	University College London Hospitals Foundation Trust
VAS	visual analog scale
VBP	value-based pricing
VOI	value of information
VSI	value of sample information
WHO	World Health Organization
WTP	willingness to pay
YLL	years of life lost
ZIN	Zorginstituut Nederland

1

Introduction to Cancer

1.1 Cancer

The term 'carcinoma' is derived from the Greek word 'karkinos,' meaning crab. Hippocrates associated cancer with the shape of a crab, because of the way it spreads through the body and its persistent nature (Long, 1999).

Cancer is prevalent worldwide and impacts not only millions of people but also their families, carers, health systems, and even employers. Cancer impacts people's physical, cognitive, and functional ability as well as their health-related quality of life (HRQoL) and economic well-being. The National Cancer Institute's *Dictionary of Cancer Terms* (NCI, 2015) defines cancer as:

> A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Carcinoma is cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukaemia is cancer that starts in blood-forming tissue, such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myelomas are cancers that begin in the cells of the immune system. Central nervous system cancers are cancers that begin in the tissues of the brain and spinal cord.

1.2 Epidemiology of Cancer

An estimated 14.1 million new cases of cancer occurred across the world in 2018. The four most common types of cancers are lung, female breast, colorectal, and prostate cancer (Bray et al., 2018). According to the Global Cancer Incidence, Mortality and Prevalence study (GLOBOCAN) (Bray et al., 2018), prostate cancer is the most commonly diagnosed cancer among males from

87 countries, especially in North and South America and northern, western, and southern Europe. Lung cancer is the most commonly diagnosed cancer among males in eastern Europe. Among females, breast cancer is the most common cancer in North America, Europe, and Oceania. Breast and cervical cancers are the most frequently diagnosed cancers in Latin America and the Caribbean, Africa, and most of Asia. However, the most common female cancers in Asia also include lung, liver, and thyroid.

Due to more screening, earlier detection, and improved treatment, cancer mortality rates are either plateauing or decreasing, particularly in the high-income regions.

Table 1.1 summarizes the types of cancers and some key symptoms and features, along with the common clinical and economic outcomes collected in clinical cancer research.

These endpoints will be discussed in more detail in Chapter 2. For indolent malignancies with long survival, other endpoints such as cytogenetic response and minimal residual disease are used to assess the effectiveness of new drugs, particularly in earlier lines of treatment. Surrogate endpoints are also discussed in more detail in Chapter 2. For a single cancer type, there are likely to be further subtypes (e.g. adenocarcinoma) for which some treatments might work better for patients belonging to this subpopulation.

1.2.1 Cancer Trends

Mortality rates in several developing and low-income regions are increasing for some of these cancers due to increases in smoking, excess body weight, and physical inactivity. In 2011, there were nearly 8 million cancer-related deaths. All cancers, taken together, are now a leading cause of disease-related death worldwide, responsible for about 14% of the total of 55 million deaths from all causes in 2011. Cancer incidence in the UK is reported to have increased between 1993 and 2015 especially for females (Figure 1.1).

On the other hand, cancer incidence appears to be decreasing globally for many cancers in the United States, Europe, and other high-income countries. In low- to middle-income countries, the trend for cancers is unclear. Liver cancer, however, is reported to be increasing globally. Table 1.2 provides a summary of mortality trends for different cancer types between the years 2000 and 2019 (Hashim, 2016).

Example 1.1: Lung Cancer

Lung cancer is one of the leading causes of cancer-related deaths in the world and accounts for nearly 1.4 million deaths per year worldwide, with a yearly incidence of over 41,000 in the UK alone (Cancer Research UK [CRUK] Statistics, 2012). More than 8 out of 10 lung cancer cases occur in people aged 60 and over. Rates of lung cancer in Scotland are among the highest in the world, owing to the high prevalence of smoking.

TABLE 1.1

Examples of Some Common Cancers Regarding Clinical and Economic Outcomes

Cancer	Tumor Type	Common Symptoms	Key Features	Clinical Outcomes	Key Economic Outcomes
Lung cancer	Solid	Cough, blood in sputum, pain, weight loss	Short survival, diagnosed late	PFS, OS[a]	– Cost of treatment – Radiotherapy – Biomarker testing – Palliative Care – Quality of Life – Nursing visits – GP visits – Hospital visits – Physiotherapy aids/equipment – family support – childcare costs
Melanoma	Solid	Changing mole, mass, symptoms due to distant disease spread	Aggressive	PFS, OS	
Diffuse large B cell lymphoma	Solid	Enlarged lymph nodes, pain, weight loss, fever, night sweats, local symptoms due to enlarged mass e.g. intestinal obstruction	Aggressive lymphoma, short survival without treatment	PFS, OS	
Chronic myeloid leukemia	Blood	Incidental diagnosis on routine blood tests, fatigue, bone pain, weight loss, sweats	Indolent	Cytogenetic response	
Glioblastoma	Solid	Headache, vomiting, neurologic symptoms	Aggressive, short survival	PFS, OS	
Colorectal carcinoma	Solid	Blood in stools, pain, mass in abdomen, unexplained changes in bowel habits	Aggressive, short survival time	PFS, OS	
Hepatocellular carcinoma	Solid	Nonspecific symptoms due to underlying liver disease, mass in abdomen	Aggressive, short survival time		
Gastric cancer	Solid	Mass in abdomen, pain, weight loss, vomiting, blood in vomit, symptoms due to obstruction	Aggressive, short survival time	PFS, OS	

[a] *Note*: OS: overall survival; PFS: progression-free survival.

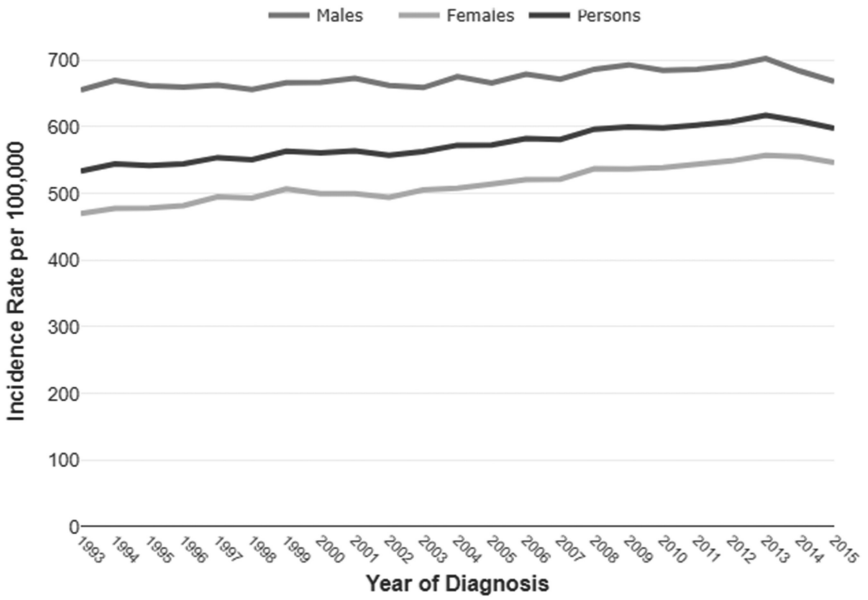

FIGURE 1.1
All cancers excluding non-melanoma skin cancer, European age-standardized incidence rates, UK, 1993–2015.

Source: CRUK Cancer Statistics.

TABLE 1.2

Summary of Countries by Cancer Type Showing Where Deaths from Each Type of Cancer are Increasing/Decreasing

Cancer	Increasing[a]	Decreasing
All	Brazil, Cuba, Latvia, Moldova, Serbia, and Malaysia	Decreasing for other countries
Stomach cancer	Not increasing in any country	Decreasing for all countries
Colorectal cancer	Latin America, Asia, South Africa, Romania, Malaysia, Kuwait, and Latvia	Decreasing for other countries
Liver cancer	North America, Asia, and Latin America	Decreasing for other countries
Lung cancer	Women: most countries: North America, Spain, Belgium, and Denmark Men: Venezuela, Moldova, Malaysia, Serbia, Bulgaria, Portugal, and Romania	Decreasing for: Ireland, Asian countries, Lithuania, and some Latin American countries
Breast cancer	Japan/Korea, Malaysia, Philippines, South Africa, and Latin America	Decreasing for other countries
Uterine cancer	Puerto Rico, Malaysia, and Philippines	Decreasing for other countries
Prostate cancer	Malaysia, Latvia, Serbia, Moldova, Ukraine, Belarus, USSR, and Korea	Decreasing for other countries

[a] *Note:* See Hashim et al. (2016) for list of country studies.

Lung cancer incidence in a given country is directly linked with the level of tobacco smoking in that country. Lung cancer-related deaths occur approximately two to three decades after the widespread uptake of smoking in any given country, with mortality trends approximating the incidence trends. Among males, lung cancer mortality rates have peaked and are now decreasing in many developed countries, reflecting the uptake and subsequent decline in male smoking prevalence. Lung cancer incidence in women lagged behind that in males because women began smoking later.

In countries with the earliest uptake of smoking among women (e.g. US, UK, and Australia), lung cancer mortality rates have peaked, whereas they continue to climb in countries where women began smoking later. Lung cancer is often diagnosed later in life, frequently with aggressive disease progression leading to high mortality rates for this cancer. In the 1950s, for every 1 lung cancer case diagnosed in women in the UK, there were 6 in men. That ratio is now 3 cases in women for every 4 in men. The lowest lung cancer rates in the world for men and women are in Northern, Western, and Middle African countries and South-Central Asia; but this will also change if the current trends in the uptake of smoking persist (Jemal et al., 2011; Toms, 2004; CRUK Statistics, 2012).

1.3 Prognostic Factors Associated with Cancer Outcomes

Prognostic factors are known or unknown factors that may be related to either an increased or decreased chance (risk) of a (cancer-related) outcome such as death (overall survival), disease progression, or any other outcome of interest, including surrogate outcomes (Chapter 2). The relationship between prognostic factors and cancer outcomes can influence the value of cancer treatments. For example, if the survival benefit for patients with a poor prognosis, defined by, say, an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or 4, is lower (in general, higher values of ECOG suggest the patient has a worse prognosis) compared to patients with better prognoses (e.g. ECOG of 0 to 1), then ECOG would be considered an important prognostic factor. The survival benefit may be greater in lower ECOG patients (because patients might be relatively healthier or fitter for, say, surgery or chemotherapy). Consequently, the treatment might be more cost-effective for patients who are ECOG (0–1) compared to ECOG (2–3). Therefore, prognostic factors play an important role in trial design considerations from *both* a clinical and a health economic perspective.

One example of this is the use of a biomarker, a chemical test conducted to determine the genetic disposition of a patient. The result of the test could be related to a higher or lower clinical benefit. For example, the epidermal growth factor receptor (EGFR) is one type of marker that a patient might have. Patients with a known biomarker status (e.g. EGFR +ve for the drug

Erlotinib, used to treat lung cancer patients) are reported to have longer survival than those who are EGFR –ve. Despite the costs of the biomarker test and other health resource use, including the cost of the drug, the targeted treatment might still therefore offer greater value (be more cost-effective) for future patients who test EGFR +ve.

Risk factors may not act independently but may be additive or multiplicative in nature. That is, higher survival rates associated with ECOG status might also depend on the ages of patients. It may be that better ECOG status and age (younger patients might be relatively fitter) are associated with higher survival rates compared to the survival rates of those who are older and have poorer ECOG status. Hence treatment benefit may be dependent on a combination of factors. These are called interactions. Such interactions can play an important role in subgroup analyses from both a clinical and health economic perspective.

Several risk factors common to different cancer types have been reported. Some of these factors include age, genetic disposition (e.g. biomarker status), smoking, lifestyle (e.g. insufficient physical activity, alcohol, diet), obesity, and infections. These factors are associated with a high proportion of cancers worldwide but may also vary by region or country. Smoking, in particular, is the single most preventable cause of cancer death in the world; around a third of tobacco-caused deaths are due to cancer. Excessive alcohol consumption is reported to be associated with 13% of cancer-related deaths (Ferlay et al., 2010).

1.4 Economic Burden of Cancer

1.4.1 Health Expenditure

The constraint on healthcare resources, particularly during times of economic turmoil and instability, may result in governments taking a hard look at all public expenditure, including the medicine budget. Policymakers have a limited budget from which to decide how healthcare resources are provided for its citizens. What this means in practice is that the 'payers' (i.e. governments or health insurance providers who contribute toward the cost of healthcare provision for their citizens or customers) are likely to be more selective and choose with greater care from the healthcare options (i.e. new treatments) available to patients (due to budget constraints). Just like most individuals cannot have all the things they want, either because they do not have sufficient resources (e.g. money, time), healthcare systems also have similar constraints when trying to meet the demands of its consumers (patients).

Figure 1.2 shows the worldwide healthcare annual expenditure between 2000 and 2013 as a percentage of gross domestic product (GDP) as reported by the World Health Organization (WHO). It shows that health expenditure as a

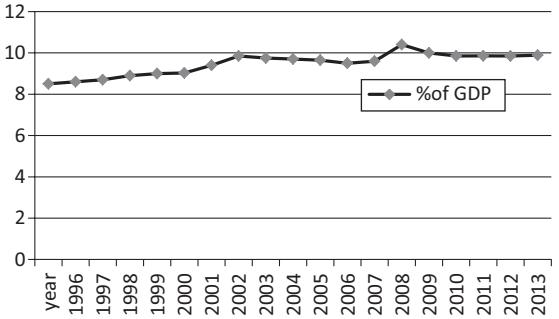

FIGURE 1.2
Health expenditure as a fraction of GDP between 1996 and 2014.

Source: https ://da ta.wo rldba nk.or g/ind icato r/SH. XPD.C HEX.G D.ZS.

percentage of GDP has generally increased over the past 20 years, although with some cyclical variation. Hence, the expenditure on health relative to available resources (GDP) is increasing at a significant rate. An examination of similar graphs per country shows an increasing expenditure trend for developed and mid-sized undeveloped countries (WHO Report, 2014).

1.4.2 Healthcare Expenditure on Drugs

The economic burden of treating cancer is high worldwide. Cancer has the most devastating economic impact in the world compared to other diseases. The exact worldwide economic costs of cancer are unknown but are estimated to be at least US $895 billion. With a growing and aging population, prevention efforts are critical for reducing new cancer cases, human suffering, and economic costs. Since 1995, the cost of cancer drugs has increased by an average of 10% annually (NCI, 2016). The largest economic burden for cancer patients is often related to the direct cost of cancer treatment, namely treatment drugs, and the costs to treat associated toxicities.

In 2014, the cost of every new cancer drug approved in the US exceeded $120,000 per year of treatment. An American Society of Clinical Oncology (ASCO) statement highlighted that in the decade from 2010 to 2020, between $125 billion and $158 billion will have been spent on cancer care (Lowell et al., 2015). Drug cost is a major (but not the only) cost component associated with treating cancer. Other costs include the costs of treating side effects, surgery, or radiotherapy, all of which can be significant. Given that one in three people will be diagnosed with cancer in their lifetime, the future cost of cancer treatment and care is likely to be a serious economic burden.

In the UK, the annual economic burden of cancer is estimated to be £15 billion. The National Health Service (NHS) increased its budget for

cancer drugs from £200 million in 2013 to an expected £340 million in 2015 (NHS Statistics, 2015), a 70% increase in the so-called Cancer Drug Fund (CDF, NHS Statistics 2013, 2014). This represents the cost of cancer drugs alone.

The CDF was set up in 2011 by the UK government to make funds available for paying for cancer drugs. It was changed in 2016 as its form had become economically unsustainable. One critical change was an explicit reference to cost-effectiveness (CE) and resolving its uncertainty, which underlines the importance of the costs of treating cancer:

> Managed access agreements between NHS England and pharmaceutical companies, setting out the terms of a drug's entry into the CDF and the means by which data will be collected to resolve any uncertainty relating to a drug's clinical and *cost-effectiveness*. (NHS Statistics 2013, 2014)

One objective of government health departments is the desire to optimize the use of cancer drugs by a combination of negotiated price reductions (of drugs) and improved clinical effectiveness. Some cancer drugs were removed from the CDF list due to their lack of cost-effectiveness. The National Institute of Health and Care Excellence (NICE), the UK body that publishes guidelines on the value of new health technologies, has defined acceptable cost-effectiveness thresholds as high as £50,000 per quality-adjusted life-year (QALY). A QALY (see Section 1.6.1.8) is a composite measure of the length of life and the quality of life experienced during this period. Hence, a survival time of 1 year in perfect quality of life is 1 QALY, but if the quality of life was scored at 0.5 (using a 0 to 1 scale, 0 being death and 1 being full health), the QALY would be 0.5 (6 months). In 2016 the CDF underwent a review of which one key objective was to ensure cancer drugs (in fact all drugs) offer strong value for money (Cohen, 2017).

As an example, in the UK the total annual cost of treating lung cancer in 2012 was about £3 billion (20% of cancer costs) – the yearly average cost per patient was £9,071. This was comparable to £2,756 for bowel cancer, £1,584 for prostate cancer and £1,076 for breast cancer (ACS, 2016). Therefore, the costs associated with treating and managing lung cancer can be three times higher compared to the other types of cancer. In the US, the mean *monthly* cost of treating lung cancer patients was estimated at £1,669 (no active treatment) and £5,814 for chemoradiotherapy (exchange rate of £1 = $1.61).

Example 1.2 Costs and QALYs Reported in Some Published Cost-Utility Studies

Table 1.3 shows the key results from 47 published cost-effectiveness analyses in a lung cancer setting. About 20% did not report QALYs. Of the 80% that did report the cost per QALY (36 out of 47), only 13 out of 36 (36%) reported this to be below £30,000 (see Chapter 2 on ICERs).

TABLE 1.3

Published Costs and QALYs in Lung Cancer

Treatment	Cost (£)	QALY	Cost/QALY (£)	Year	Source (See Bibliography)
Paclitaxel	28,210	0.53	53,227	2011	Goulart et al.
	27,902	0.923	30,230	2010	Brown et al.
	21,967	NR	NR	2000	Berthelot et al.
	24,216	NR	NR	2000	Berthelot et al.
	26,228	NR	NR	2000	Berthelot et al.
	33,685	0.4513	74,639	2009	Klein, R.
Gemcitabine	27,837	0.934	29,804	2010	Brown et al.
	27,401	0.966	28,365	2010	Brown et al.
	18,129	NR	NR	2000	Berthelot et al.
	47,876	1.96	24,427	2013	Wang et al.
	38,859	0.4676	83,102	2009	Klein, R.
Vinorelbine	23,516	0.888	26,482	2010	Brown et al.
	16,678	NR	NR	2000	Berthelot et al.
	17,482	NR	NR	2000	Berthelot et al.
	6,901	NR	NR	2010	Maniadakis
Docetaxel	4,129	0.1606	25,712	2012	Thongprasert et al.
	13,956	0.206	67,748	2010	Lewis et al.
	27,409	0.42	65,260	2010	Asukai et al.
	24,798	0.225	110,215	2008	Araujo et al.
	24,904	0.42	59,296	2008	Carlson
	11,622	0.42	27,672	2011	Vergnenge et al.
	20,903	NR	NR	2011	Cromwell et al.
Pemetrexed	5,791	0.1715	33,767	2012	Thongprasert et al.
	29,387	0.52	56,514	2010	Asukai et al.
	27,764	0.241	115,205	2008	Araujo et al.
	37,119	0.41	90,533	2008	Carlson
	14,239	0.41	34,729	2011	Vergnenge et al.
	17,455	0.97	17,995	2010	Greenhalgh et al.
	41,731	0.5016	83,195	2009	Klein, R.
	8,905	0.41	21,720	2012	Fragoulakis
Gefitinib	3,973	0.1745	22,766	2012	Thongprasert et al.
	NR	1.111	NR	2010	Brown et al.
	19,787	0.79	250,47	2013	Zhu
	7,704	0.79	9,752	2013	Zhu
	28,471	0.91	31,287	2012	Gilberto de Lima Lopez
	8,980	0.2881	31,170	2010	Ontario Health
	10,536	0.3188	33,048	2010	Ontario Health
Erlotinib	13,730	0.238	57,689	2010	Lewis et al.
	22,439	0.25	89,756	2008	Araujo et al.

(*Continued*)

TABLE 1.3 (CONTINUED)

Published Costs and QALYs in Lung Cancer

Treatment	Cost (£)	QALY	Cost/QALY (£)	Year	Source (See Bibliography)
	23,567	0.42	56,112	2008	Carlson
	5,286	0.1745	30,292	2012	Thongprasert et al.
	25,546	1.4	18,247	2013	Wang et al.
	23,503	0.51	46,085	2012	Chouaid et al.
	12,909	0.33	39,119	2013	Chouaid
	8,104	0.42	19,296	2012	Fragoulakis
	22,744	NR	NR	2011	Cromwell
	7,488	NR	NR	2010	Bradbury et al.

In the UK, the cost-effectiveness threshold is set to between £20,000 and £30,000. The data in Table 1.3 shows the difficulties and challenges involved in finding cost-effective lung cancer drugs. The variation in costs and QALYs in Table 1.3 may be due to any number of factors, including variations in populations, geography, clinical trial design (e.g. patient follow-up), how costs were collected, and so forth. We will discuss these aspects in later chapters.

1.5 Treatments for Cancer

Common approaches for treating cancer (solid tumors) include (i) surgery, followed by (ii) chemotherapy, and (iii) radiotherapy (though not necessarily in that order). Despite treatment with chemotherapy, cancer recurrence is not uncommon. Recent novel chemotherapy (e.g. immunotherapy) treatments use the body's immune system to fight and kill cancer cells. Although some of these drugs have proved to be cost-effective, others have not (see later in Chapter 10 for examples). For blood cancers (e.g. leukemia), surgery is not an option and chemotherapy is often the first choice of treatment.

An example of treatment options for a patient diagnosed with non-small-cell lung cancer (NSCLC) in the UK is shown in Figure 1.3. Often, a particular treatment may be used for several different tumor types, often resulting in similar side effects across tumors, with a marked impact on HRQoL.

HRQoL and patient-reported outcomes are a central part of economic evaluation. (HRQoL will be discussed more fully in Chapter 3.)

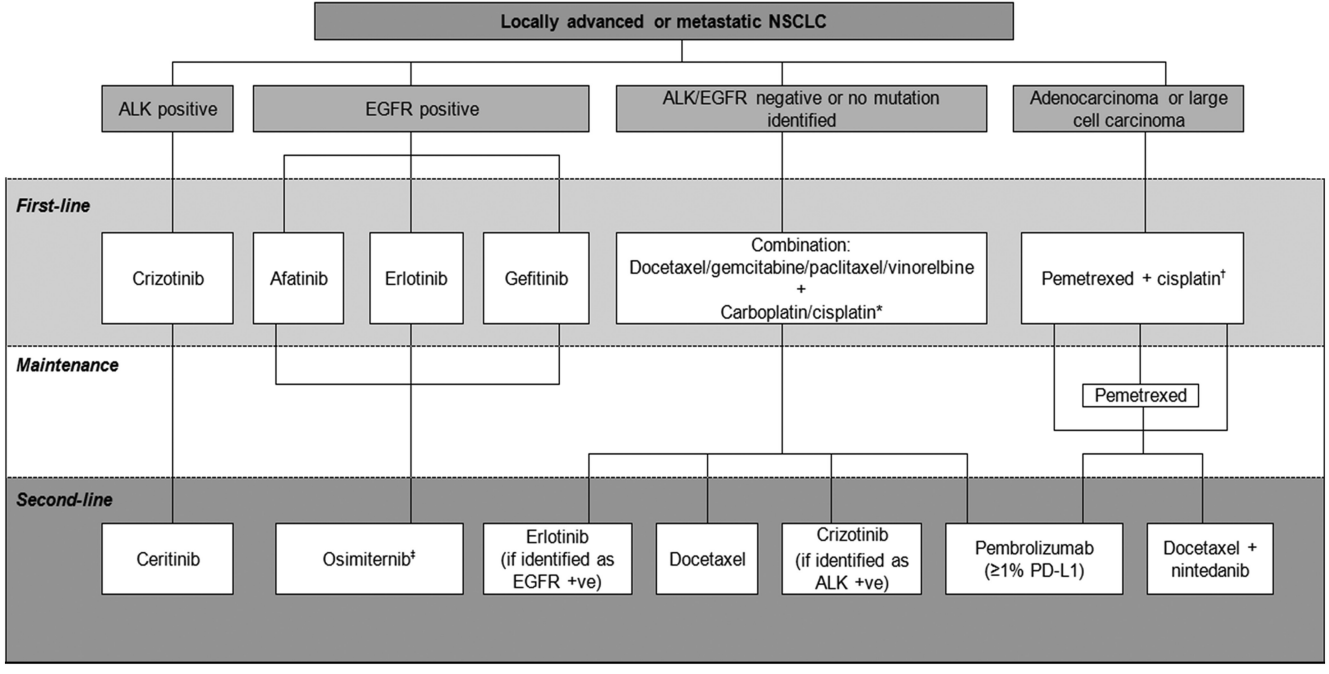

FIGURE 1.3
Example of common treatment options for NSCLC: advanced or metastatic NSCLC treatment pathway based on NICE guidance CG121.

1.6 Important Economic Concepts for Cost-Effectiveness of Cancer Interventions

Economic evaluation is the process of systematic identification, measurement, and evaluation of the inputs and outcomes of two (or more) alternative activities (health interventions) and their subsequent comparative analysis (Drummond, 2002, 2015). Economic evaluation in the context of cancer involves assessing the value of various cancer treatments, often through a metric that combines the quantity (length) of life and the quality of life experienced during that time, called a QALY. This is particularly valuable when some expensive cancer drugs demonstrate modest or small improvements in survival (e.g. 1 or 2 weeks). In later chapters of this book, we will discuss the importance of HRQoL for economic evaluation in a cancer context.

Concerns have been raised as to whether healthcare should be considered an economic good (Morris et al., 2012; Santerre & Neun, 2000). Some think these concerns are unfounded because, ultimately, healthcare resource is finite and scarce. There is a limited supply of doctors, nurses, and healthcare staff, so it is unlikely that any healthcare system in the world can achieve a level of spending on the health of its citizens that would meet all their healthcare needs. In some cases, access to cancer treatments might be more readily available in one region of a country and not in another, creating regional equity issues (Chamberlain et al., 2015). It is reported, using real-world data from registries, that women and those living in economically deprived areas have less access to cancer treatment compared to other groups (Chamberlain et al., 2015). Some have controversially argued that we can achieve healthcare for most individuals by *not* treating criminals, smokers, and alcoholics, whereas others have argued that healthcare is a basic human right and that it is not appropriate to treat it like an 'economic good,' as if it were any consumer good or service (Morris et al., 2015). We will leave these questions to the economic philosophers and policymakers because they involve complicated judgments, which need not concern us here.

1.6.1 Economics, Health Economics, Economic Evaluation, and Pharmacoeconomics

Economics is the science of scarcity and choice. Health economics is related to the supply and demand for healthcare. Although health itself is not an economic good, healthcare resource *is* an economic good. Healthcare resource refers to items such as hospital beds, treatments, drugs, surgeries, GP time, and so on. These resources usually have costs associated with them. For example, a visit to the doctor might be valued at £100 for one hour. Government institutions might make decisions at the national level on how the total healthcare demand and supply can be met for a given budget constraint.

However, what is usually of concern in the pharmaceuticals context for comparing new treatments is pharmacoeconomics. Pharmacoeconomics uses certain principles of health economics for making policy decisions on the supply and demand for medicines – particularly in clinical trials. The methods (analysis techniques) used in pharmacoeconomics involve the description and analysis of the costs of drug therapy to healthcare systems and society. It identifies, measures, and compares the costs and consequences of pharmaceutical products and services (Rascati, 2009). The process of using these methods is called 'economic evaluation.' Economic evaluation applies mathematical and statistical methods to compare the costs and consequences of alternative healthcare options (Drummond 2002, 2005).

The term pharmacoeconomics might be considered as nothing more than a generic term for economic evaluation of medical interventions (specifically drugs). Rather than the cumbersome 'economic evaluation of drugs,' pharmacoeconomics is a simpler term. However, pharmacoeconomics might also address questions on affordability (and not just efficiency) of a new drug, using budget impact models (BIMs). A BIM measures the net cumulative cost of a particular treatment for a given number of patients in a specific population. This is accomplished by implementing comparative cost-determination analyses for competing scenarios, both including and excluding the product of interest (Sullivan et al., 2014).

For over a decade, economic evaluation has become an increasingly important component of clinical trials. The number of Phase III clinical trials with a health economic component has also increased substantially. In particular, submissions to reimbursement authorities – e.g. government-led subgroups that assess the evidence for the 'value' a new treatment offers, such as the Scottish Medicines Consortium (SMC) and the National Institute for Clinical Health Excellence (NICE) in the UK, have also increased by more than 45% over the same period.

In this book, we consider economic evaluation in the context of pharmacoeconomics, i.e. evaluating the costs and benefits of treatments from clinical trials where data are collected prospectively in the trial. However, we also extend this to determining costs and effects outside a controlled clinical or experimental setting (in the real world). Economic evaluation uses various techniques to assess the value of pharmaceutical interventions and health strategies. In short, the terms 'pharmacoeconomics,' 'cost-effectiveness,' and 'economic evaluation' may be used interchangeably when describing approaches to estimate the economic value of new cancer interventions.

1.6.1.1 Value

When it comes to healthcare, the average person has no idea about the price for surgery or a treatment plan, especially when healthcare is considered to be 'free of charge,' such as with the NHS in the UK. We might all be aware of the price of diamonds or footballs, and most of us can value them (in relative

terms), or at least we are likely to put the price of diamonds higher than that of footballs. Consequently, people may pay a premium price for diamonds and similar goods. However, it is likely that, in a severe drought, someone could well exchange diamonds for a cup of water (due to its scarcity).

Health products (or services) are not items we can buy 'off the shelf.' Therefore, it is harder to value and subsequently put a price on them. This is true whether the health item is a new treatment or something as complex as surgery. Some economists have suggested that the problem of value could be determined by how much one was prepared to pay for a certain good, assuming certain market conditions were satisfied. Economic theory was then formulated to explain how value could be determined by the demand and supply for goods (for a useful introduction, see Morris, 2012; Santerre & Neun, 2000). Allocation of goods was determined simply by how much one was prepared to pay (i.e. price paid) for that item – leading to French economist Jules Dupuit (Ekelund, 1999) to surmise in his 1844 paper that 'the value of a good is the amount someone is prepared to pay for it' – or how much one is willing to pay (WTP) for it.

In the context of health, the buyer is not necessarily the same as the consumer. The buyer of the health product is likely to be a government institution or an entity responsible for healthcare provision. The consumer is the patient. In other words, allocation of healthcare goods is based on the price that governments (taxpayers) are prepared to pay. This is not necessarily true in all countries however, and it will depend on the structure of the healthcare system of each country.

Valuing health, or for that fact, any product, by how much people are prepared to pay does not take into account the impact on the wider society – or the welfare of everyone. For example, richer people are less likely to suffer from prices going up than the poor. This was not considered equitable, therefore, to address this, a further development in economics: (extra) welfare economics took place, which need not concern us here (see bibliography for more details). What is important for our purposes is to appreciate that the economic evaluation techniques encountered in this book are tools for decision-making to determine which treatments or health technologies offer the greater relative value in terms of a price (or cost) people (i.e. society) are prepared to pay, termed the cost-effectiveness threshold.

1.6.1.2 Allocative Efficiency

Allocative efficiency is where health resources are deployed across an economy in the most efficient manner to match patient needs and preferences. Allocative efficiency is where decision-makers use the evidence (results) from economic evaluation to determine the best set of allocations of treatments that gives an optimum for a given medicines budget. For example, if only £100,000 were available for providing two cancer treatment options, drug A and drug B, the question might be how best to spend the £100,000 on

these two treatments. If the price of drug A is £2,000 per year and B is £5,000 per year, one could treat 50 patients with treatment A or 20 patients with treatment B. The other option is to have some patients take treatment A (so long as it works) and some take treatment B. The exact mixture of treatments A and B that will make up the £100,000 is for the decision-maker to determine. The comparative value that A and B offer will influence this decision.

Following the above example further, with £100 million to spend, treatment A could be effective in patients with a particular genetic disposition (biomarker). An optimal allocation might be to treat some patients who have the presence of the biomarker (e.g. EGFR +ve) with the new treatment and treat those that are EGFR-ve with the current treatment.

One technique for such comparative economic evaluation is called cost–utility analysis (CUA), which seeks to address the question of (optimal) allocative efficiency within the health sector. In the assessment of the cost-effectiveness of cancer drugs, CUA is the one that is most pertinent. By using such methods, it is hoped patients will have access to 'value for money' treatments through an efficient allocation of various medicines subject to a 'budget constraint.'

1.6.1.3 Technical Efficiency

Technical efficiency is when the minimum amount of resource (e.g. lowest dose, or shortest duration of dosing) is used to elicit a given level of response, i.e. when one produces a certain level of output with the least amount of input – for example, the lowest dose that achieves a 20% reduction in lipid levels. Economic efficiency occurs when the production cost of a given output is as low as possible: for example, the least costly way of resolving a peptic ulcer. Cost-effectiveness analysis (CEA) is one such tool used to address the issue of economic efficiency.

In health economics, we distinguish between efficacy, e.g. whether a drug or intervention actually works in a technical sense, which is mainly assessed through randomized clinical trials (RCT) when feasible. Effectiveness is whether the same intervention actually works in everyday operating conditions, e.g. after market authorization or a license is given. Generally, (clinical) effectiveness will be lower than, or at best equal to trial effectiveness due to the inherent limitations of clinical trials.

Reimbursement

In the context of pharmaceuticals, once a drug has been approved for licensing by the relevant regulatory body, such as the Food and Drug Administration (FDA), European Medicines Agency (EMA), or some other national agency, the pharmaceutical company will seek a price for its newly licensed drug. Reimbursement, in simple terms, means the price the pharmaceutical company would like to obtain from the decision-maker (payer) for the new drug it has produced. For example, the pharmaceutical company might want £120 per tablet, but the payer might want to pay only £95 per tablet, based on the

assessment of evidence of 'value' presented by the company. The price could be on a per tablet basis or for a supply of 28 days – such as £50 per tablet, or for 28 days £1,400. The price of, say, £50 is what the payer has agreed to pay for each tablet. The price set is usually agreed between the payer (e.g. the Department of Health in the UK) and the pharmaceutical company. For example, the price per tablet of lenolidamide (in 2011) was agreed at £249.60 for a single 25 mg tablet. This price is recorded in publications such as the British National Formulary (BNF, 2017).

In some countries, a dual-price system exists, whereby a market price is set at a certain level and then, at a second stage, a reimbursement price is set at a fraction of the market price. The difference between the two is the price charged to patients; it constitutes the so-called patient's 'out-of-pocket expense.' The market price is typically calculated to cover the research and development costs of the pharmaceutical company as a minimum, and to make a profit to sustain future R&D activities. From the payer perspective, the lower the price, the better. However, the price should not be set so low that innovation is discouraged. A premium price is usually a price higher than the current market price for similar existing products (for example when there is a similar reference price set for all drugs within a therapeutic group). A premium price may be awarded if the drug demonstrates improved 'value for money' through economic evaluation techniques.

It is for this reason that, when a health economic evaluation is undertaken, the payer perspective is considered carefully. That is, who is the economic evaluation for? Is it from the perspective of a health insurance company (in the US and some other countries, there is no equivalent of the NHS) or for the local or national government (as in Spain where local provinces can influence decisions)? In short, who will be reimbursed?

In the UK, the Pharmaceutical Price Regulation Scheme (PPRS) is a voluntary agreement between the payer (the government) and industry with the objective that (effective) medicines are available on reasonable terms to the NHS, and this in turn maintains a strong, efficient, and profitable pharmaceutical industry. The workings of these groups are complex, but details can be found in the official publications, such as those of the UK Department of Health and Healthcare. Similar schemes exist for other countries. In France, for example, the Health Products Pricing Committee (Comité Economique des Produits de Santé) and drug manufacturer sign a number of agreements allowing a variety of flexible means to monitor prices and drug use while ensuring that public resources are properly allocated.

1.6.1.4 Opportunity Cost

A very important concept in health economics, and economics in general, is the notion of opportunity cost. Opportunity costs are defined as "the value of the next best alternative" (Polley, 2015; Folland et al., 1997). This applies

especially for health resources without market prices, such as informal care. A shadow price is then derived from alternative marketed resources (for example the cost of hiring a home-visiting nurse) to approximate the social value of the non-marketed resource. However, market prices are only considered as adequate under ideal market conditions in perfect competition. This may not apply to many resources in the healthcare sector. (For a recent discussion on the application of opportunity costs to hospital bed days see Sandmann et al., 2017.)

For some activities, like childcare, alternative market prices exist that yield an upper price limit for these services; for others (e.g. the market price for studying) one could use an opportunity cost approach by valuing the activity performed by the cost of forgone leisure time (this implicitly assumes that everyone prefers leisure to work, or 'work as punishment'). In this case, a 'proxy price' needs to be established using contingent valuation methods, such as willingness-to-pay or willingness-to-accept elicitation for non-market, or some other stated preference method (Ryan, 2008; McIntosh et al., 2010). Opportunity costs also arise in fixed-budget constraints.

Economic evaluation is often set against the background of an opportunity cost when comparing treatments. In the context of medicines, for example, assuming a fixed budget of £100 million, the payer may have the difficult decision of allocating all £100 million to pay for drug A for 10,000 patients, which might improve survival by 1 year (cost of £10,000 per year per patient). The opportunity cost might be spending the £100 million on treatment B for 20,000 patients, which might improve survival on average by 6 months (£5,000 per year per patient). In practice, a combination of treatments A and B may give an optimal allocation of available funds.

1.6.1.5 Discounting

Most people prefer to receive benefits sooner and pay costs later, rather than sooner. For example, people prefer to enjoy smoking now and give less importance to their future health. As someone becomes older, his or her time preference may change.

In health economic evaluation, future costs and benefits are discounted so that their value can be judged in present terms. This is achieved by applying an annaul constant discount rate, e.g. 3.5% in the UK (based on the Treasury Department's so-called 'Green Book'). The consequence of the discount rate is that less weight is given to later costs than to the present costs. We use the discounted values of future costs and benefits in cost-effectiveness calculations.

Some cancer trials run for a long time and costs of any health resource used at the beginning of a 7-year trial starting in 2015 may be different to costs at the end of the trial, finishing in 2022. If the trial stops following up patients after 4 years, costs might be determined at 2019 prices. However, for

the remaining 3 years (2020, 2021, and 2022), in each year, the future costs would be discounted.

For example, the future costs of treatment for a single patient who experiences disease progression in 2015 (and withdraws from the trial) in each of years 2020, 2021, and 2022 are expected to be: £3,000, £5,000, and £7,000 (total £15,000 over 3 years) – because the patient may have other subsequent treatment or care. After discounting at 3% per year, the future costs are valued as:

Year 2020 $£3{,}000 \times 1/(1+0.03)^1 = £2{,}912.62$ 1 year after withdrawal
Year 2021 $£5{,}000 \times 1/(1+0.03)^2 = £4{,}712.98$ 2 years after withdrawal
Year 2022 $£7{,}000 \times 1/(1+0.03)^3 = £6{,}405.99$ 3 years after withdrawal

The total future costs of £15,000 for this patient after discounting are £14,031.59. In this example, only costs are discounted. In practice, health benefits are also discounted. The debate about whether or not we should discount costs only and not benefits or discount them at different rates, is discussed elsewhere (e.g. see Drummond, 2002) and not considered further. The current practice, however, is to discount both future health benefits and costs. Note that if a trial is 7 years long (1-year recruitment plus a further 6 years follow-up) then discounting is important. However, if in a 7-year trial where recruitment is over 6 years with a 1-year follow-up (e.g. a very rare tumor), then a key concern is the application of a consistent price year. Discounting is applied on expected future costs and effects beyond the first year of follow-up.

1.6.1.6 The Incremental Cost-Effectiveness Ratio

The incremental cost-effectiveness ratio (ICER) is the basis of most economic evaluations. It is a numerical quantity that expresses the relative (mean) differences in costs between two or more treatments compared to the relative effects. It is often written as a simple equation:

$$\text{ICER} = \frac{\text{Mean Costs A} - \text{Mean Costs B}}{\text{Mean Effect A} - \text{Mean Effect B}} \tag{1.1}$$

The numerator is called the mean incremental cost. The denominator is called the mean incremental effect. The higher the value of the ICER, the less cost-effective a treatment is (A vs. B). As can be seen from the denominator, when two treatments are similar regarding their effectiveness, the ICER is likely to be large. Hence cancer treatments that are cost-effective are expected to show mean differences in effectiveness to be somewhat larger than zero. The ICER is judged against a willingness-to-pay (WTP) threshold, a term introduced earlier. The WTP is a value that is also referred to as the cost-effectiveness threshold expressed by the term λ, or the shadow price. The value of λ represents the cost in terms of health forgone elsewhere when