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Budget-Impact Analysis of Health Care Interventions

A Practical Guide

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For my husband Sy

—Josephine Mauskopf

For our mentor Jo Mauskopf

—Stephanie Earnshaw,
Anita Brogan,
Sorrel Wolowacz, and
Thor-Henrik Brodtkorb

Author Contributions

All authors contributed to conceptualizing the outline of the book and to authoring their respective chapters. In addition to being chapter authors, Dr. Mauskopf and Dr. Earnshaw integrated the chapters, ensured consistency throughout, and edited the book.

Foreword

Now more so than ever, both public and private payers desire budget-impact analysis as part of "the fourth hurdle" to gain market access and reimbursement for pharmaceutical, health technology, or biotech products. Despite the growing number of guidance documents worldwide that address budget-impact analyses, to date there has not been a practical handbook for those creating budget-impact analysis models and spreadsheets. Jo Mauskopf and Stephanie Earnshaw have produced the perfect balance between scientific rigor and pragmatic considerations for designing accurate and transparent budget-impact analyses. This book is consistent with the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Task Force Report in Budget-Impact Analysis, yet provides a more in-depth description of how to implement best practices for budget-impact analyses. The examples and case studies clearly articulate how to put into operation the analytic framework and calculations of an informative budget-impact analysis.

Dr. Mauskopf was one of the primary authors of both the original and revised ISPOR Budget-Impact Analysis Principles of Good Practice and has published more budget-impact analysis articles than anyone else I know. I have taught budget-impact analysis with Jo Mauskopf for more than a decade, so I can attest to the fact that she really knows the nuances of designing a budget-impact analysis for both flexibility and precision. A budget-impact analysis model typically is designed to be adaptable for other payers or geographies. At the same time, a budget-impact analysis is only credible and useful when there is predictive accuracy. This book provides a roadmap for those who design budget-impact analyses to achieve the simultaneous goals of accuracy in estimation while "keeping it simple."

I highly recommend this book to professionals in the pharmaceutical, biotech, or health technology assessment fields as well as payers and policy makers who are accountable for health-care spending and coverage decisions. As a professor who has taught cost-effectiveness analysis and pharmacoeconomics, I also recommend the book as a text for students and instructors.

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Preface

We have written this book in response to the continued increasing interest in budget-impact analysis we have observed over the years. While several resources are available that describe methods that should be used for developing these types of analyses, we have noted that researchers in a variety of roles continue to seek practical, hands-on training. In addition, several reviews have concluded that published budget-impact analyses frequently do not use appropriate methods. In response, we have been actively teaching clients, students, and budget holders the methods and practical issues associated with budget-impact analysis through the development of these analyses for real-world use and by serving as faculty for various seminars and short courses. Over time, we have recognized the potential usefulness of a practical guide to help researchers develop these analyses and to help budget holders critically assess them. We hope that this book will serve as such a guide for readers wishing to understand the essentials of designing, constructing, and critically assessing these analyses.

This book is organized to provide readers with a basic overview of budget-impact analysis, the essential elements involved in these analyses, and recommendations to maximize their credibility and usefulness. We have designed the book to offer a step-by-step approach to designing and building these analyses and to understanding the various issues to consider during this process. We have aimed to keep this book very practical to help researchers develop budget-impact analyses that can be used to address real-world questions about new health-care technologies for both acute and chronic conditions. For this reason, we have provided examples, exercises, and a fully programmed budget-impact analysis in Microsoft Excel to help readers work through real-world issues.

We are acutely aware of the fast-moving environment in the field of pharmacoeconomics and outcomes research. The methods presented in this book provide the reader with one perspective on the approach to these analyses. As health-care technologies improve and more problems concerning budget assessment are presented to various budget holders, there undoubtedly will be advancement in methods and techniques. We hope that this book will provide a well-grounded foundation for budget-impact analysis even as the field continues to evolve.

Particular thanks go to Allen Mangel and RTI International for their support in enabling us to write this book. We would also like to thank Daniel Mullins for his valuable comments and guidance on the content of each chapter, Ashley Davis for helping construct the sample budget-impact analysis included with this book, Daniel Siepert and Jason Mathes for their editorial and graphics support, and Betsy Falvey and Valerie Tower for their assistance with various logistics. We are also very grateful to the multiple course participants and clients who have constantly presented us with new challenges in the design, construction, and presentation of these analyses.

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Abbreviations

ACE	Angiotensin-converting enzyme
ADAP	AIDS Drug Assistance Program
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse event
AHP	Allied health professional
AHTA	Agency for Health Technology Assessment
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ASCT	Autologous stem cell transplant
ASP	Average sales price
AWP	Average wholesale price
BIA	Budget-impact analysis
CADTH	Canadian Agency for Drugs and Technologies in Health
CBC	Complete blood count
CDC	USA Centers for Disease Control and Prevention
CDR	Canadian Common Drug Review
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
Chl	Chlorambucil
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CPT	Current Procedural Terminology
DA	Darbepoetin alfa
DAA	Direct-acting antiviral (drug)
DCCPS	Division of Cancer Control and Population Sciences
DES	Discrete-event simulation
DLQI	Dermatology Life Quality Index
DM	Disease-related mortality
DMARD	Disease-modifying antirheumatic drug
DMT	Disease-modifying therapy
DPP-4	Dipeptidyl peptidase-4

DRG	Diagnosis-related group
EA	Epoetin alfa
EGFR	Epidermal growth factor receptor
EU	European Union
GDP	Gross domestic product
GM	General mortality
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General practitioner
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
ICD-O-3	International Classification of Diseases for Oncology
ICS	Inhaled corticosteroid
IFN	Interferon
INR	International normalized ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LAI	Long-acting injectable
MPH	Methylphenidate
MPH-EX	Methylphenidate extended release
MPR	Medication possession ratio
MRgHIFU	Magnetic resonance-guided high-intensity focused ultrasound
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NICE	National Institute for Health and Care Excellence
NMO	Neuromyelitis optica
NSCLC	Non-small cell lung cancer
OChl	Ofatumumab in combination with chlorambucil
PA	Prior authorization
PASI	Psoriasis Area and Severity Index
PBAC	Pharmaceutical Benefits Advisory Committee
PDC	Proportion of days covered
PegIFN	Peginterferon beta-1a
PMPM	Per member per month
PsA	Psoriatic arthritis
Q3W	Every 3 weeks
QALY	Quality-adjusted life-year
QW	Every week
RA	Rheumatoid arthritis
RBRVS	Resource-based relative value scale
RChl	Rituximab in combination with chlorambucil
SEER	Surveillance, Epidemiology, and End Results
SMDM	Society of Medical Decision Making
TNF	Tumor necrosis factor
UAE	Uterine artery embolization

UK	United Kingdom
USA	United States
VBA	Visual Basic for Applications
VHA	Veterans Health Administration
XR	Extended release

Contents

Chapter 1
Introduction to Budget-Impact Analysis

Josephine Mauskopf and Stephanie Earnshaw

Abstract This chapter provides an introduction to budget-impact analysis. Because of concerns about rising health-care expenditures, health-care budget holders are interested in estimates of how new health-care interventions will change expenditures or budgets for health systems. Budget-impact analyses develop estimates of these changes with the introduction of the new intervention. These estimates are based on the expected changes in resource use and cost for the mix of interventions and the condition-related outcomes in the population of interest over a given period in the future. Budget-impact analysis differs from cost-effectiveness analysis in perspective, population, interventions compared, time horizon, and outcomes. Many jurisdictions worldwide have developed guidance documents for individuals who perform such analyses and for individuals who review them. Based on these guidelines, we present an overview of the components that should be included in every budget-impact analysis.

Keywords Budget-impact analysis • Cost of medical care • Budget-impact analysis guidelines • Budget-impact analysis components

Chapter Goal
To provide an introduction to budget-impact analysis, the questions that it can answer, who uses it for what, the availability of published guidelines, and an overview of the components required to complete a budget-impact analysis.

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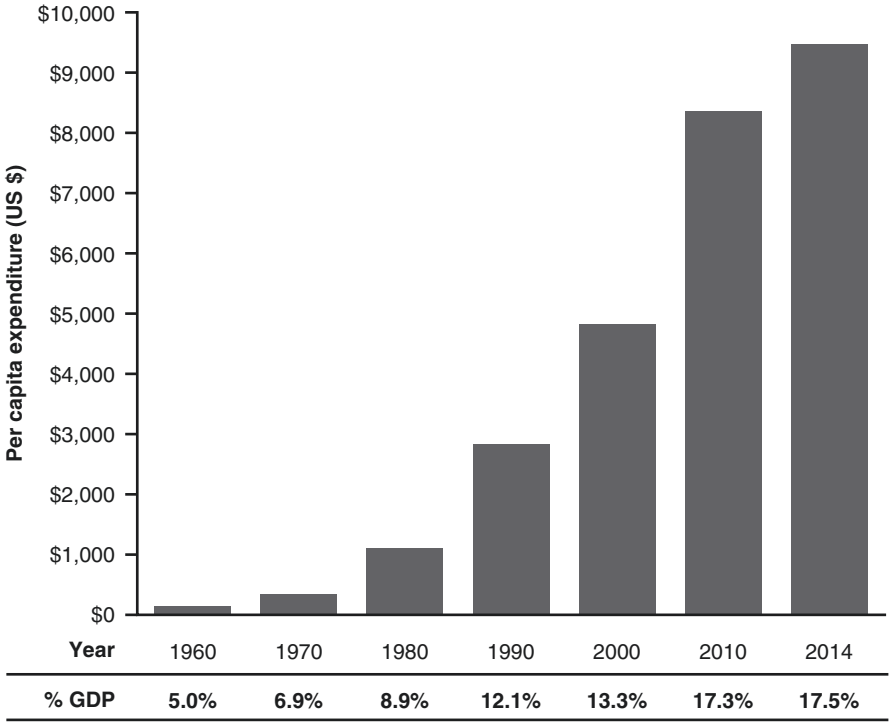

Fig. 1.1 National health expenditures per capita, 1960–2014 (Centers for Medicare and Medicaid Services, 2016). *GDP* gross domestic product

Life expectancy and population size worldwide have increased in the last 100 years because of public health measures and advances in medicine. From 1950 to 2050, the United Nations (2001) estimated a change in the world population from 2.519 billion in 1950 (observed) to 9.322 billion in 2050 (projected). For the more developed regions, these population figures range from 0.814 billion in 1950 to 1.181 billion in 2050, and for the less developed regions, they range from 1.706 billion in 1950 to 8.141 billion in 2050. With this increase in population size, total health-care expenditures would be expected to increase. These may be accompanied by increasing tax revenues and health insurance premiums.

In addition to the expected increases in health-care spending because of population growth, there have been increases in the per capita expenditures for health care. This is illustrated in Fig. 1.1 for the USA. The two primary reasons why per capita health-care expenditures might increase are (1) an aging population with a greater prevalence of chronic illness and (2) increases in the availability and prices of health-care services that can successfully treat both acute and chronic conditions. In Fig. 1.2, we illustrate the United Nations projections for the growth in the proportion of the population older than 65 years between 1950 and 2050 both for more and less developed countries.

In any economy, in the short run, increasing expenditures on health care, whether by governments using tax money, health insurers using revenue from premiums, or individuals using personal income, may leave fewer resources for expenditures on

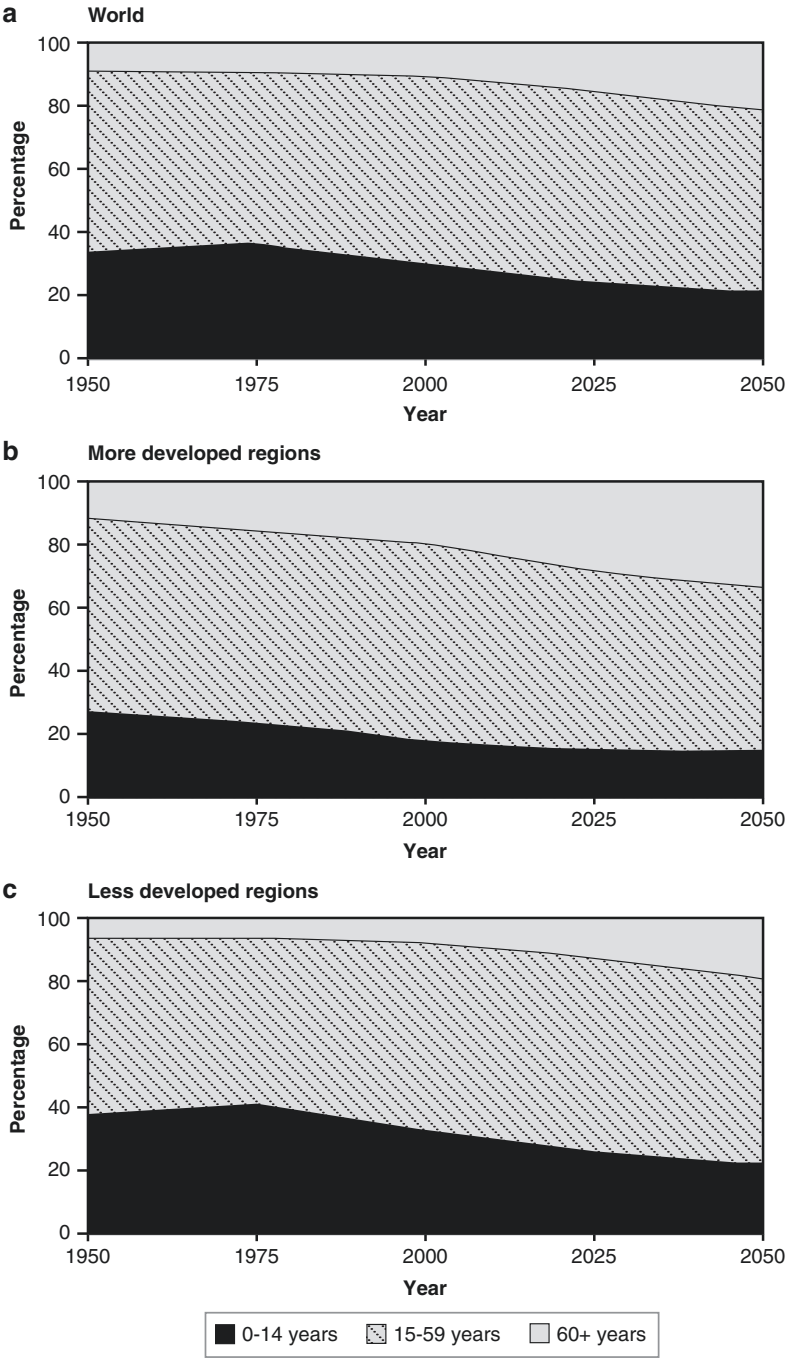

Fig. 1.2 Changes in the age distribution of the world's population: 1950–2050 (United Nations 2001, Section III, Figure 13) (From *World Population Ageing: 1950–2050*, by United Nations Department of Economic and Social Affairs, © 2001 United Nations (Reprinted with the permission of the United Nations))

other goods and services. Increases in expenditures on health care can be justified when there are significant gains in health outcomes associated with the increase in expenditures that will have immediate positive effects on individuals and families as well as on the overall economy in the long run. But when resources are scarce, such increases in expenditures may result in unacceptable losses in purchasing power outside the health-care system in the short run. For this reason, rising health-care expenditures may be viewed with concern.

1.1 What Is Budget-Impact Analysis?

Because of concerns about rising health-care expenditures, budget holders are interested in estimates of how new interventions that change health outcomes and service use will affect expenditures or budgets for health systems. Budget impact has been defined in *The Directory of Health Economics* (Cuyler 2014) as follows:

> Budget impact is a forecast of rates of use (or changes in rates of use) with their consequent short and medium-term effects on budgets and other resources to help health service managers plan changes that result from the introduction of a new technology.

Thus, when a new intervention is introduced for a specific indication, budget-impact analyses estimate the resource use and cost for the mix of interventions and condition-related outcomes expected in the population of interest for a health-care budget holder over a given period of time after the introduction of the new intervention. These estimates are then compared with the resource use and cost over the same time frame for the mix of interventions and condition-related outcomes if the new intervention were not introduced. The resource and budget impact associated with the introduction of the new intervention is calculated as the difference in population resource use and costs, respectively, between these two scenarios.

Budget-impact analyses consider all patients who would be eligible for the new intervention within the jurisdiction of the health-care budget holder whether they use the new intervention or not. The mix of all interventions used for these patients is projected over the time frame of the analysis if the new intervention is introduced and if it is not. All costs associated with the new and competing interventions (e.g., drug acquisition, administration, monitoring, and management of side effects) are then considered. The analysis may also consider predicted changes in other condition-specific management costs arising from the introduction of the new intervention. For example, a reduction in hospitalization costs after the introduction of a more effective stroke prevention medication may be considered because this reduction may affect a health-care budget holder's total budget. The total costs for a scenario in which the new intervention is introduced are then compared with the total costs for a scenario in which the new intervention did not exist (i.e., the status quo) over the time frame of the analysis.

In a budget-impact analysis, the costs of interest to the budget holder are typically the undiscounted accounting costs expected to be incurred by the budget

holder net of discounts or patient co-pays when relevant. This is in contrast to cost-effectiveness analyses, where included costs represent discounted opportunity costs for the resources used for the intervention and condition-related treatment (Drummond et al. 2015).

In some budget-impact analyses, population health effects and changes in population resource use are also presented to the budget holder. For example, the expected reduction in the annual number of strokes and stroke-related deaths within the population after the introduction of the new intervention for stroke prevention within the budget-impact analysis period may be presented in addition to the estimates of the impact of these changes on the budget. The population use of health or other resources for the condition of interest, such as hospital days or physician visits within the budget-impact analysis period, may also be presented. This allows budget holders to understand both the impact of the new drug on their budget and the impact on population health and/or health-care resources during the same time period. These estimates can be useful for reaching population health targets and planning resource needs.

1.2 Budget-Impact Analyses Compared with Cost-Effectiveness Analyses

Budget-impact analyses are very different from cost-effectiveness analyses. Budget-impact analyses estimate the changes in the budget holder's costs for the total population who are eligible for treatment with the new intervention in the budget holder's jurisdiction when the new intervention is added to the treatment mix being used to treat these patients. Cost-effectiveness analyses estimate the value of treating eligible patients with the new intervention compared with standard of care or the next best treatment alternative. In Table 1.1, we present an overview of the key differences between budget-impact analyses and cost-effectiveness analyses.

1.3 Uses of Budget-Impact Analyses

Estimates of the budget impact of new health-care interventions are now widely used by health-care budget holders in jurisdictions with different types of health-care systems to help them understand affordability and make decisions about the use of these interventions. Particular uses include the following:

- Health technology assessment agencies and health plans may use the results of budget-impact analyses to inform reimbursement recommendations or to determine whether restrictions in coverage of an intervention are desirable (e.g., restrict use to more severely ill patients or those for whom current interventions have failed).

Table 1.1 Key differences between budget-impact analysis and cost-effectiveness analysis

	Cost-effectiveness analysis	Budget-impact analysis
Comparators	• A single treatment or treatment approach compared with a standard of care treatment or treatment approach (e.g., drug A vs. drug B)	• Projected mix of treatments used by the population without the new intervention in the treatment mix compared with a projected mix of treatments that includes the new intervention. (i.e., a budget scenario without the new intervention versus a budget scenario with the new intervention)
Population studied and treatment shares	• Single patient or cohort of patients who all (100%) will initiate treatment with either the new intervention or an alternative intervention • Subpopulations, all of which will use the new intervention or an alternative intervention	• Population of patients who are eligible for the new and competing intervention, where treatment share for the new intervention in the treatment mix will generally be much less than 100% and may change over the model time horizon • Subgroups of the patient population (e.g., patients with a specific level of condition severity or with specific prior treatment history) eligible for the new intervention might also be studied
Time span	• Condition duration (range from a few days to remaining lifetime)	• Year by year (i.e., annual budgets) • Typically present annual budgets for the next 3–5 years
Example outcome measures	• Incremental discounted lifetime costs • Incremental discounted life-years or QALYs • Incremental cost per life-year gained • Incremental cost per QALY gained	• Eligible population changes in treatment-related costs and total health-care costs (undiscounted) for each budget year • Eligible population changes in condition-specific morbidity measures or mortality (undiscounted) for each budget year • Eligible population changes in hospital bed-days or physician visits for each budget year

Value to budget holder	• Understanding the value for money of a new intervention
	• Used for:
	Resource allocation decisions among different interventions
		• Understanding the budget impact of the new intervention
		• Used for:
		  • Budget planning
		  • Reaching target population health outcomes
		  • Planning health resource needs

QALY quality-adjusted life-year

- Budget holders and payers may use the results of budget-impact analyses to estimate the impact of providing patients unrestricted or restricted access to a new health-care intervention based on the estimated changes in health services use or budgets.
- Local budget holders or third-party payers may use budget-impact analyses to support requests for additional health-care funds from national budget holders or for justification of higher insurance premiums.

In Box 1.1, we present some examples of uses of budget-impact analyses and the budget holders who use them.

Box 1.1. Use of Budget-Impact Analyses by Health Technology Assessment Agencies and Other Health-Care Budget Holders

Uses of budget-impact analysis by health-care budget holders	Examples of budget holders using budget-impact analysis in specific use
Budget-impact analysis used to determine the financial consequences of the introduction of the assessed health technology into the jurisdiction	USA health plans, USA federal and state health policy makers, Canadian provinces, Australia (PBAC), Colombia, Poland
Budget-impact estimates for a new pharmaceutical used by national or regional drug plans to inform decisions about drug formulary placement or reimbursement	Canadian provinces, USA health plans, Australia (PBAC)
Budget-impact estimates used to inform requests for additional government funding or higher insurance premiums to support coverage of new health-care interventions	USA government or private health plans
Interactive costing templates estimating budget impact provided as a tool for regional budget holders to use to support the implementation of reimbursement recommendations	England and Wales (NICE)
Budget-impact analysis used to ensure that the group of publicly funded interventions produces the biggest gain in population health subject to budget limits and equity constraints	Colombia
Budget-impact analysis only an optional inclusion in submission for formulary approval and/or reimbursement	Taiwan

NICE National Institute for Health and Care Excellence, *PBAC* Pharmaceutical Benefits Advisory Committee, *USA* United States

1.4 Guidelines for Budget-Impact Analyses

Because of the growing importance of budget-impact analysis for decision making, many jurisdictions worldwide have developed guidance documents for individuals who perform such analyses and for individuals who review them. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) issued a set of guidelines for performing these analyses first in 2007 (Mauskopf et al. 2007), with an update in 2014 (Sullivan et al. 2014). Other guidelines published in English include those for Canada (Marshall et al. 2008; Patented Medicine Prices Review Board [PMPRB], 2007), Belgium (Neyt et al. 2015), Australia (Pharmaceutical Benefits Advisory Committee [PBAC] 2015), Poland (Agency for Health Technology Assessment [AHTA] 2009), WellPoint in the USA (WellPoint 2008), and England and Wales (National Institute for Health and Care Excellence [NICE]

2013). Some of these guidelines provide jurisdiction-specific how-to guidance and suggested input data sources (PBAC 2015; NICE 2013; Marshall et al. 2008), while others provide more general guidance on the estimation framework and types of input data sources (Sullivan et al. 2014; AHTA 2009; WellPoint 2008). Although some of the jurisdictions post the final results of the analyses for specific technologies (e.g., Australia), only NICE posts their budget-impact analyses (costing templates) including the model structure, assumptions, inputs, and results on a public website for review by all interested parties.

1.5 Overview of Chapters in This Book

In this book, we provide detailed instructions for creating a credible budget-impact analysis for a new health-care intervention. We also present many examples showing how the different components of a budget-impact analysis have been completed for different types of health conditions. The components of a credible budget-impact analysis that are presented in this book are shown in Fig. 1.3 and include the following:

- A determination of the analytic framework needed for estimating the budget impact based on health system budget-impact analysis guidelines, health system and condition characteristics, decision-maker needs, and data availability

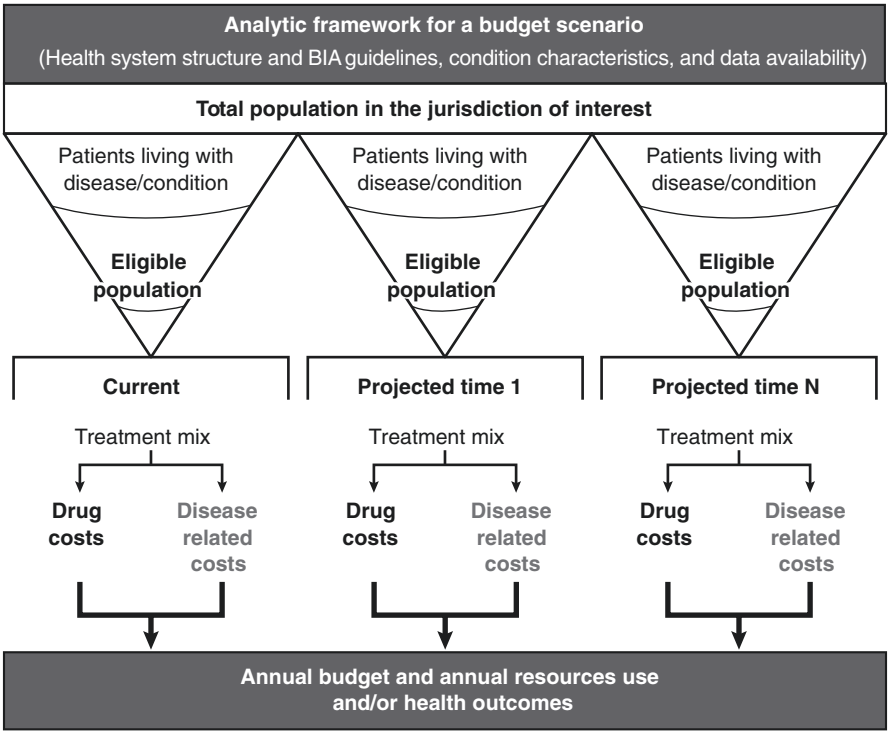

Fig. 1.3 Conceptual diagram for completing a budget-impact analysis. *BIA* budget-impact analysis

- Estimation of the treated population size and relevant descriptors without and with the new intervention in the treatment mix
- Determination of the time horizon
- Determination of the current treatment mix and changes in this treatment mix over the analysis time horizon with and without the new intervention
- Estimation of changes in the intervention-related costs in the treatment mix over the analysis time horizon
- Estimation of changes in condition-related costs over the analysis time horizon
- Choice of computing framework to reflect the chosen analytic framework, condition and intervention characteristics, and data availability
- Presentation of the results in a format useful for the budget holder
- Estimation of the uncertainty of the budget-impact analysis estimates
- Validation of the budget-impact analysis estimates

In Fig. 1.3, we present a general conceptual diagram that illustrates the calculations needed to estimate the budget impact of the current or future treatment mix.

To keep the exposition simple, this book focuses on the budget impact of adding a new drug to current drugs for disease treatment. However, in Chap. 13 we describe approaches that can be used to address challenges that might be encountered when applying the methods described in this book to budget-impact analyses for other types of health-care interventions, such as vaccines, diagnostics, surgical procedures, and devices. Throughout the book, we illustrate each component of a budget-impact analysis with examples. Each chapter also includes exercises to allow interested readers to develop their skills for completing each component of the analysis.

Exercises

Exercise 1.1 Discuss the importance of budget-impact analyses for developed versus developing nations.

Exercise 1.2 Discuss the importance of budget-impact analyses for acute versus chronic conditions and for rare versus common conditions.

Exercise 1.3 A nation has not observed an increase in the average age of the populations for over 50 years. In fact, the population size within the nation has remained constant during this time. Explain why a budget-impact analysis may or may not be important to be performed when a new drug is introduced.

Exercise 1.4 List five different types of bodies (e.g., USA Managed Care Organizations) that might be interested in budget-impact analyses. Why might these bodies be interested in budget-impact analyses versus a cost-effectiveness analysis?

Exercise 1.5 Identify a drug that has just been introduced for a particular condition. Identify attributes of this drug that may affect a budget holder's overall health-care budget.

Exercise 1.6 Identify a drug that has just been introduced for a particular condition. Discuss how the population characteristics, competing drugs, resource use/costs, and results presented may differ when examining the impact that this drug has on a budget holder's budget versus when examining the cost-effectiveness of this drug. Identify issues specific to the chosen drug and condition.

Exercise 1.7 Obtain budget-impact analysis guidelines from at least two countries. Compare and contrast components of the guidelines. How do the guidances differ? What level of detail is presented in the different guidance documents?

Exercise 1.8 Obtain guidelines for budget-impact analyses and cost-effectiveness analyses for one country. Compare and contrast the guidance around the population, competing drugs, resource use/costs, and results.

Exercise 1.9 A new drug enters the market at a cost that is comparable to or lower than other drugs currently being used to treat the condition. Discuss the importance of the use of a budget-impact analysis to support the affordability of this new drug.

Exercise 1.10 Identify situations in which a budget-impact analysis might be more important to a budget holder than a cost-effectiveness analysis.

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Chapter 2
Determining the Analytic Framework

Sorrel Wolowacz, Josephine Mauskopf, and Stephanie Earnshaw

Abstract Before the inputs needed for a budget-impact analysis for a new drug can be determined and their values derived and before the computer model can be designed to perform the analysis, an analytic framework must be established. The analytic framework provides the overall approach to the analysis, and its components are described in this chapter. This framework might vary from jurisdiction to jurisdiction and from budget holder to budget holder within the same jurisdiction. Design of the analytic framework requires an understanding of jurisdiction requirements for a budget-impact analysis. Also required is an understanding of the health system and the relationship between the characteristics of the health system and how the new drug will affect the budget for a specific health plan or region. The introduction of a new drug can affect the budget in multiple ways. The most important components to understand for a jurisdiction when constructing a budget-impact analysis are the eligible population, the potential use of the drug in the treatment pathway, and the budget holder cost perspective and time horizon. Once these are understood, model specifications can be prepared to guide the analysis.

Keywords Budget-impact analysis • Analytic framework • Eligible population • Time horizon • Treatment pathway • Cost perspective • Model specifications

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Chapter Goal
To identify and discuss the analytic framework that will determine the components of a budget-impact analysis for a new drug for the jurisdiction(s) of interest. The components of a budget-impact analysis include the eligible population size and relevant descriptors, time horizon, treatment mix, cost perspective, and results presentation. They will be used in a set of specifications for the analyses and may be used to formulate a detailed flow diagram to guide the budget-impact analysis.

The goal of a budget-impact analysis for a new drug[1] is to assess the impact that introducing the new drug into the treatment mix for patients who are eligible for the new drug will have on the annual budget for a health plan or region. The first step in developing the budget-impact analysis is to establish an analytic framework that defines the overall approach to the analysis. The design of the analytic framework should be consistent with jurisdiction-specific guidelines or requirements for a budget-impact analysis if they are available. The design of the framework might vary from jurisdiction to jurisdiction and from budget holder to budget holder within the same jurisdiction.

The analytic framework requires an understanding of the health system and the relationship between the characteristics of the health system and how the new drug will affect the budget for a specific health plan or region. The introduction of a new drug can affect the budget in multiple ways. The following components are important to understand for a jurisdiction when constructing a budget-impact analysis:

- Eligible population within the jurisdiction
- Budget holder time horizon
- Potential use of the new drug within the treatment mix
- Budget holder cost perspective

Once these are understood, a flow diagram and model specifications can be prepared to guide the analysis. Each of these components is described in the following sections.

[1] In this chapter, we will make the simplifying assumption that the analytic framework is being designed to evaluate the introduction of a new drug for one jurisdiction and one type of budget holder within that jurisdiction. In practice, it may be more efficient to choose an analytic framework that can be readily adapted for use in multiple jurisdictions and for several types of budget holders or that can be used to evaluate other types of health-care interventions. Building flexibility for use in multiple jurisdictions or by different budget holders into the analysis will be discussed further in Chap. 7. Changes in the analytic framework needed for budget-impact analyses for other health-care interventions are described in Chap. 13.

2.1 Eligible Population in Jurisdiction

One of the most important differences between a budget-impact analysis and a cost-effectiveness analysis is that a budget-impact analysis estimates the impact of the introduction of a new drug on the annual costs for treating the population eligible for the new drug within a particular jurisdiction. Costs are estimated for patients receiving the expected mix of all available treatments in two scenarios: (1) if the new drug is introduced and (2) if the new drug is not introduced. The changing pattern of use of the alternative treatments (or no active treatment) for each scenario is projected into the future. The budget impact is estimated by comparing the total costs for all treatments in budget scenario 1 (the new drug is introduced) with the total cost for budget scenario 2 (the new drug is not introduced). In contrast, a cost-effectiveness analysis examines the value for money offered by a new drug in comparison with currently available treatments (measured as the incremental cost per unit of incremental outcome). In a cost-effectiveness analysis, costs and outcomes are estimated for a representative cohort of patients with the condition of interest receiving the new drug compared with those expected for these same patients receiving an alternative comparator treatment, where the comparator treatment could be standard of care or the next most effective treatment or no treatment.

In a budget-impact analysis, the population is characterized as an "open" population, with people entering and leaving each year as new patients require treatment and existing patients no longer require treatment. The primary focus for the analysis is not to follow individuals over the course of their health condition but to assess the annual treatment and condition-related expenditures for the total population being treated for the condition of interest in the jurisdiction each year, reflecting the pattern of use of the new drug and other competing treatments within the population. Thus the estimation of the treated population size and its relevant descriptors each year are a critical component for any budget-impact analysis.

As part of the analytic framework, it is important to include a carefully considered definition of the population of interest and identify any factors that might influence the population size relevant to the analysis. The starting point is to define the population expected to be eligible for the new drug. This definition is often the same or similar to the licensed indication, but may differ, for example, if it is expected that treatment will be limited to a specified subgroup of patients within the licensed indication or a proportion of patients may be too frail or have contraindications for the new drug. In many cases, it will also be important to define the position of the new drug in the treatment pathway. For example, is it intended for use as a second-line treatment or in patients who have had an inadequate response to specified drugs or for whom these drugs are unsuitable?

Once the population has been defined, it is important to identify any factors that might alter the population size over time or upon introduction of the new drug and ensure that these are appropriately accounted for in the analysis. For example, population growth, demographic change, or trends in the incidence or prevalence of the condition over time may alter the number of people with the condition of interest over the course of the analysis time frame. In addition, the positioning of the drug in the treatment pathway, regulatory or reimbursement decisions, and attributes of the new drug also may affect the size of the eligible population. These factors are considered in Sects. 2.1.1 through 2.1.5.

2.1.1 *Impact of Positioning of the New Drug Within the Current Treatment Pathway on Eligible Population Size*

The number of patients eligible for the new drug will depend upon current treatment patterns and the positioning of the new drug in the treatment pathway. Treatment patterns in routine clinical practice are influenced by regulatory and reimbursement restrictions, local clinical guidelines and protocols (including the extent to which local guidelines or protocols are followed), provider training, and patient expectations and may differ among and within jurisdictions. For example, while there are many drugs indicated for treatment of a specific condition, some drugs might be recommended for first-line use, while others are reserved for treatment failures or subsequent lines of treatment or disease subtypes. For some drugs, a diagnostic test may be required to identify a subset of patients eligible for treatment, where it would be important to consider the proportion of patients selected by the test. Different patterns of acute treatment, prophylaxis, and/or secondary prevention may also be relevant and need to be considered when designing the budget-impact analysis.

In Box 2.1, we present an example of treatment patterns by patient subtype or line of therapy.

Box 2.1. Treatments Used for Different Patient Subpopulations

Treatment	Use in the population
Targeted therapy	
Indication: first-line locally advanced or metastatic breast cancer (Electronic Medicines Compendium 2015)	
Erlotinib and gefitinib	Patients with epidermal growth factor receptor-activating mutations
Pemetrexed in combination with cisplatin	Patients with other than predominantly squamous cell histology
Docetaxel	Broadly indicated
Line of therapy	
Indication: advanced/metastatic soft-tissue sarcoma (Electronic Medicines Compendium 2015)	
Anthracycline (doxorubicin or epirubicin) single agent or in combination with ifosfamide	First-line predominant therapy (Leahy et al. 2012)
Many single-agent and combination therapy options	Subsequent lines of treatment (Leahy et al. 2012)

To estimate the size of the eligible patient population for the budget-impact analysis, a review of the following (as relevant for the jurisdiction of the analysis) can be useful: regulatory indications, reimbursement restrictions, clinical guidelines (international, national, and local), consensus statements, local treatment protocols, and data describing current treatment patterns. Outlining a treatment pathway in a diagram for the condition of interest for the jurisdictions for which the budget impact is to be estimated can be useful to serve as a resource for the analysis and will help in the estimation of the eligible population size. Such a diagram can be used to show the current pattern of treatment for patients with the condition of interest under the patterns of use and/or reimbursement restrictions relevant to the analysis. If such a diagram is constructed, it should include a qualitative description of the jurisdiction-specific treatment patterns, such as which drugs are used in first line, second line, and so on. In addition, details of the reasons that patients follow different treatment paths (e.g., treatment failures or intolerance) may prove beneficial. We present a specific method for estimating the eligible patient population by funneling down to the relevant patient group(s) and position(s) in the treatment pathway in Chap. 3. The impact of regulatory and reimbursement restrictions on the eligible population size is summarized in Sects. 2.1.2 and 2.1.3, respectively.

2.1.2 Impact of Regulatory Approval on Eligible Population Size

Restrictions on use of the new drug may be imposed by the licensed indication, such as use only after failure of one or more current treatments, and such restrictions may vary by jurisdiction. For a budget-impact analysis that estimates the impact of on-label use, the approved indication for the jurisdictions where the analysis will be performed should be used to estimate the eligible population size. Discussion of the inclusion of off-label use is presented in Chap. 12. In addition, it will be important to consider the contraindications for the drug and the likely proportion of patients having contraindications for treatment.

In Box 2.2, we present some examples of differences in the approved marketing indications for drugs in the USA and the UK taken from the product labels. Based on the first example, the eligible population in a budget-impact analysis for natalizumab for the USA would include all patients with relapsing multiple sclerosis. In contrast, in an analysis for the UK, the population would be restricted to patients with highly active relapsing-remitting disease despite treatment with a beta-interferon or glatiramer acetate and patients with rapidly evolving severe relapse-remitting disease. In the second example, the eligible population in a budget-impact analysis for liposomal doxorubicin for treatment of AIDS-related Kaposi sarcoma for the USA would be predominantly patients receiving second-line therapy, because the indication in the USA is restricted to after failure of prior systemic chemotherapy or intolerance to such therapy. In contrast, an analysis for the UK would include patients receiving first-line or subsequent-line treatment, but only those with low CD4 cell counts and extensive mucocutaneous or visceral disease.

Box 2.2. Difference in Approved Marketing Indication for a New Drug

Drug	USA indication	UK indication
Natalizumab	Multiple sclerosis: monotherapy for patients with relapsing forms of MS Crohn disease: adult patients for whom conventional therapies and TNF-α inhibitors have failed	Multiple sclerosis: monotherapy for highly active relapsing-remitting MS despite treatment with a beta-interferon or glatiramer acetate or for those with rapidly evolving severe relapse-remitting MS Crohn disease: not indicated
Liposomal doxorubicin	AIDS-related Kaposi sarcoma after failure of prior systemic chemotherapy or intolerance to such therapy	AIDS-related Kaposi sarcoma in patients with low CD4 cell counts (< 200 CD4 lymphocytes/mm^3) and extensive mucocutaneous or visceral disease. May be used as first-line systemic chemotherapy or as second-line chemotherapy in patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin, and standard doxorubicin (or other anthracycline)

AIDS acquired immune deficiency syndrome, *CD4* cluster of differentiation 4, *MS* multiple sclerosis, *TNF-α* tumor necrosis factor alpha, *UK* United Kingdom, *USA* United States of America

2.1.3 Impact of Reimbursement Decisions on Eligible Population Size

Restrictions on use of the new drug also may be imposed by reimbursement agencies or third-party payers beyond those imposed by the licensed indication, and these restrictions are likely to vary by jurisdiction. For example, use of the new drug may be restricted to patients with a specific level of severity of the condition, based on a finding by a health technology assessment agency that the drug was only cost-effective within these specific severity categories. In countries with health technology assessment agencies that make recommendations about the use of or reimbursement for new drugs approved for marketing within a specific indication, it is not uncommon for these agencies to recommend reimbursement for only a subgroup of the patients covered by the marketing indication or to not recommend use of the new drug at all despite marketing approval. The frequency with which this happens varies from jurisdiction to jurisdiction. For example, a study of recommendations by the UK National Institute for Health and Care Excellence (NICE), the Australian Pharmaceutical Benefits Advisory Committee (PBAC), and the Canadian Common Drug Review (CDR) (Clement et al. 2009) showed that, respectively, only

87.4, 49.6, and 54.3% of submissions of new drugs approved for marketing were recommended for reimbursement. More recent studies of NICE and PBAC recommendations (Mauskopf et al. 2013a, b) found that only 77.8% (NICE) and 58.8% (PBAC) of new drugs with marketing approval were recommended for reimbursement. Moreover, restrictions that reduced the size of the indicated population were proposed in 55% (NICE) and 30.7% (PBAC) of those recommended.

In Box 2.3, we present examples of differences between marketed indications and NICE recommendations for use in the UK National Health Service.

Box 2.3. Examples of NICE Restrictions Within Licensed Indications

Licensed indication	NICE recommendation
Ofatumumab in combination with chlorambucil or bendamustine has a marketing authorization in the UK for treating chronic lymphocytic leukemia in people who have not had prior therapy and who are not eligible for fludarabine-based therapy	NICE gave a restricted recommendation for use of ofatumumab only in combination with chlorambucil and only for patients within the licensed indication for whom bendamustine treatment is not suitable (NICE 2015a)
Sacubitril valsartan has a UK marketing authorization for the treatment of symptomatic chronic heart failure with reduced ejection fraction	NICE gave a restricted recommendation for use of valsartan as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people: • With New York Heart Association class II to IV symptoms • With a left ventricular ejection fraction of 35% or less • Who are already taking a stable dose of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (NICE 2016)
Vortioxetine has a marketing authorization in the UK for the treatment of major depressive episodes in adults	NICE gave a restricted recommendation for use of vortioxetine as an option for treating major depressive episodes in adults whose condition has responded inadequately to two antidepressants within the current episode (NICE 2015d)

NICE National Institute for Health and Care Excellence, *UK* United Kingdom

In the USA commercial health-care system, where payer coverage decisions are made by managed care organizations and their pharmacy benefit managers, the reimbursement eligible population can be limited in the indicated population through prior authorization requirements for certain patients and by "step edits," which require a course of a generic or preferred treatment to have failed before the patient is eligible for the new drug. In Box 2.4, we present examples of step edits for drugs for lipid reduction or diabetes for a USA health plan.

Box 2.4. Step Edits for Drugs for Lipid Reduction and Diabetes in Aetna National Health Plan

3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors[a]

Health plan	Statins	Coverage status	PA	Step edit[b]	Notes
Aetna 5 Premium Tier Open Formulary 23.5 million members	Altoprev (lovastatin) 60 mg oral 24-h extended release tablet	Tier 3	No	Yes	Trial of one generic statin medication: atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin
	Atorvastatin calcium 80 mg oral tablet	Tier 1	No	No	
	Crestor (rosuvastatin) 40 mg oral tablet	Tier 2	No	No	With availability of generic rosuvastatin, the brand-name drug may be covered at a higher nonpreferred co-payment and/or added to the Formulary Exclusion List. Branded rosuvastatin may also be subject to precertification and/or step therapy
	Lescol (lovastatin) 40 mg oral capsule	Tier 3	No	Yes	Trial of one generic statin medication: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin

PA prior authorization
[a]Representative sample; not all are shown here
[b]Step edit/step therapy requires members to try a first-line medication, usually a generic first-tier therapy, first

Dipeptidyl peptidase-4 (DPP-4) inhibitors

Health plan	DPP-4 inhibitor	Coverage status	PA	Step edit[a]	Notes
Aetna 5 Premium Tier Open Formulary 23.5 million members	Januvia (sitagliptin) 100 mg oral tablet	Tier 2	No	No	

Health plan	DPP-4 inhibitor	Coverage status	PA	Step edit[a]	Notes
	Nesina (alogliptin) 25 mg oral tablet	Tier 3	No	Yes	Step edit. Trial of 1 month of two of the following medications: Jentadueto (metformin + linagliptin), Kombiglyze XR (metformin + saxagliptin), or Janumet/ Janumet XR (metformin + sitagliptin)
	Onglyza (saxagliptin) 5 mg oral tablet	Tier 2	No	No	
	Tradjenta (linagliptin) 5 mg oral tablet	Tier 2	No	No	

DPP-4 dipeptidyl peptidase-4, *PA* prior authorization, *XR* extended release
[a]Step edit/step therapy requires members to try a first-line medication, usually a generic first-tier therapy, first

2.1.4 Impact of New Drug Attributes on Initial Population Size

The "starting" population or total population eligible for treatment with the new drug within its marketed indication in a year will depend not only on the incidence and/or prevalence of the condition but also on the proportion of patients who are diagnosed and the proportion seeking treatment in the jurisdiction. The proportion diagnosed and/or seeking treatment might change when a new drug is introduced due to the effects of the drug and/or the environment in which the drug is being introduced, and this proportion may vary by jurisdiction. For example, with the introduction of a new drug with a better efficacy or safety profile than current treatments, people who were not seeking treatment due to concerns over efficacy or safety may decide to seek treatment.

If such changes are expected, they should be considered in designing the budget-impact analysis. We describe methods for estimating the initial size of the eligible population with and without the new drug in Chap. 3.

In Box 2.5, we present examples of when the introduction of a new drug has changed the size of the population seeking treatment.

2.1.5 Impact of New Drug Attributes on Population Size Over Model Time Horizon

As well as affecting the size of the population initially seeking treatment, the introduction of a new drug may also affect the size of the population over time as a direct impact of its efficacy. Specifically, improved efficacy such as a reduction in

Box 2.5. Changes in the Number of People with a Diagnosis and/or Seeking Treatment when a New Drug Was Introduced

New drug class for a specific condition	Reason for expected increase in population with diagnosis and seeking treatment
Neuraminidase inhibitors for influenza treatment	• No disease-specific antiviral treatment was previously available for influenza, generally a self-limiting disease. As a result, most people did not seek medical care. The availability of an effective new treatment encouraged people to seek treatment with the antiviral drugs
Direct-acting antiviral drugs for treatment of chronic infection with hepatitis C virus	• Previous treatments were not well tolerated and not very effective. Direct-acting antiviral agents are very effective, need a shorter duration of treatment, and will likely achieve a cure, preventing progression to severe liver disease. Thus more people with the diagnosis are likely to accept treatment. • In early disease, the infection is asymptomatic and thus may not be diagnosed. The availability of new effective drugs might encourage screening of those with risk factors for chronic hepatitis C virus infection

mortality or disease progression for a chronic condition may increase the size of the treated population and/or change its relevant descriptors during the analysis time horizon. For example, the treated population size might increase if, during the analysis time horizon, a new drug reduces mortality in patients with congestive heart failure. Improved efficacy in terms of increasing time to disease progression for those with advanced cancer may result in people being treated for a longer period of time, thereby increasing the size of the treated population at a given time. Reducing disease progression for a progressive disease like HIV infection through increasing CD4 cell counts might change the proportion of patients in the different stages of the disease being treated over a given period of time. We present methods for estimating these effects in Chap. 3.

In Box 2.6, we present examples of a new drug's impact on the size of the population and whether this change was accounted for in published budget-impact analyses. The magnitude of these effects will depend on the incremental efficacy of the new drug.

2.2 Budget Holder Time Horizon

The time horizon of interest to the budget holders should be considered. Typically those responsible for budget planning have only a short time horizon, ranging from 1 to 5 years. In some cases, the bulk of any cost offsets arising from the introduction of a more effective treatment may not be realized within 1–5 years. For example, drugs to prevent microvascular complications of diabetes might not show a reduction in these outcomes until patients have been treated with the new drug for more

Box 2.6. More Effective New Drug Altering Population Size and/or Relevant Descriptors

Drug and condition	Reason for expecting a change in the number of people being treated and how accounted for in publications
Valsartan was shown to reduce hospitalizations and deaths when added to usual care for heart failure patients not receiving ACE inhibitors	With reduced mortality, more patients would be alive and included in the treated population size each year. However, this effect was not included in the budget-impact analysis, which just included the offsetting costs of reduced hospitalizations (Smith et al. 2005)
Letrozole was shown to increase progression-free survival time and was approved as an additional aromatase inhibitor for the treatment of metastatic breast cancer	With increased time to disease progression and additional treatment choice, patients may stay on therapy longer. Assuming constant incidence of new cases and improved efficacy, more patients will be alive and will be treated each year. This effect on both drug and monitoring costs was included in the budget-impact analysis (Mauskopf et al. 2003)
Erlotinib was introduced as a targeted therapy for the first-line treatment of patients with EGFR mutation-positive advanced non-small cell lung cancer for a USA managed health-care plan. In trials, erlotinib was shown to increase progression-free survival time	With extended progression-free survival when drugs are given until disease progression, patients may be on treatment for a longer period of time. A budget-impact analysis for erlotinib included increased drug-related costs to account for an extended duration of treatment due to prolonged progression-free survival. However, this analysis did not account for the changes in nondrug costs because of the extended progression-free survival (Bajaj et al. 2014)
When highly active antiretroviral therapy with protease inhibitors was introduced for the treatment of people with HIV infection, treated patients experienced an increase in their CD4 cell counts, boosting their immune function and reducing the incidence of opportunistic infections	With an increase in CD4 cell counts, the distribution of the treated population among different CD4 cell count ranges shifted upward (reflecting higher CD4 counts), reducing the annual nondrug-related treatment cost per patient. However, the mortality rate in those with HIV decreased at the same time, increasing the number of patients in the treated population, which was not explicitly accounted for in the analysis (Mauskopf et al. 2000)

ACE angiotensin-converting enzyme, *EGFR* epidermal growth factor receptor, *HIV* human immunodeficiency virus, *USA* United States of America

than 5 years. Similarly, for slow-progressing chronic diseases such as multiple sclerosis or chronic hepatitis C infection, disease-modifying or curative drugs that are given early in the disease might not show a reduction in the costs within a 5-year time horizon. If these downstream cost savings are relevant to those using the results of the budget-impact analysis, they could be included in the model as a summary of predicted future cost offsets realized beyond the end of the analysis time horizon but

not included in the annual cost estimates. In any case, these long-term benefits will be captured in the cost-effectiveness analysis if one is conducted.

In Box 2.7, we present an example of a new drug class that might have both short-term and long-term health benefits that would have budget impacts.

Box 2.7. Time Horizon for Budget-Impact Analysis (NICE 2006)

Pegaptanib, a new vascular endothelial growth factor inhibitor, was approved for the treatment of age-related macular degeneration. The drug is given to patients for up to 2 year and discontinued early in patients who do not gain any improvement in vision. Use of this new drug is expected to result in improved visual outcomes such as fewer patients being registered as blind and reduced need for low-vision aids, rehabilitation, community services, and residential care. The table below presents the impact that the drug may have in both the short and long-terms.

Time horizon	Outcome
1–5-year time horizon	• In an analysis submitted to NICE (2006), the direct cost associated with pegaptanib treatment was estimated at approximately £1.2 million in 2006, rising to £22.4 million in 2010 • Cost offsets were estimated to total £101,000 in 2006, rising to £3.8 million in 2010 • The introduction of pegaptanib in England and Wales was estimated to result in a net direct cost of approximately £1.1 million in 2006, increasing to £18.5 million in 2010
Beyond the 5-year time horizon	• Due to the disease-modifying effect of pegaptanib, additional cost savings were predicted beyond 2010 • For a 10-year follow-up, additional cost offsets such as services for blind people (i.e., blind registration, low-vision aids, community care and residential care due blindness) and treatment of conditions (e.g., depression and fractures) in people with vision impairment were estimated to total an additional £18.3 million between 2011 and 2015

NICE National Institute for Health and Care Excellence

2.3 Potential Use of the New Drug Within the Treatment Mix

In developing the analytic framework for the budget-impact analysis, it is important to define the current mix of treatments in the population eligible for the new drug and likely changes to the current mix over the budget-impact analysis time horizon. It is also important to understand how the new drug will be used in the context of these current treatments. For example, will the new drug be used as an add-on to current treatments, as a substitute for current treatment, or as a treatment where none was available before? Will it be used in different ways for different patient

subgroups and in different jurisdictions? The budget impact of a new drug will largely depend on how it will be added to the current treatment mix for each patient subgroup in the treatment pathway. Clearly, the impact on the drug budget will be higher if it will be used as an add-on to other treatments or in those who have previously not received drug treatment. However, in these cases, savings in condition-related costs might partially or totally offset these budget increases.

In Box 2.8, we present examples of how a new drug might be used when introduced and how it might change the use of other drugs.

Box 2.8. Differing Uses of New Drugs in the Context of Current Treatments

New drug	Place in treatment mix	Likely impact on use of other drugs
Ofatumumab for first-line treatment of chronic lymphocytic leukemia (NICE 2014a)	Add-on to the existing treatment, chlorambucil monotherapy	Unlikely to change use of chlorambucil; reduction in use of other drugs used in combination with chlorambucil (chlorambucil monotherapy and chlorambucil combination therapy will be replaced by ofatumumab plus chlorambucil for some patients)
Dabigatran for the treatment and secondary prevention of thromboembolism (NICE 2014b)	Substitute for the existing treatment, oral anticoagulants such as warfarin and rivaroxaban	Reduction in use of warfarin and rivaroxaban (replaced by dabigatran for some patients)
Tolvaptan for treatment of autosomal dominant polycystic kidney disease (NICE 2015b)	New treatment; no alternative active treatment was available	None

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Another consideration when designing a budget-impact analysis is whether to include the possibility that the new drug will be used off-label in the jurisdiction and also if the existing treatments include drugs that are used off-label. The extent of current off-label use and/or potential for off-label use of the new drug will depend partly on restrictions on such use as well as availability of treatments for a condition and a provider's predisposition to use off-label treatments. Although drug companies may not promote their drugs off-label, in jurisdictions where such use for the new drug is likely, budget holders might be interested in budget-impact estimates that include this possibility. If off-label drugs are used in the current treatment mix and their use is likely to change with the addition of the new drug, they should be included in the analysis.

In Box 2.9, we present some comments from budget holders on the inclusion of off-label use for a new drug in the budget-impact analysis.

Box 2.9. Budget Holder Comments on Off-Label Use of New Drugs in Budget-Impact Analyses (Watkins and Danielson 2014, Page 3; Goettsch and Enzing 2014, Page 2)

Source	Position on off-label use
Watkins and Danielson (2014) Editorial commenting on the revised ISPOR Budget Impact Task Force Report	• "The task force recommends that model developers not model off-label use of the new product routinely but provide this additional analysis on user request; however, they agree that budget models are descriptive rather than normative. Inclusion of off-label use should not be construed as advocating it, because the models merely depict existing practice patterns without judging appropriateness. We encourage users to request it routinely because off-label use is to be expected in most cases. A model that does not include it is unlikely to reflect the user's setting realistically. For this reason, the Academy of Managed Care Pharmacy's Format for Formulary Submissions includes a specific request for 'significant off-label uses and potential new indications being studied'"
Goettsch and Enzing (2014) Editorial commenting on the revised ISPOR Budget Impact Task Force Report	• "In 2009, the Dutch minister of health care asked the Health Care Insurance Board (CVZ) to calculate the budget impact of the inclusion of the combined lifestyle intervention (GLI) in the basic insurance package. The GLI is an intervention aimed at overweight and obese persons, advising them on food and eating habits, supporting behavioral change, and supporting physical exercise. The intervention had a potential target group containing 35% of all Dutch inhabitants, and budget restrictions were getting tighter because of the declining economic situation. So, a BIA was needed, for which the CVZ contracted an independent academic group from the Erasmus University of Rotterdam, the Netherlands" • "After the BIA became public, two leading Dutch professors on (health) economics … authored an article in 'Het Financieele Dagblad' [van den Brink and Groot 2011] in which they suggested that the cost estimates could be an underestimation because indication criteria will often expand. Because off-label use was not part of the BIA, the budget holder could not use the BIA to quantify the effect of the suggested expansion. We think that it would have been better if she had taken off-label use into account"

BIA budget-impact analysis, *ISPOR* International Society for Pharmacoeconomics and Outcomes Research

Another factor that can make a difference to the budget impact of a new drug is the rate of uptake that is expected for the new drug in the eligible population. In addition, likely changes in the current treatments related to the uptake of the new

drug need to be understood for the jurisdictions of interest. Uptake of the new drug may reduce the number of patients not being treated or may reduce the number of patients taking older, less expensive, drugs. For example, if the treatment shares for the new drug will be taken from another branded drug of similar price to the new drug, the budget impact will be smaller than if they are taken from a low-cost generic drug. In Chap. 4, we describe how to estimate the uptake of a new drug and changes in the use of current treatments.

In Box 2.10, we present two examples of treatment mixes assumed for different budget scenarios and how NICE estimated the changes in the treatment mix with the addition of a new drug.

Box 2.10. Current and Projected Treatment Mixes from NICE Costing Templates

New drug costing template	Current share: treatment shares without new drug after 5 years		Projected share: treatment shares with new drug after 5 years	
Secukinumab was a new drug for treating moderate to severe plaque psoriasis in patients eligible for biologic treatment in England and Wales Current and projected treatment share were considered: • Current share: mix of shares without secukinumab was obtained from the manufacturer's submission • Projected share: mix of shares with secukinumab was obtained from clinical expert opinion (NICE 2015c)	Adalimumab	50%	Adalimumab	40%
	Etanercept	21%	Etanercept	14%
	Infliximab	7%	Infliximab	6%
	Ustekinumab	22%	Ustekinumab	20%
	Secukinumab	0%	Secukinumab	20%
Alemtuzumab was a new drug for treating active relapsing-remitting multiple sclerosis. A current and projected treatment mix was considered for each budget compared. Data for each treatment mix scenario was obtained from expert opinion (NICE 2014c)	Interferon beta 1a (total)	19%	Interferon beta 1a (total)	12%
	Interferon beta 1b	3%	Interferon beta 1b	1%
	Glatiramer acetate	10%	Glatiramer acetate	7%
	Teriflunomide	40%	Teriflunomide	34%
	Fingolimod	7%	Fingolimod	5%
	Natalizumab	11%	Natalizumab	8%
	Alemtuzumab	0%	Alemtuzumab	24%
	No DMT	10%	No DMT	10%

DMT disease-modifying therapy, *NICE* National Institute for Health and Care Excellence

2.4 Budget Holder Cost Perspective

The analytic framework needs to include a definition of the cost perspective of the budget holders who will use the budget-impact analysis. Cost perspectives are likely to vary among budget holders within a jurisdiction as well as across jurisdictions for the following reasons:

- Costs of producing health-care services are important to providers of services, while reimbursement rates for services provided may represent the costs incurred by payers.
- Fixed or variable costs within the analysis time horizon may differ among budget holders.
- Cost categories of interest, for example, direct costs (drug-related and condition-related), personal and social services costs, indirect costs, and caregiver costs, may differ among budget holders.

2.4.1 Service Delivery Cost Versus Reimbursement Rate

In determining the cost perspective to define in the analytic framework, it is important to understand the budget holder's perspective. This is likely to vary by jurisdiction, depending on the organization of the health-care system, and will affect the cost data selected for the analysis. The data may represent production costs (the monetary amount needed for a medical practice to provide goods and services), charges (the amount that the medical practice will invoice for the goods and services), or reimbursed amounts (the amount that a payer will pay the medical practice for its goods and services). A payer (e.g., a public or private health insurer in the USA) may be more interested in the reimbursed amount because this is what the insurer will actually pay the medical practice for the goods and services. Decision Makers acting on behalf of a health-care provider (e.g., NICE for the UK National Health Service) may be most interested in production costs because this is the amount the provider will incur in providing the service. A medical practice or hospital may be interested in understanding the impact on their production costs in providing the services as well as the reimbursement amount, which represents their income from the services provided.

Costs may be published in the case of a public or governmental provider and/or payer, such as the UK National Health Service reference costs and the resource-based relative value scale (RBRVS) for outpatient Medicare reimbursement. However, in the case of the private insurer making payments to the provider of health-care services, these reimbursed amounts are less accessible to the public. The reimbursed amounts are often negotiated values between the payer and the medical provider. Discounts and rebates may be offered for some medical goods and services, but may not be available for others. Variability among payers in reimbursed amounts is particularly evident in the USA jurisdiction where the payer system is dominated by many private payers, but it is also seen in jurisdictions with a single national health system. For example, NICE sometimes recommends drugs within patient access schemes in which the drug prices payable by the UK National Health

Service are not made public. We present methods for estimating drug and condition-related costs in Chap. 5 and 6, respectively.

2.4.2 Fixed Versus Variable Costs

It should be noted that in some cases, although a more effective drug may reduce resource use, this may not translate into reduced costs for all budget holders within the analysis time horizon. For example, a reduction in length of hospital stay due to lower complication rates when using a new drug may not be of sufficient magnitude to cut staffing costs for the provider, and the beds made available might not be filled with additional patients if the occupancy rate is low. This differentiation between fixed and variable costs is not often accounted for explicitly in budget-impact analyses. Generally, all costs are presented as if they are variable costs. Drug treatment costs are correctly considered as variable costs, but other condition-related costs may be more likely to have fixed and variable components. The budget-impact analysis should include only the variable components in the analysis if the fixed costs are unlikely to change within the analysis time horizon for the budget holder. For example, if the third-party payer pays for a hospital stay using a per-case amount (such as a diagnosis-related group), then reducing length of stay will not affect their budgets unless and until the per-case amount is reduced. However, if the third-party payer pays for a hospital stay on a per diem basis, then reducing the length of stay will affect their budgets. Variable costs may be different depending on the perspective for the analysis. For example, reducing the number of patients hospitalized may reduce the budget for a third-party payer but may not have much impact on the costs for running the hospital if staffing or other costs are fixed in the short run.

2.4.3 Cost Categories of Interest

In addition to an understanding of how the introduction of a new drug might affect service costs or reimbursement rates and fixed or variable costs, the analytic framework needs to reflect the costs encountered by the budget holders who will use the budget-impact analysis in the jurisdiction of interest. In particular, will the budget holders only be concerned with direct medical care costs, or are indirect costs (lost productivity), caregiver costs, or patients' out-of-pocket expenses also of interest? Within direct medical costs, will their focus be on drug acquisition costs, or will they be interested in all drug-related costs, including administration, monitoring, supportive medications, side effects, and any diagnostics that may be required prior to treatment initiation? Will they also be interested in the broader range of direct medical care costs, including condition-related costs that might change with the addition of the new drug to the formulary (e.g., cost offsets that might be expected due to a more effective treatment such as reduced hospitalizations for cardiovascular events resulting from a more effective antiplatelet agent)? And are there credible data to support estimates of offsetting condition-related costs?

In Box 2.11, we present examples of different categories of costs included in published budget-impact analyses.

Box 2.11. Budget-Impact Analyses Considering Different Types of Costs

Budget-impact analysis	Costs included
Budget impact of introducing prasugrel as an antiplatelet agent as an alternative to clopidogrel for patients experiencing acute coronary syndromes requiring an immediate percutaneous coronary intervention	In a budget-impact analysis developed for NICE (2009), the following were included: • Drug acquisition costs • Rehospitalizations in the year after an acute coronary syndrome episode because of lower recurrence of cardiovascular events and drug-related increased rates of bleeding (data from a head-to-head trial for the two drugs were available)
Budget impact of introducing targeted therapy with erlotinib for the first-line treatment of patients with EGFR mutation-positive advanced non-small cell lung cancer for a USA managed health-care plan	In a study by Bajaj et al. (2014), drug-related costs, including impact of improved efficacy through longer time to disease progression while on treatment, were considered. Costs included: • EGFR testing • Drug acquisition • Drug administration • Drug-related side effects But the analysis did not estimate the extra costs needed for disease monitoring and treatment during prolonged progression-free survival
Budget impact of new antiretroviral drugs for HIV entering the market between 2015 and 2019 and the introduction of generic versions of existing drugs for the Italian National Healthcare Service	• In a study by Restelli et al. (2015), drug acquisition costs were the only costs considered. • This study did not include any possible changes in costs for opportunistic infections because of new more effective or convenient treatment regimens or lower adherence with generic multi-tablet regimens
Budget-impact analysis of everolimus for the treatment of hormone receptor-positive, human EGFR-2-negative advanced breast cancer in Kazakhstan (Lewis et al. 2015)	In a study by Lewis et al. (2015), drug-related plus disease-related costs were considered. Costs included: • Drug acquisition • Drug administration • Grade 3 and 4 side effects • Disease-related costs pre- and postprogression, including subsequent lines of active anticancer therapy, hospital visits, general practitioner visits, home visits, radiotherapy, ambulance transports, hospitalizations, laboratory tests, imaging, supportive drugs, and palliative care

EGFR epidermal growth factor receptor, *HIV* human immunodeficiency virus, *NICE* National Institute for Health and Care Excellence, *USA* United States

Other annual costs for the population with the condition of interest that might change with the reimbursement and use of the new drug include social services costs, indirect costs associated with productivity changes, patients' out-of-pocket expenses, and informal care costs from family members. Will the budget holders using the results of the budget-impact analysis be interested in these costs? Should they be included in the analysis?

In Box 2.12, we present examples of the full range of treatment-related and condition-related costs that could be included in a budget-impact analysis for Alzheimer's disease and schizophrenia.

Box 2.12. Full Range of Treatment and Condition-Related Costs that Could Be Included in a Budget-Impact Analysis

Condition	Costs associated with condition
Alzheimer's disease	• Symptomatic treatment or disease-modifying drugs, including acquisition, administration, monitoring, and side effects • Other direct medical care • Nursing home care • Adult day care • Formal caregiver time • Informal caregiver time • Productivity loss for patient • Productivity loss for informal caregiver
Schizophrenia	• Symptomatic treatment drugs, including acquisition, administration, monitoring, and side effects • Other direct medical care • Productivity loss for patients • Productivity loss for family • Assertive community treatment • Sheltered residential care • Institutional care • Criminal justice system costs

2.5 Compilation of Analytic Framework

The final step in the process of developing the analytic framework specifications for the budget-impact analysis is to pull all the information considered in this chapter together by constructing a detailed set of specifications for the analysis that reflects the analytic framework for the jurisdiction(s) and budget holder(s) of interest and translates it into a plan for the analysis. The specifications should consider the following features:

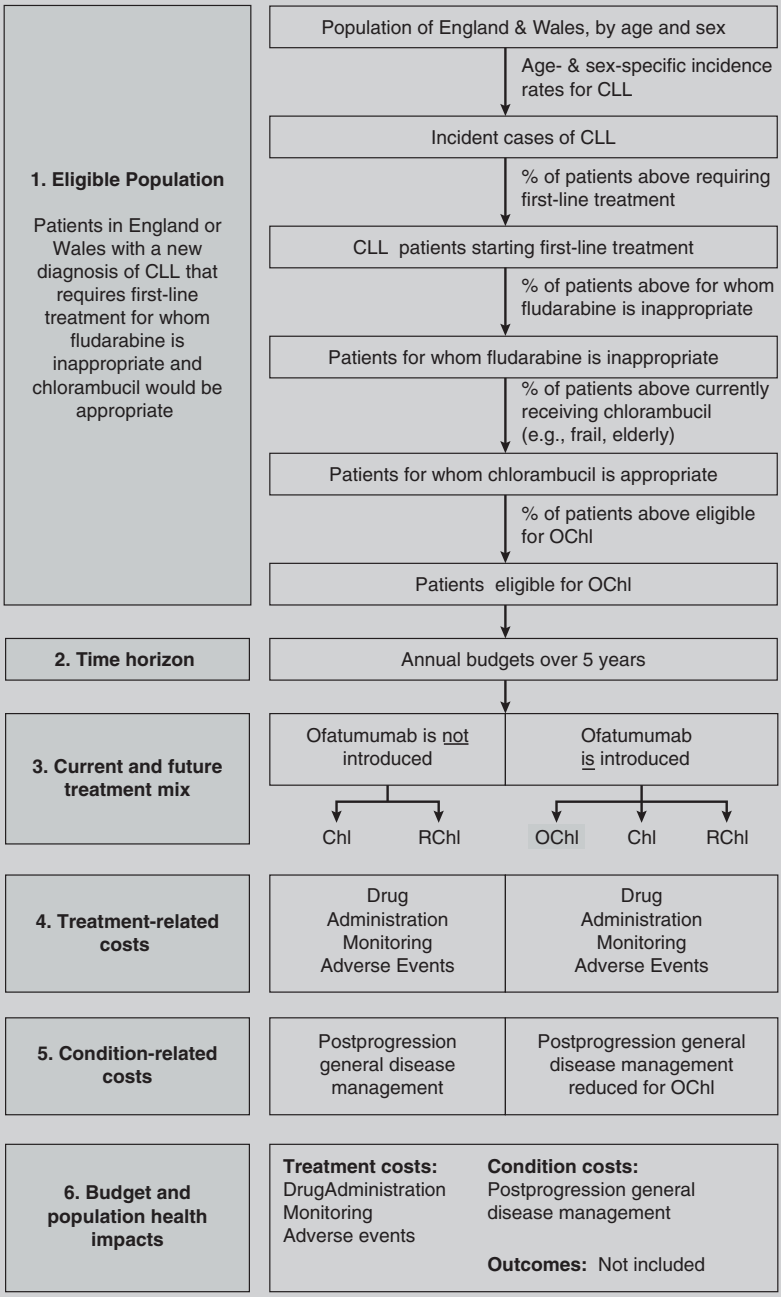
- The jurisdiction(s) of the analysis (and any anticipated future adaptations to other jurisdictions). If there is more than one jurisdiction, the features below should be considered for each jurisdiction, as they may differ.

- A description of the eligible population in the jurisdiction, including the following:
  - A definition of the population indicated for treatment with the new drug, any patient subpopulations of special interest, and any reimbursement or other eligibility restrictions for patients indicated for treatment in the jurisdictions of interest
  - The position of the new drug in the treatment pathway (a treatment pathway diagram in the jurisdictions of interest may be helpful)
- A description of any expected changes in population size over time and whether the new drug may alter the population size or severity mix.
- The time horizon preferred by budget holders in the jurisdiction of interest.
- Potential use of the new drug in the treatment mix in the jurisdiction of interest:
  - A listing of the current treatments used at the points in the treatment pathway where the new drug will be used
  - A description of how the current treatment mix is expected to change over the analysis time horizon if the new drug is introduced, including whether the new drug will be added to current treatments or replace some or all of them
  - If relevant to the budget holder, a description of the types of changes expected in condition-related costs due to the introduction of the new drug over the analysis time horizon
- The budget holder cost perspective, including the following:
  - Cost of production of services or reimbursement rate
  - Definition of variable costs within the analysis time horizon
  - Requirements for inclusion of different cost categories such as drug costs (acquisition, administration, monitoring, diagnostic, and side effect treatment costs), other condition-related direct medical care costs, personal and social services costs, indirect costs, and informal care costs
- A listing of the base-case and scenario/sensitivity analysis results to be presented, including relevant scenarios for different cost categories and patient subgroups.

As part of the specifications, a flow diagram may be helpful to illustrate the parameters that will be included in the budget-impact analysis and the cost categories that will be estimated.

In Box 2.13, we present a flow diagram for a budget-impact analysis for a new drug for treatment of chronic lymphocytic leukemia based on NICE description of their budget-impact analysis.

Box 2.13. Flow Diagram for an Analysis of the Budget Impact of Ofatumumab for the First-Line Treatment of Chronic Lymphocytic Leukemia (NICE 2014a)



In this chapter, we have described the main elements that make up the analytic framework for a budget-impact analysis. We have also presented examples of how the elements have been considered in published budget-impact analyses and how a detailed set of specifications can be constructed to document the analytic framework. A clear understanding of the analytic framework within which budget-impact estimates will be made is necessary; a flow diagram can be helpful in determining the input parameter values and budget-impact analysis estimates needed by the budget holders in the jurisdictions of interest. Once the analytic framework is complete, the input values can be derived from available data sources, and a computing framework can be developed to calculate the budget impact of the new drug. The derivation of the input parameter values and the computing framework form the topics covered in Chap. 3 through 7 in this book.

Exercises

Exercise 2.1 Describe a condition around which a budget-impact analysis might be created for multiple budget holders within a jurisdiction.

Exercise 2.2 Describe a condition around which a budget-impact analysis might be created for multiple jurisdictions.

Exercise 2.3 List differences between a cost-effectiveness analysis and a budget-impact analysis in terms of objective, population, comparators, time horizon, inputs, sources of data, results presented, and sensitivity analysis.

Exercise 2.4 Give examples of restrictions that may be placed on a newly approved drug or medical technology by a reimbursement or health technology assessment agency that might greatly affect the budget impact.

Exercise 2.5 Explain how clinical guidelines or approved treatment patterns may affect the development of a budget-impact analysis.

Exercise 2.6 Explain how co-payments, discounts, and/or rebates may affect a payer's budget.

Exercise 2.7 Discuss how the need to train physicians in how to perform a new procedure may affect reimbursement and the estimation of the impact to a payer's budget.

Exercise 2.8 Discuss how the budget impact may differ for a treatment of a rare condition such as hemophilia versus a common condition such as diabetes. How might the model framework differ?

Exercise 2.9 Explain how condition duration and treatment duration may affect the design of a budget-impact analysis.

Exercise 2.10 Identify a recently approved treatment for a condition and outline the framework for assessing the impact that the treatment will have on the budget holder's budget.

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Chapter 3
Estimating the Diagnosed, Treated, and Eligible Population

Stephanie Earnshaw and Josephine Mauskopf

Abstract One of the most important activities for completing a budget-impact analysis is understanding the population dynamics in order to estimate the size of the population eligible for the new drug. Determining those who are eligible for the new drug in the jurisdiction(s) of interest is a key determinant of the changes in costs and outcomes that may occur from the budget holder's perspective. The credibility of the analysis will depend on the model correctly identifying those eligible for the new drug based on the treatment pathway in each jurisdiction. In this chapter, we present methods for estimating the size of the eligible incident and prevalent populations, including changes in the size and condition severity mix of these populations over the analysis time horizon. Issues around patient subgroups and catch-up are also presented.

Keywords Incidence • Prevalence • Eligible population • Subgroups • Catch-up

Chapter Goal
To understand concepts and issues to be considered when estimating the population within a budget-impact analysis. Also to show how to estimate the population size and any changes in population size or condition severity mix that might occur over the analysis time horizon.

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One of the most important inputs to a budget-impact analysis is the estimate of the size of the population eligible for the new drug[1] and how this might change over the analysis time horizon with or without the new drug in the treatment mix. Also important is understanding the disease severity mix and other relevant characteristics of the population that is eligible for the new drug in each year of the analysis time horizon with and without the new drug in the treatment mix. This information is important as it is a key determinant of the expected budget impact of a new drug.

3.1 Incident and Prevalent Populations

The makeup of the population eligible for the drug each year of the analysis time horizon can be categorized into two groups: (1) those with the condition who may already be eligible for the new drug and (2) those who are not yet identified with the condition or who have the condition but do not yet meet the requirements for eligibility but may become newly eligible during the analysis time horizon. We refer to the first group as the prevalent population, whereas we refer to the second group as the incident population.

When estimating the population that is eligible for the new drug, a key determinant of the use of incident and/or prevalent populations is whether the drug is approved for treatment of an acute event or for treatment of a chronic condition. For treatment of an acute condition or acute exacerbation of a chronic condition, we are generally only interested in the incident population each year of the analysis time horizon. Since the acute event treatment duration is generally short, an acute event can be assumed to be resolved (with or without long-term sequelae) before the end of the budget-impact reporting period. As a result, consideration of a prevalent population (patients living with the acute event) is not relevant. Consideration of any long-term sequelae of an acute event (e.g., after acute meningitis) might be important to include in the budget-impact analysis, but their occurrence will only change with the addition of the new drug for incident populations during the analysis time horizon.

For chronic conditions where long-term treatment is needed either to slow disease progression, prevent acute relapses, or cure the condition, the budget-impact analysis should consider both incident and prevalent populations. Specifically, we need to include an incident population of those whose condition is newly diagnosed in a given year or those with the condition newly meeting the requirements for eligibility for the new drug in a given year (e.g., reaching specified severity level, failure of a previous treatment). We also need to include a prevalent population, patients with the condition who became eligible for the new drug in previous years but are either currently not being treated who might start treatment with the new drug or are being treated with other less effective, less tolerable, or less convenient interventions who might switch to the new drug.

[1] In this chapter, we make the simplifying assumption that the budget-impact analysis is based on the introduction of a new drug to the current mix of drugs for treatment of a condition. Changes in our recommended approaches to estimate the budget impacts of other types of health-care interventions (i.e., vaccines, diagnostics, surgery, and devices) are discussed in Chap. 13.

In Box 3.1, we present some examples of whether to include incident or incident plus prevalent populations in a budget-impact model.

Box 3.1 When to Include an Incident or Incident/Prevalent Populations

Treatment	Population to consider in a budget-impact analysis
New antibiotic for otitis media	Incident population only will impact budget, as treatment for the infection is short term. Patients newly eligible for the new antibiotic will be identified each year
New drug for treatment of an acute exacerbation of chronic obstructive pulmonary disease (COPD)	Incident population only will impact budget, as treating the exacerbation is short term. Patients having an exacerbation will be newly eligible for the new drug and will be identified each year
New drug for rheumatoid arthritis (RA)	Incident and prevalent populations may impact budget. The drug may be an option for patients with newly diagnosed RA, those with RA progressing to more severe disease, or those for whom previous treatments failed. New patients become eligible for treatment each year. In addition, the new drug may now be an option for current patients with RA who met eligibility requirements before the new drug became available and for whom other currently approved treatments may not be as efficacious, tolerable, or convenient as the new drug
New drug for HIV for use in highly treatment-experienced patients for whom a fully suppressive regimen is not available	Incident and prevalent populations may impact budget. The new drug may be an option for patients whose third treatment regimen is newly failing and for whom a fully suppressive regimen is not available. In addition, the new drug may now be an option for those whose third or fourth regimens failed in previous years and who are currently taking a nonsuppressive regimen
New drug for relapsing/remitting multiple sclerosis (MS) with restrictions to be used only if other marketed treatments have failed	Incident and prevalent population will impact budget. The new drug will be an option for a prevalent population of patients with MS who are having relapses on current treatment as well as for patients with MS who have stopped taking MS treatments because all other treatments were not tolerated or were not efficacious. An incident population of patients for whom current treatments are newly determined to be failing each year may also be added
New daily oral drug approved for second-line use in non-small cell lung cancer (NSCLC)	Incident and prevalent populations will likely impact budget. The new drug is an option for patients with NSCLC for whom first-line treatment has just failed. These incident patients will be identified as new patients each year. In addition, the new drug will be an option for a prevalent population of patients with NSCLC who have stopped taking NSCLC treatments because all other treatments were not tolerated or were not efficacious

HIV human immunodeficiency virus, *MS* multiple sclerosis, *NSCLC* non-small cell lung cancer, *RA* rheumatoid arthritis

3.2 Estimating the Eligible Population Size

To arrive at an estimate of the eligible population size, we recommend a process of "funneling down" from the total population in the jurisdiction of interest to those eligible for the new drug. This funnel-down approach may be accomplished through a series of calculations using data such as the following:

1. Total jurisdiction population size
2. Age and sex distribution in the population
3. Annual age- and/or sex-specific incidence for an acute condition or age- and/or sex-specific incidence and prevalence for a chronic condition
4. Percentage of the incident or prevalent population with a diagnosis of the condition and who are under a physician's care
5. Percentage of the incident or prevalent population with a diagnosis of the condition and who are under a physician's care who are included in the marketing indication for the new drug (eligible population)
6. Percentage of the eligible population who are not restricted for reimbursement of the new drug by additional criteria imposed by the reimbursement decision maker or health plan such as failure of previous treatments or prior authorization (reimbursement-eligible population)

Using these data, typically derived from a mixture of published, Internet, and other data sources, and starting from the jurisdiction or health plan total population, we can estimate the size of the incident and prevalent populations that might need to be included in the budget-impact analysis.

Although both incident and prevalent populations should be considered in a budget-impact analysis for a chronic condition, it is sometimes possible to estimate the eligible population size by combining these two subgroups into a single estimate of the annual treated prevalence. By doing this, the modeler is making the assumption that the treatment efficacy and mix will be the same for both the incident and prevalent populations.

In Box 3.2, we present two examples of the funnel-down approach. The example for asthma illustrates an approach combining the incident and prevalent populations into a single estimate of annual treated prevalence, whereas the example for HIV infection illustrates the approach when estimating the size of the incident and prevalent populations separately.

Box 3.2 Funneling Down to Estimate Eligible Population Size

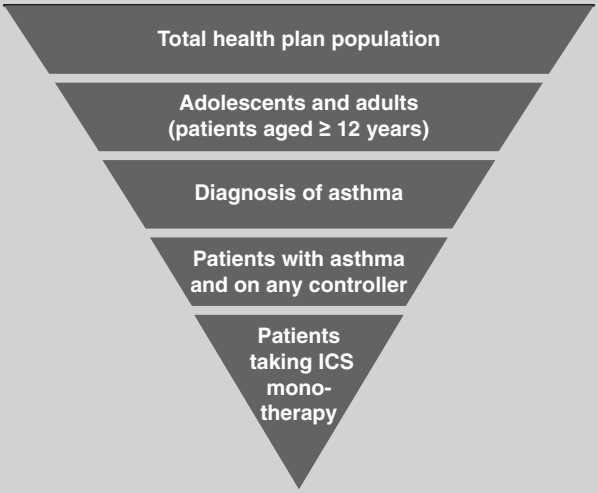
Identifying Patients Within a Health Plan Who May be Eligible for a First-line Inhaled Corticosteroid

Assume that a new inhaled corticosteroid has been approved in the USA for adolescents and adults (≥12 years of age) for prophylactic, maintenance treatment in asthma. Health plans want to understand the potential impact that including this new asthma drug on the formulary will have on their budgets. We can create the funnel-down approach for identifying patients who would

currently be eligible for treatment with this new drug out of the total health plan population.

1. We start with the total number of people within the health plan.
2. Since the drug is approved for adolescents and adults, the proportion of the members of the health plan that are adolescents and adults is estimated.
3. From these individuals, those with asthma are identified based on estimates of the national or local prevalence of asthma by age group.
4. Among these individuals, we further identify those who are on any maintenance controller treatment and those who are eligible for maintenance treatment with monotherapy with an inhaled corticosteroid depending on their disease severity using data from published studies or health plan data.

Funnel down to eligible asthma patients. ICS inhaled corticosteroid



The calculation to derive the number of patients taking ICS monotherapy then is as follows:

Number of patients taking ICS monotherapy
= total health plan population × percentage of population who are ≥12 years of age × percentage of patients who are ≥12 years of age with a diagnosis of asthma × percentage of patients with asthma on any controller × percentage of patients with asthma on any controller who are taking an ICS as monotherapy

Identifying Patients Within a Health Plan Who May be Eligible for Salvage Treatment Regimens for HIV Infection.

Assume that an antiretroviral treatment regimen has been approved in the USA for treatment for those with HIV infection who are highly treatment experienced and for whom no fully suppressive treatment regimens are currently available. Health plans want to understand the potential impact that

including this new HIV treatment regimen on the formulary will have on their budgets. We can create the funnel-down approach for identifying patients who would be eligible for treatment with this new regimen out of the total health plan population (the prevalent population) as well as those who would become newly eligible each year of the analysis time horizon (incident population).

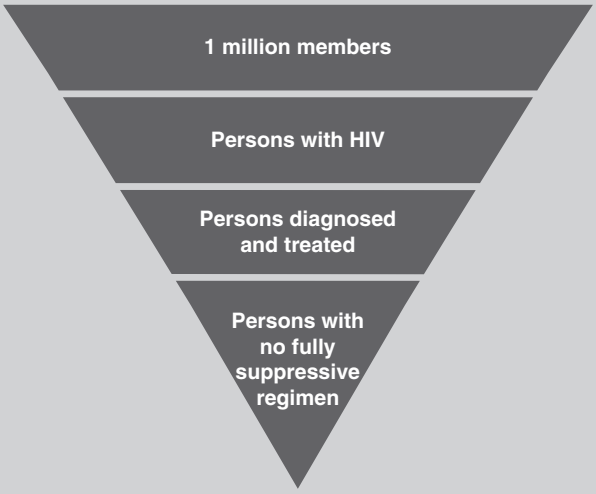
For those who would be eligible for the new regimen now (prevalent population):

1. We start with the total number of people within the health plan.
2. Since the treatment is approved for those with HIV infection, the proportion of the members of the health plan that are living with HIV infection is estimated based on local or national prevalence data.
3. From these individuals, the proportion with a diagnosis and who are treated with antiretroviral therapy is estimated based on national or local data.
4. Among diagnosed and treated individuals, we further identify those for whom three lines of treatment have failed and/or who have no fully suppressive regimens remaining. These estimates are based on published estimates of the prevalence of multiclass-resistant HIV from observational data cohorts or from estimates of the life expectancy after initiating first-line treatment and the average duration on the first three lines of treatment from modeled data.

For those who would become newly eligible each year (incident populations):

5. We divide those whose third regimen has failed and/or those who do not have a fully suppressive regimen (the prevalent population) by their average life expectancy to estimate the number of people who are newly eligible for the new regimen each year.

Funnel down to HIV patients eligible for a new fully suppressive regimen. HIV human immunodeficiency virus



The calculation to derive the prevalent population taking salvage therapy then is as follows:

Number of patients currently taking nonsuppressive therapy
= total health plan population × percentage of population who are infected with HIV × percentage of patients with a diagnosis and who are treated with antiretrovirals × percentage of patients with multiclass-resistant HIV and who have no fully suppressive regimens available.

The calculation to derive the incident population eligible for the new regimen each year is as follows:

Number of patients newly eligible for new regimen each year
= total number of patients currently taking regimens that are not fully suppressive / average life expectancy after starting a regimen that is not fully suppressive

3.3 Data for Identifying the Eligible Population

In the ideal situation, jurisdictions, health plans, or other users of the analysis would use data for identifying the eligible population either by using their own population rates at each level of the funnel-down approach or by obtaining estimates of the reimbursement-eligible population directly from health plan data. However, those performing the budget-impact analysis may not have access to these data. In addition, even if the data were available, the required analyses are time-consuming and would need to be performed separately for each jurisdiction or health plan. As a result, initial or default data may be used in the analysis by those developing budget-impact models, with the final model users able to substitute their own jurisdiction- or health plan-specific data when available.

Identifying the eligible patient population typically starts with the population of the jurisdiction, whether it be a health plan that covers one million lives or the population of a country or region in which health care is provided via a social system. If the jurisdiction's total population is that of a country or region, these data may be extracted from national or regional census statistics, which are typically available online.

This total population may be broken down by age and sex since most medications are approved for patients within a specific age range (adults versus adolescents versus pediatrics) and frequently incidence and prevalence of the condition of interest vary by age and/or sex. If total jurisdiction population age and sex distribution are needed and are not readily available from the specific jurisdiction population, then, as noted above, national or regional census data can be used as default values. Incidence and prevalence data for the condition will also be available from national or regional statistics or from published epidemiological studies in the region of interest or in another region with similar population characteristics, living conditions, climate, etc. The actual use of general census, age- and sex-specific population statistics, and incidence/prevalence estimates can be

advantageous and can help ensure that changes in the size of the population eligible for the new drug that could occur due to demographic changes will be accounted for in the budget-impact analyses (e.g., an increase in the number of patients requiring treatment for age-related macular degeneration due to population aging). If prevalence data for a chronic condition are not available, they may be estimated based on annual incidence rates and life expectancy after onset of the chronic condition.

It is important to note that since the population in a budget-impact analysis is an "open population" with people entering and leaving each year, any changes in incidence/prevalence over the analysis time horizon for both acute and chronic conditions should be accounted for. If the incidence of the condition is increasing over time, the size of the eligible incident population will also increase over time and can be estimated using published estimates of past changes in incidence and extrapolation to the future.

In Box 3.3, we present examples of possible data sources for estimating prevalence of different conditions.

Box 3.3 Estimating Prevalence for Various Conditions

Below we have listed examples of prevalence estimates and their sources that could be used within a budget-impact analysis for supporting reimbursement in various countries.

Prevalence	Source
Stroke prevalence in the USA extrapolated to 2010 (≥20 years) = 2.8%; new and recurrent strokes (all ages) = 795,000 Prevalence rate of heart failure in 2010 (≥20 years) = 2.1%; prevalence (≥45 years) = 825,000	Go et al. (2014)
COPD prevalence in Ontario = 10.13% (≥35 years)	Crighton et al. (2015)
Prevalence of sexually transmitted infections in Africa • *Chlamydia trachomatis* = 2.6% in females and 2.1% in males • Syphilis = 3.5% in females and 3.9% in males • *Neisseria gonorrhoeae* = 2.3% in females and 2.0% in males • *Trichomonas vaginalis* = 20.2% in females and 2.0% in males	World Health Organization (2012)
Prevalence of chronic conditions in the UK (≥65 years) • Hypertension = 19.6% in females and 22.8% in males • Coronary heart disease = 18.5% in females and 12.7% in males • Depression/anxiety = 6.8% in females and 14.8% in males • Non-insulin-treated diabetes = 4.2% in females and 3.1% in males • Insulin-treated diabetes = 1.0% in females and 0.9% in males	Carter et al. (1999)

COPD chronic obstructive pulmonary disease; *USA* United States of America; *UK* United Kingdom

Total population numbers and incidence and prevalence data represent the first few steps in obtaining an estimate of the number of individuals eligible for a new drug for a budget-impact analysis. The next steps are to identify those who are currently being treated for the condition for which a new drug is approved and who are eligible for treatment and reimbursement for the new drug. Identifying these individuals may include determining the following:

- What proportion of the individuals with the condition actually receives a diagnosis?
- What proportion of the individuals would actually consider taking a specific type of treatment and/or will seek treatment by a physician?
- What proportion of the individuals is actually eligible for the new drug according to the specific marketing indication in the jurisdiction of interest and has no contraindication?
- What proportion of the individuals who are eligible for the new drug according the marketing indication will be eligible for government or private reimbursement?

The percentage of those with the condition with a diagnosis and who are under a physician's care will vary depending on the condition as well as on its severity. For example, for influenza, many individuals have mild or subclinical cases that are never diagnosed and for which no treatment is sought, whereas others with more severe symptoms or of a particular patient demographic (e.g., elderly or pediatrics) might access the health-care system. Thus, only a subset of individuals with the condition will actually receive a diagnosis or use health-care services. Other conditions such as depression, bipolar disorder, or rare conditions might be underdiagnosed or misdiagnosed even for those who access the health-care system. Depending on how the incidence and prevalence of the condition has been measured, undiagnosed, misdiagnosed, and untreated cases might have already been filtered out in the incidence and prevalence estimates. Thus, care must be taken in understanding the numbers presented in epidemiological studies that are used to estimate incidence and prevalence for the budget-impact analysis.

The drug indication might also narrow the population. Specifically, the drug indication might specify that the drug is to be used for treating any individual with a diagnosis of the condition, or it might only be indicated for those with a specific treatment history, condition symptoms, or condition severity. Furthermore, the reimbursement recommendation might restrict reimbursement to a subset of the indicated population. The magnitude of these filters that need to be applied to the incident or prevalent population who have a diagnosis and seek medical care may vary by jurisdiction or health plan. The best source for these data is the budget holder's population, but when these data are not available, published or unpublished analyses of health-care claims data may prove a useful source.

In Box 3.4, we present an example of the complete funnel-down approach to estimate the eligible population for those with asthma treated with monotherapy with inhaled corticosteroids.

Box 3.4 Total USA Health Plan Population Using Monotherapy with Inhaled Corticosteroid to Control Asthma

The eligible population for a new drug for prophylactic, maintenance treatment in asthma is identified for a health plan covering 1 million lives.

Inputs and their respective data sources

Parameter	Source
Total health plan population	Assumption
Adolescents and adults (≥12 years of age)	US Census Bureau (2013)
Asthma prevalence by age group	Moorman et al. (2012)
Percentage of patients with persistent asthma on any type of controller medication	Carlton et al. (2005)
Percentage of patients on a controller who are taking an inhaled corticosteroid only	Lee et al. (2010)

We start with a population size of 1 million. Since the new asthma treatment is approved for use in individuals ≥12 years of age, the population is disaggregated by age using data from the US Census Bureau. The population is also subdivided by age ranges (12–34, 35–64, 65 + years), because the prevalence of asthma varies by age. The portions of the population aged 12–34, 35–64, and 65 + years have been reported as 31.44%, 39.70%, and 13.04%, respectively (US Census Bureau 2013). From the incorporation of these percentages, we can calculate the number of individuals who are in each age group.

For each age group considered by the analysis, the prevalence of asthma is identified from the published literature (Moorman et al. 2012). The prevalence of asthma within the 12–34, 35–64, and 65 + age groups are 8.9%, 8.1%, and 8.1%, respectively. Using these prevalence numbers, we calculate the number of individuals within each age group with asthma.

Because not all individuals with asthma may be on a controller, we obtain from the published literature the percentage of individuals with asthma on any type of controller, 59.99% (Carlton et al. 2005). This is further refined by identifying individuals from another published study who are on a controller that is an inhaled corticosteroid only, 26.27% (Lee et al. 2010). The end result is the number of individuals within each age group who are candidates for the new inhaled corticosteroid. The calculations are as follows:

Number of individuals aged 12–34 years who are candidates for treatment
= 1,000,000 × 0.3144 × 0.089 × 0.5999 × 0.2627
= 4410

Number of individuals age 35–64 years who are candidates for treatment
= 1,000,000 × 0.3970 × 0.081 × 0.5999 × 0.2627
= 5068

Number of individuals age 65 + years who are candidates for treatment
= 1,000,000 × 0.1304 × 0.081 × 0.5999 × 0.2627
= 1665

Total number of individuals who are candidates for treatment
= 4410 + 5068 + 1665
= 11,143

3.4 Estimating Population Size by Subgroup

Patient subgrouping may be necessary for identifying the individuals eligible for a new drug as well as for estimating changes in condition-related costs. This may include a breaking out of the incident and/or prevalent population by age, condition severity, or history of previous treatment failure. As noted earlier, the new drug's indication or restrictions on reimbursement or both might dictate this subgrouping.

Information for identifying patient subgroups by condition severity or based on a reimbursement recommendation may not be easy to obtain. The manufacturer of the new drug will generally have estimated the size of these subgroups, but these estimates may not be based on publicly available sources. As a result, these estimates might not be considered credible to use in the budget-impact analysis. The health technology assessment agencies or health plans may also estimate the size of the relevant population subgroups. However, these estimates also may need data to which access is limited.

In the case of reimbursement being restricted to only those with a specific level of condition severity or with a particular stage of disease (e.g., an indication limited to individuals with HIV infection with multiclass drug resistance and no remaining fully suppressive treatment regimens, individuals with multiple sclerosis with relapsing disease only, or individuals with chronic plaque psoriasis for whom conventional immunosuppressants have failed), information about the disease stage and/or treatment history may be taken from published epidemiology studies or estimated using disease-progression models. Types of studies that provide this information include large cross-sectional observational database and registry studies that estimate the proportion of patients at different disease stages (e.g., Pugliatti et al. 2006, for multiple sclerosis or Buist et al. 2008, for COPD) or long-term disease-progression modeling studies from which the proportion of time in different disease stages or on different lines of therapy can be estimated and applied to those with the indication of interest. Since these latter estimates might not be available in the published literature, the budget-impact analyst might need to develop a disease-progression model to estimate these values.

In Box 3.5, we present an example set of estimates of population prevalence by disease severity for COPD.

Box 3.5 Prevalence by Condition Severity

A budget-impact analysis is being developed for a new maintenance treatment in chronic obstructive pulmonary disease (COPD). As part of this budget-impact analysis, patients who are eligible for this new maintenance treatment need to be identified. Patients with COPD are typically categorized as having mild, moderate, severe, or very severe COPD, which is based on a patient's lung function. Only patients with moderate COPD plus at least one exacerbation per year or those with severe or very severe COPD regardless of the number of exacerbations per year qualify for this new maintenance treatment.

To determine the size of the eligible population for the budget-impact analysis, we need to identify prevalence by COPD severity.

Buist et al. (2008) set out to estimate the prevalence of COPD in those aged ≥40 years using a population-based sampling plan and survey and spirometry testing before and after administration of 200 micrograms of salbutamol in a minimum of 600 participants (300 men and 300 women) in 12 sites across various countries around the world. In this study, they estimated the prevalence of COPD by sex and disease severity and its risk factors.

This study provides consistent and credible estimates for COPD prevalence by disease severity. Specifically, it reports a prevalence of 1.9% for no airflow obstruction, 1.1% for mild COPD, 1.4% for moderate COPD, and 1.0% for severe/very severe COPD within the USA site. If we needed to split the prevalence of severe/very severe COPD or if we needed to understand the prevalence of moderate COPD plus at least one exacerbation per year, we could combine these data with data from Hurst et al. (2010). Hurst et al. (2010) performed a large observational study in which they examined the occurrence of exacerbations in patients with different levels of disease severity. They reported that 39% of patients with moderate, GOLD stage 2 COPD had at least one exacerbation in the previous year. Using these data, we can estimate the prevalence of moderate COPD plus at least one exacerbation per year in the USA at 0.55% (=1.4% × 39.0%).

For estimating the prevalence of severe versus very severe COPD, we can use data from Hurst et al. (2010) to estimate the percentage of patients who have severe versus very severe COPD from the full study population. The numbers of patients in the study with severe and very severe COPD were 900 and 293, respectively. As a result, we have 75.4% (= 900/[900 + 293]) of severe/very severe patients have severe COPD and 24.6% (= 293/[900 + 293]) of severe/very severe patients have very severe COPD. In the USA, this translates to 0.75% (= 1.0% × 75.4%) with severe COPD and 0.25% (= 1.0% × 24.6%) with very severe COPD.

An example of a common marketing indication that requires patient subgrouping and one in which information in order to identify those subgroups may not be readily available is the approval for a specific line of treatment where failure of earlier lines of treatment is required for eligibility. With this marketing indication, the number or proportion of patients who may be eligible for second, third, and/or subsequent lines of treatment must be estimated.

Consider a new drug that is approved for second-line treatment of an acute condition. One possible way to estimate the proportion of patients with a diagnosis and a history of failed first-line treatment would be to multiply the number of patients who receive treatment each year by 1 minus the success rate of the standard first-line treatment or 1 minus the weighted average of success rates for the mix of standard first-line treatments.

For a chronic condition, the proportion of prevalent patients seeking active treatment and eligible for second-line or subsequent lines of treatment may be estimated by multiplying the condition prevalence by 1 minus the ratio of the mean time on first-line treatment to either the mean life expectancy or the mean total time on active treatment. If there are no published estimates of the mean time on first-line treatment, a treatment pathway model could be constructed based on published clinical trials and observational studies that provide data on discontinuation and treatment failure rates.

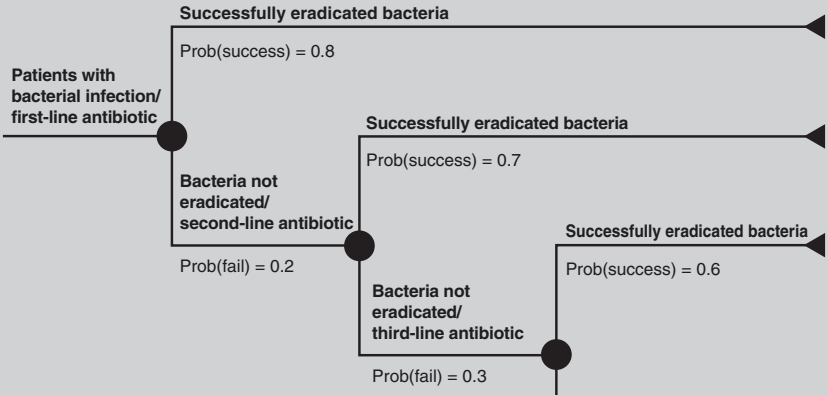
In Box 3.6, we present two examples of estimating the number of patients on later lines of treatment, one for an acute condition and one for a chronic condition.

Box 3.6 Estimating Number of Patients on Second-Line Treatment

Acute Condition

Patients with a specific bacterial infection will be reimbursed for a new antibiotic if it is used for second-line treatment only. Currently, there is only one antibiotic approved for treatment of the bacterial infection that has an 80% probability of successfully eradicating the bacteria. The new antibiotic has been proven to successfully eradicate the bacteria 70% of the time in those for whom first-line treatment fails. If this treatment fails, a third antibiotic can be used that is very expensive but is 60% successful in eradicating difficult-to-treat bacterial infections. Within a health plan, 10% of patients tend to contract the bacterial infection each year. How many patients out of a health plan of 1 million lives qualify for second-line treatment each year?

Treatment pathway for estimating number of patients on second-line treatment of a bacterial infection



Number in health plan	1,000,000
Proportion of patients diagnosed with bacterial infection	x 0.1
First line Prob(fail)	x 0.2
Number of people needing second line	20,000

Chronic Condition

A USA health plan with 1 million members has 3142 members with diagnosed and treated HIV infection based on CDC estimates of 0.3928% of members with an HIV diagnosis and an 80% chance of being treated once diagnosed. A new drug regimen has been approved to treat those for whom at least three prior drug regimens have failed and provides efficacy superior to those drug regimens currently being used in the eligible population. The mean total duration of treatment for patients on first-, second-, and third-line regimens is estimated at 11.2 years. Life expectancy after failure of the third regimen is 8.5 years. How many people in this region qualify for the fourth-line drug regimen?

To estimate the number of patients who qualify for the fourth-line drug regimen, we need to estimate both the prevalent and incident populations. The prevalent population or the number of patients with a diagnosis who are treated and whose first-, second-, and third-line drug regimens have already failed is as follows:

Proportion of diagnosed and treated patients with HIV eligible for the new drug regimen
= 1 – (11.2/[11.2 + 8.5])
= 43.1%

Number of patients in the prevalent eligible population
= 3142 × 43.1%
= 1354

The incident population (newly eligible patients) each year or those whose third drug regimen newly fails during each year is as follows:

Number of patients in the incident eligible population
= number in prevalent population on fourth-line or subsequent drug regimens/mean life expectancy after failure of the third regimen
= 1354/8.5
= 159

3.5 Changing Size of the Eligible Population Over the Analysis Time Horizon

The size of the population has a major impact on the results of the budget-impact analysis. Specifically, as the size of the population considered in the analysis changes, so does the budget impact. For example, if the size of the population increases over time, more and more patients become eligible for treatment. Thus, higher costs occur, which can potentially increase the impact to the payer's budget. As a result, it is important to account for any changes in population size over the analysis time horizon. The population in a budget-impact analysis is an open population with individuals entering and leaving each year. Because of this, the size of the incident and prevalent populations may change over time regardless of the introduction of the new drug. It is important to account for the changes in size of the overall population and the condition severity mix over the time horizon of the analysis.

3.5.1 Changing Population Size Regardless of Introduction of the New Drug

Without the new drug, population size and the condition severity mix would be predicted to remain constant over the analysis time horizon only if (1) jurisdiction population size and sex and age mix are predicted to be constant; (2) the age- and sex-specific condition incidence, prevalence, and diagnosis rates are expected to remain constant; and (3) cure rates, disease-progression rates, and mortality rates with the mix of treatments over the analysis time horizon without the introduction of the new drug are expected to remain constant. If changes are expected in population and/or condition incidence, these can be accounted for by using multiplication factors to change the population size. If changes in diagnosis, cure, disease-progression, and/or mortality rates are expected without the introduction of the new drug, these need to be estimated using the same techniques as those described below for the situation when the new drug is expected to change these factors.

3.5.2 Changing Population Size and Condition Severity Mix due to the Introduction of the New Drug

If the population size and/or condition severity mix is expected to change because of the introduction of the new drug into the treatment mix, then these changes need to be estimated. These changes are typically related to the new drug's effects either on (1) the age- and sex-specific condition incidence, prevalence, diagnosis, and/or seek-treatment rates or (2) cure, disease-progression, and mortality rates or (3) both. How these are included in the budget-impact analysis will depend on their timing and magnitude.

An example of a treatment that might affect the size of the incident population is a drug for an infectious disease that reduces the duration of viral shedding and the related duration of infectivity. This drug might reduce the number of new cases of the disease in susceptible individuals. Clinical trial data can be used to estimate these changes by entering them into a dynamic transmission or epidemic model or by using a simple multiplication factor based on published data to estimate the likely reductions in cases of the disease.

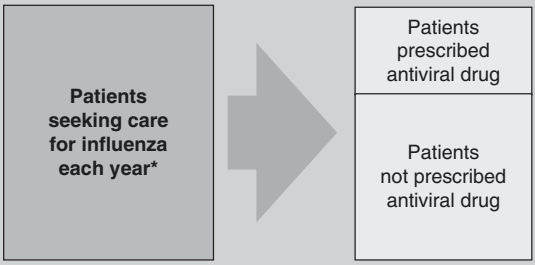
An example of a treatment that might affect diagnosis rates in both incident and prevalent populations is a newly approved, more effective drug. A more effective drug might result in changes in the number of individuals with the condition who have a diagnosis, are under a physician's care, and are eligible for reimbursement, because the awareness of a good treatment might encourage individuals to be screened for a chronic condition (e.g., hepatitis C infection) or to visit their physician for an acute condition (e.g., for influenza treatment). In addition, patients for whom previous treatment has failed and who have ceased to take active treatment may reenter the actively treated population. This is frequently referred to as the "woodwork" effect. There are typically no data to support these estimates. Rather expert opinion or examples from similar situations in the past should be used.

In Box 3.7, we present an example of the estimation of changes in population size with the introduction of a new drug because of the "woodwork" effect.

Box 3.7 Example of Changing Population Size with the New Drug Due to the "Woodwork" Effect

A new antiviral drug is approved to treat influenza. Assume there is currently one antiviral drug on the market approved to treat influenza. However, this current drug is not very effective in shortening the duration of symptoms. The new drug has shown to be 90% effective in relieving influenza symptoms within 1–2 days. If the incidence of influenza in 2016 is expected to be the same as the incidence of influenza in 2015, show the woodwork effect.

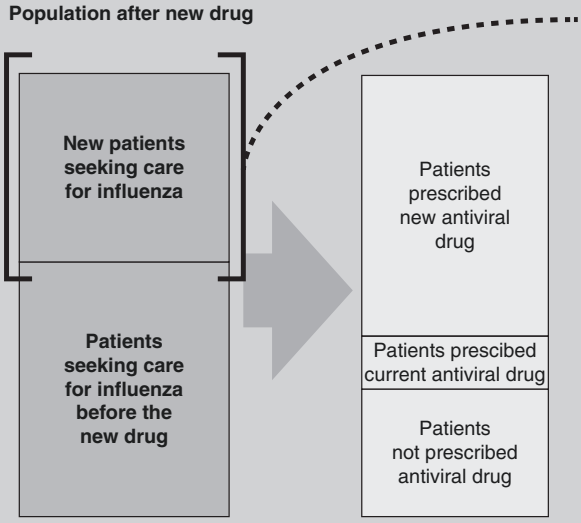
Population before new drug



* Patients include those who seek treatment immediately after becoming ill who may be prescribed antiviral drugs and those who seek treatment after having been ill for several days who may be prescribed antibiotics.

Changes in population size due to "woodwork" effect

Population after new drug



This is the woodwork effect. These patients did not seek care last year because perhaps they felt the current drug would not be effective. As a result, they felt there was no point in going to the doctor because they would not be treated anyway.

This year there is a new drug that is very effective. Because the patients have heard that this drug is very effective, more patients will seek care early and be treated with the new drug.

Changes in cure, disease-progression, and/or mortality rates with the new drug may also affect the estimates of size of the incident or prevalent populations over the analysis time horizon. An increase in cure rates for a chronic condition (e.g., chronic hepatitis C infection) would decrease the size of the eligible population over time, while a decrease in mortality rates (e.g., HIV infection or congestive heart failure) or an increase in time to treatment failure (e.g., progressive disease in metastatic cancer) would increase the size of the treatment-eligible population over time. Slowing or reversing disease progression (e.g., HIV infection, multiple sclerosis, or Alzheimer's disease) would change the condition severity mix in the treated population by either moving people to less-severe disease stages (e.g., HIV infection) or slowing the rate of transition to the next disease severity level (e.g., Alzheimer's disease or multiple sclerosis). Data from clinical trials can be used directly or as inputs to disease-progression models (frequently developed to estimate cost-effectiveness of new drugs) to estimate changes in treatment-eligible population size and condition severity mix due to the new drug's impact on mortality or disease progression. However, if disease progression is slow (e.g., multiple sclerosis), changes in disease progression or mortality might not occur until after the end of the budget-impact analysis time horizon and therefore need not be included in the analysis. As a result, changes in population size or condition severity mix should be considered carefully before deciding to include them in the budget-impact analysis.

In Box 3.8, we present three examples of the measurement of changes in population size attributable to the impact of the new drug on mortality (congestive heart failure), disease progression (metastatic breast cancer), and disability outcome (COPD).

Box 3.8 Estimates of Changes in Population Size with the Introduction of a New Drug

Estimating Changes in Population Size in Congestive Heart Failure

A new drug for congestive heart failure was shown to decrease hospitalizations and mortality over an observation period of 22.68 months (range 0.03–36.73) in a population who had a diagnosis of congestive heart failure for an average of 4.7 years before and who were not currently treated with angiotensin-converting enzyme (ACE) inhibitors (Maggioni et al. 2002). Mortality over the trial follow-up period averaged 17.3% with the new drug and 27.1% in the placebo group. Because of this reduction in mortality, the size of the population being treated for congestive heart failure would increase.

Using the clinical trial results, the expected increase in treated population size because of the reduction in mortality with treatment with the new drug can be estimated as follows:

Life expectancy based on mortality observed within the trial for patients on placebo
= 7.0 years
= 1/(0.271/[22.68/12])

Life expectancy based on mortality observed within the trial for patients on the new drug
= 10.9 years
= 1/(0.173/[22.68/12])

If the initial prevalent treated population size is 1000 for the health plan, assuming constant annual incidence rate, the incident number of cases that occurs within a year when all patients are receiving placebo = 1000/7.0 = 143.

With increased life expectancy, if all patients are switched to the new drug, the prevalent population size will increase from 1000 gradually to 143 × 10.9 = 1559 because of the reduction in mortality with the new drug. With lower treatment share for the new drug, the increase in prevalent treated population size will be decreased proportionately.

Alternatively, the change in the size of the population alive and being treated could be estimated more precisely using a disease-progression model.

Estimating Changes in Population Size in Metastatic Breast Cancer

A new endocrine therapy indicated for metastatic breast cancer was shown to have median progression-free survival of 9.6 months compared with 6.1 months for current standard of care in a head-to-head clinical trial (Mouridsen et al. 2001). Treatment in this population is given until disease progression occurs. If the prevalent treated population is 500 women in the presence of current standard of care, the average number of new women entering the treated population each month = 500/6.1 = 82.

With the new drug, there will be an increased duration on treatment because of longer time to disease progression. If all patients are treated with the new drug, the treated prevalent population will increase from 500 to 82 × 9.6 = 787. With lower treatment share for the new drug, the increase in prevalent treated population size will be decreased proportionately.

Alternatively, the change in the size of the population alive and being treated could be estimated more precisely using a disease-progression model.

Estimating Population Size and Condition Severity Mix in COPD

A new drug has been approved for maintenance treatment for chronic obstructive pulmonary disease (COPD) in which it has been shown to decrease disease progression compared with current standard of care. Patients on maintenance treatment may have moderate, severe, or very severe disease. Both newly diagnosed and currently treated patients are eligible for the new drug. Since COPD is a progressive disease, the developer of the analysis has decided to use a Markov model in which the health states are moderate, severe, very severe, and death to perform the analysis with annual cycle times.

To estimate the size and condition severity mix of the population each year, we start with the prevalent population as the initial distribution (i.e., the current number of patients eligible for treatment distributed among the different health states) to the Markov model. Each year, the incident (i.e., newly diagnosed) population is added to the Markov calculations. A Markov model will be set up for patients on standard care, whereas a separate Markov will be set up for patients on the new drug. Patients on standard care will receive the disease progression (i.e., transition probabilities) associated with standard care. Patients on the new drug will receive the disease progression associated

with the new drug. Each year of the Markov model containing the prevalent and incident cohorts represents the population size and condition severity mix for each budget year for those patients on their respective treatments. The population size with a mix of patients on standard care and the new drug can be estimated through a weighted average of each budget year. This approach is discussed in more detail in Chap. 7.

3.6 Including Catch-Up Effects for the Prevalent Population

As noted earlier, in developing estimates for the population size for a budget-impact analysis for a new drug for a chronic condition, two distinct subpopulations need to be considered: (1) the newly eligible population in each year of the budget-impact analysis time horizon (incident population) and (2) the population who became eligible in previous years before the new drug was available (prevalent population). The primary reason for including the prevalent population is because of the potential for uptake of the new drug in this population, which we refer to as "catch-up." The extent to which there will be a catch-up effect, with members from the prevalent population switching to the new drug or, if not currently being actively treated, starting treatment with the new drug, can greatly affect the budget impact in the first few years after a new drug is added to the formulary for a chronic condition. If catch-up is not expected for the prevalent population, then a prevalent population does not need to be included in the budget-impact analysis.

The budget-impact of catch-up can be captured in one of two ways: (1) the estimated eligible population including both the incident and prevalent population can be assumed to have the same treatment shares and efficacy for the new drug after it is added to the formulary or (2) the catch-up population can be assumed to have a different treatment share and efficacy for the new drug. The advantage of the first approach is that the incident and prevalent populations can be combined into a single treated prevalent population. The second approach is preferable when the treatment share and possibly the effectiveness of the new drug are likely to be different for the two populations.

In Box 3.9, we present an example of catch-up in a prevalent population for chronic hepatitis C infection.

Box 3.9 Estimation of the Extent of Catch-Up in the Prevalent HCV Population

Chronic hepatitis C virus (HCV) infection is a slowly progressing disease that may lead to liver failure and/or hepatocellular cancer, both with very high mortality after 10–30 years. Several new interferon-free treatment regimens, including direct-acting antiviral (DAA) drugs, have been approved for patients with chronic HCV infection with several of the commonly occurring genotypes. The new treatment regimens have been studied in clinical trials in both

treatment-naive and treatment-experienced patients who have symptoms of liver fibrosis or compensated cirrhosis. The new treatments result in cure of the chronic HCV infection in most patients treated. Since chronic HCV infection is asymptomatic in the early stages, many cases are undiagnosed. In addition, earlier treatment regimens required at least 24 weeks of treatment, included injectable drugs, had unpleasant side effects, and were not as effective as the oral DAA regimens. Thus, there is a large prevalent population of people with chronic HCV infection who are untreated by choice or for whom the earlier generation of treatments has failed. How do we estimate the size of the catch-up effect of the new treatment regimens in the prevalent population?

Funnel-down of HCV population to estimate both incident and prevalent catch-up populations

Populations	Estimated treatment-eligible population
Total population	1,000,000
Incident population	
Incidence of diagnosed chronic HCV infection (= 0.000096 × 0.85 × 50%)	0.00004
Annual number of newly diagnosed cases of chronic HCV infection	40
Percentage of those with incident HCV infection each year during the analysis time horizon who are newly diagnosed and eligible for treatment and agree to be treated each year of the analysis time horizon	10%
Annual size of incident treated population	4
Catch-up prevalent population	
Prevalence of diagnosed chronic HCV infection (= 0.0122 × 50%)	0.00610
Number diagnosed with chronic HCV infection in previous years	6100
Percentage of patients with prevalent chronic HCV infection who are diagnosed and are eligible for treatment and agree to be treated each year of the analysis time horizon	5%
Annual size of prevalent treated population	305

HCV hepatitis C virus

We first estimate the size of the population with a new diagnosis of chronic HCV. Patients with newly diagnosed disease have not already received treatment and do not have decompensated liver disease (incident population). These individuals will be eligible for the new treatment regimens. Assuming the incidence of acute HCV infection is 0.000096 (CDC 2016; US Census Bureau 2014) with 85% becoming chronic (CDC 2016) and 50% assumed

diagnosed in a health plan of 1 million lives, we estimate 40 patients with newly diagnosed disease will be eligible for treatment. Of those with a new diagnosis, we assume that only 10% each year (4 people) will agree to be treated since the disease is slow to progress.

The new DAA drug regimens have been tested both for first-line treatment and for treatment after previously failed treatment. The prevalence of those with the HCV antibody and active viremia indicating chronic HCV infection was estimated by the CDC to be 0.01223 (CDC 2016; US Census Bureau 2014), of whom we assume 50% would not receive a diagnosis. We assume that 5% of these patients each year of the analysis time horizon will be eligible for treatment (e.g., have not progressed to decompensated liver disease) and will agree to be treated.

3.7 Which Eligible Population Should We Include in the Budget-Impact Analysis?

In this chapter, we have provided instructions for how to estimate the population size for the indicated and reimbursement-eligible population. As described above, this population will often not include all those with a diagnosis of the condition of interest but will be restricted to a subset based on condition severity, treatment history, or other factors. These restrictions may be part of the marketing indication or added as restrictions for public or private reimbursement. Although the size of the indicated and reimbursement-eligible population will be a key determinant of the budget impact of the new drug, there may be circumstances where it is more appropriate to include all those with the condition of interest in the budget-impact analysis.

As we will describe in the next chapter, the budget impact will also depend on the treatment mix with and without the new drug. In many cases, the only data available on the current treatment mix for a specific condition will be for all patients with that condition rather than broken out by condition severity or treatment history. For example, the current drug treatment mix for children and adolescents with attention-deficit/hyperactivity disorder (ADHD) will be available from market research data for all drug-treated patients but may not be available specifically for those who are intolerant of stimulants or for whom treatment with a stimulant has failed. However, the indication and reimbursement-eligible population for a new ADHD drug might only include those who are intolerant of stimulants or for whom treatment with a stimulant has failed. There are two options that we can use to estimate the budget impact of this new drug in this situation. We can develop estimates of the size of the indicated and reimbursement-eligible population as described in this chapter, and we can then estimate the treatment shares with and without the new drug in the treatment mix for the indicated and reimbursement-eligible population using observational database studies or expert opinion. Or we can estimate the size of the

total drug-treated ADHD child and adolescent population, without considering the restricted indication for the new drug and use the available market research data estimates for the current treatment mix (i.e., estimate the eligible population at a broader level and use the available treatment mix data). If we use the first option, then the predicted uptake rates for the new drug and the new treatment mix will be those expected in the indicated and reimbursement-eligible population. If we use the second option, then the predicted uptake rates for the new drug in all drug-treated ADHD children and adolescents, a much broader population, will be much lower and the new treatment mix will be that expected in all drug-treated children with ADHD. Instructions for estimating the treatment mix for the budget-impact estimates with and without the new drug are presented in Chap. 4.

Exercises

Exercise 3.1 Explain the differences in incidence and prevalence and how they affect a budget-impact analysis.

Exercise 3.2 Explain the difference between the prevalence of a condition and the proportion of patients identified as having the condition.

Exercise 3.3 Why is it important to give budget holders population estimates for funneling their total population down to a population eligible for a specific treatment? Why is it important to allow the budget holders to change this information?

Exercise 3.4 How would a budget holder estimate the prevalence of a condition by using annual incidence and life expectancy?

Exercise 3.5 List some attributes of a new treatment that might change the size of a treatment-eligible population and how those attributes may change the size of the population.

Exercise 3.6 Provide an example in which the treated population may differ from the population indicated for a new treatment.

Exercise 3.7 Develop case studies in which it is important to account for changes in the population size due to a new drug's impact on cure rate, disease progression, and survival.

Exercise 3.8 Identify a condition for which a new drug may be approved and may require patient subgrouping. Outline potential sources for data that may be used to reduce the population to the reimbursement-eligible population.

Exercise 3.9 Choose a condition for which a budget-impact analysis may be constructed for a new drug. Apply the funnel-down approach to identify the number of patients in the reimbursement-eligible population. Expand the funnel down to include consideration of patient subgroups.

Exercise 3.10 A new drug has come on the market to treat acute coronary syndrome. Construct a funnel-down approach to estimate the number of patients in the reimbursement-eligible population. How would the reimbursement-eligible population change if a companion diagnostic were approved to better select patients for treatment? Discuss the impact if the companion diagnostic were con-

sidered for reimbursement versus if the companion diagnostic were not considered for reimbursement.

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Chapter 4
Estimating the Treatment Mix

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Abstract The mix of drugs used for estimating the cost and outcomes for the budget-impact analysis will likely change over the analysis time horizon even without the introduction of the new drug. This could be because of changes in treatment patterns or increasing uptake of recently approved drugs or patent expiration of current drugs. When a new drug is added to the formulary, the mix of drugs used for the budget-impact analysis will also change and depend upon the uptake of the new drug, whether it is added to currently used drugs or which of the currently used treatments it replaces. In this chapter, issues that may affect the treatment mix and methods for determining the treatment mix with and without the new drug are presented. Potential sources of data are also discussed.

Keywords Treatment mix • Generic entry • Treatment shares • Projected mix • Treatment switch • Market share • Drug uptake • Redistribution

Chapter Goals
To show how to estimate changes in the treatment mix over the analysis time horizon, both with and without the new drug in the mix, including accounting for the impact of loss of patent protection and entry of generic products over the analysis time horizon.

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Once the size of the eligible population has been estimated for each analysis year with and without the new drug[1] on the formulary, the next step is to estimate the treatment shares of the different drugs used by this population each year. Treatment shares might be expected to change over time both with and without the new drug in the treatment mix for several reasons:

- Changes in standard of care occur over time, with growing uptake of recently approved drugs and/or the new drug substituting for or being added to older drugs.
- Other new branded drugs are introduced during the analysis time horizon.
- Generic formulations of current drugs are introduced during the analysis time horizon.

To avoid excessively large numbers of drugs included in the treatment mix considered within a budget-impact analysis, the treatment mix should include only those current drugs whose use might be affected by the addition of the new drug to the formulary over the analysis time horizon. Although our focus for this book is on drugs, the current treatment mix could include drug treatments, surgical treatments, or just watchful waiting (no active treatment). If surgical treatments or watchful waiting are likely to change when the new drug is added to the treatment mix, then they need to be included in the treatment mix tables along with their price, efficacy, and safety information to use in the analysis.

4.1 Treatment Shares Without the New Drug in the Treatment Mix

Estimates of treatment shares without the new drug typically start with estimates of the current treatment shares derived either from market research data such as IMS Health marketing data or from observational databases. There are no standard sources for the estimation of changes in expected treatment shares over the analysis time horizon without the new drug. These estimates may be made by the manufacturer or the researchers after consultation with physicians who treat the condition of interest based on the current treatment patterns.

One factor that should be considered is that if other new drugs have recently been added to the formulary, their treatment share might be expected to increase over time, taking away treatment share from older, possibly less-effective drugs. If current treatment patterns have not changed recently, then the current treatment shares might be expected to remain constant.

[1] In this chapter, we make the simplifying assumption that the budget-impact analysis is based on the introduction of a new drug to the current mix of drugs for treatment of a condition. Changes in our recommended approaches to estimate the budget impacts of other types of health-care interventions (i.e., vaccines, diagnostics, surgery, and devices) are discussed in Chap. 13.

A second factor to consider is if new branded drugs are expected to be launched within the analysis time horizon. If this is the case, an attempt should be made to include estimates of uptake for these drugs in the analysis. Alternatively, the computer program created to perform the analysis can be developed to allow the user the option of adding anticipated, new branded drugs to the current treatment shares table and estimating how these shares will be taken from current treatments.

A third factor to consider is if one or more of the current branded drugs are expected to be marketed in generic formulations during the analysis time horizon. If drugs are expected to go generic, the current treatment mix could include the generic formulation with a 0% market share until the generic form becomes available. Alternatively, the drug could be listed once within the treatment mix but with the user entering detail about the portion of the drug's share that is due to the branded versus generic formulation. In this case, the mix of branded versus generic formulation of that drug may change over time. Because of the introduction of the generic formulation, it might be expected that the total share of the drug (brand plus generic) will increase with the availability of the generic formulation.

It is important that the assumptions made about changes in treatment share without the new drug are clearly stated and are both credible to and changeable by the users of the analysis to reflect their own expectations.

In Box 4.1, we present an example of a study that estimated changes in treatment shares with the introduction of generic drugs.

With entry of either a new branded drug or generic drug over the analysis time horizon, in addition to estimating impact on treatment shares, developers of the analysis need to consider treatment cost and potential impact on clinical outcomes

Box 4.1 Treatment Shares Allowing for Generic Entry

In a budget-impact analysis for understanding the impact of long-acting injectable paliperidone palmitate in the treatment of schizophrenia in Japan (Mahlich et al. 2015), risperidone and quetiapine were available in both branded and generic forms at the onset of the analysis. Olanzapine and aripiprazole were expected to enter the market in generic formulations at different times during the 4-year time horizon of the analysis. The authors estimated the current market shares by combining sales figures, dosage information according to the Japanese label, and estimated future market shares based on market research data. As can be seen from the table below authors expected that a generic formulation of aripiprazole would be introduced during the third year of the analysis and a generic formulation of olanzapine during the fourth year. Both drugs continue to have a large market share in total for all 4 years, although the market share for the branded versions is expected to fall when the generic formulations are introduced.

Market share in the treatment of schizophrenia in Japan (Mahlich et al. 2015, Table 4)

Treatment	Market share			
	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)
Paliperidone palmitate (LAI) (Xeplion)	0.03	0.19	0.35	0.74
Risperidone (LAI) (Risperdal Consta)	0.64	0.45	0.35	0.27
Risperidone (oral) (Risperdal)	12.44	10.92	9.51	8.70
Risperidone (oral) generic entry	10.68	11.74	12.73	13.04
Olanzapine (oral) (Zyprexa)	14.82	15.30	15.53	12.32
Olanzapine (oral) generic entry	0.00	0.00	0.00	3.46
Aripiprazole (Abilify)	13.76	15.35	14.84	11.43
Aripiprazole generic entry	0.00	0.00	1.55	6.07
Quetiapine (oral) (Seroquel)	13.77	10.88	8.49	7.72
Quetiapine (oral) generic entry	4.93	8.01	10.62	11.58
Blonanserin (Lonasen)	3.80	3.97	4.14	4.30
Conventionals	25.13	23.19	21.89	20.37

LAI long-acting injectable

and population size. For the new branded drug, a price similar to other branded products can be assumed with a premium if the efficacy shown in phase 2 or 3 clinical trials is superior to current products. Estimates of clinical efficacy can be taken from the published clinical data, and associated changes in population size can be estimated as discussed in Chap. 3. For a generic drug, published estimates of the branded drug price with discounts based on time since generic entry can be used to estimate the price over time. Efficacy can be assumed to be equivalent to the corresponding branded drug.

As mentioned in Chap. 3, care needs to be taken when using market research data or data from observational database studies, as they may not include the needed level of detail on the characteristics of the patient population. If the size of the indicated and reimbursement-eligible population has been estimated, then current treatment share estimates are needed for the indicated and reimbursement-eligible population rather than in the total condition population. For example, if the indicated and reimbursement-eligible population is limited to those for whom first-line treatment has failed, then data showing the treatment shares for all patients with the condition irrespective of treatment history would not be appropriate to use. However, the market research data might only report the treatment shares for all patients with the condition of interest. In this case, assumptions are needed to convert the market research data into estimates of the treatment shares for the indicated and reimbursement-eligible population, possibly using expert opinion. An alternative approach would be to expand the population included in the budget-impact analysis to all patients with the condition of interest (i.e., not just those who are indicated and eligible for reimbursement) and use the market research data on current treatment

mix for all patients with the condition of interest. With this approach, the predicted treatment shares for the new drug and the new treatment mix would be estimated, taking into account that the new drug is indicated and reimbursed only for a subset of the total drug-treated population.

In Box 4.2, we present a hypothetical example of estimates of treatment shares for the different drug-treated populations with attention-deficit/hyperactivity disorder in children and adolescents.

Box 4.2 Hypothetical Treatment Shares Over Time for Attention-Deficit/Hyperactivity Disorder in Total Drug-Treated Population and in Those Who Are Intolerant to Methylphenidate or for Whom First-Line Treatment with Methylphenidate Has Failed

The first-line treatment for children and adolescents with attention-deficit/hyperactivity disorder (ADHD) is generally methylphenidate (MPH), a stimulant that may be effective in controlling the symptoms. Both immediate-release and extended-release formulations are available. The immediate-release formulations are generic, while extended-release formulations are just beginning to reach the end of their patent life. However, it is not uncommon for patients to have issues with these drugs. Some parents are reluctant to have their children taking a stimulant. In other cases, children or adolescents may not tolerate them, or the stimulant may not be effective. In addition, stimulants should not be used when there is a high risk of abuse in the family. Atomoxetine is a drug indicated for ADHD that is not a stimulant and may be used in children and adolescents who should not take stimulants or for whom treatment with stimulants has failed. Atomoxetine is also reaching the end of its patent life.

Since MPH extended release is the most common first-line treatment and is effective in a high percentage of those treated, the current treatment shares in all drug-treated children and adolescents will be different from the treatment shares in those for whom first-line treatment with MPH has failed or in those who should not take stimulants. In these population subgroups, the non-stimulants would have a greater treatment share. In addition, since extended-release formulations of MPH and atomoxetine are losing patent protection within the next 5 years, even without a new drug, the treatment shares both in the total population and in those who should not take stimulants or those for whom first-line treatment has failed are likely to change.

The table below provides hypothetical estimates of the current treatment shares for the total drug-treated ADHD population (which could be obtained from market research data) and assumed values for the current treatment shares for the two population subgroups: first-line treatment without stimulants and subsequent lines of treatment when first-line treatment with MPH has failed. The table also provides estimates of the treatment shares for the three populations after 5 years. Current treatment shares among those for

whom first-line therapy has failed could be estimated using observational data or expert opinion from practicing physicians. Current treatment shares for those who should not take stimulants could be estimated using expert opinion or assumed to equal the treatment shares for any non-stimulant drug indicated for ADHD. In our hypothetical example, atomoxetine is the only non-stimulant drug. There are no good sources other than expert opinion for the change in treatment shares in all three population groups over time, but we have assumed in our hypothetical example that entry of a generic drug will take treatment share away only from the corresponding branded drug.

Hypothetical estimates of the current treatment shares for the total drug-treated ADHD population

	Treatment share					
	All drug-treated ADHD population		First-line treatment, no stimulants		Failed first-line treatment with MPH	
ADHD drug	Current (%)	Year 5 (%)	Current (%)	Year 5 (%)	Current (%)	Year 5 (%)
MPH, extended release, branded	75	65	0	0	70	30
MPH, extended release, generic	0	15	0	0	0	50
MPH, immediate release, generic	20	15	0	0	15	5
Atomoxetine, branded	5	2	100	35	15	7
Atomoxetine, generic	0	3	0	65	0	8

ADHD attention-deficit/hyperactivity disorder, *MPH* methylphenidate

We have assumed in this hypothetical example that, despite failure of the first extended-release MPH product used, the majority of drug-treated adolescents who continue to a second-line treatment will switch to an alternative extended-release MPH product.

4.2 Treatment Shares with the New Drug in the Treatment Mix

In budget-impact analyses, a budget scenario in which the new drug is not in the treatment mix requires estimating the treatment shares over the analysis time horizon for the current treatment mix. However, it is equally important to create budget scenarios in which the new drug is in the treatment mix, which requires estimating the treatment shares in the reimbursement-eligible population that are expected for the new drug and for other competing treatments when the new drug is added to the formulary. There are no standard data sources for these estimates. The treatment

shares for the new drug are typically based on manufacturer or researcher projections. Alternatively, they can be estimated using observed uptake rates for previously introduced new drugs in the condition or even using diffusion modeling techniques. Generally, uptake of the new drug will be assumed to increase over time. The magnitude of the uptake of the new drug over time will likely depend on the unmet need for treatment and the efficacy and safety of the new drug compared with current treatments. It is important that the assumptions made are both credible to and changeable by the users of the analysis to reflect their own expectations for the new drug.

Care should be taken when estimating uptake for the new drug to ensure it is estimated for the population included in the analysis. If that population is limited to the reimbursement-eligible population and if current treatment share data are available for this population, then the uptake estimates should also refer to the reimbursement-eligible population. However, if current treatment share data are only available for the full condition population, then the budget-impact analysis should focus on the full condition population, and estimates of treatment share for the new drug should also reflect its treatment share in the full condition population even though its use may be restricted to those with specific treatment history or condition characteristics.

There are limited data sources for estimating uptake of a new drug. Uptake will depend on the degree of unmet need and the efficacy and price of the new drug. Frequently, forecasts developed by the manufacturer of the new drug or estimates by clinical experts are used. Because of the uncertainty in these forecasts, alternative values should be tested in sensitivity analyses. The forecasted uptake will also depend on whether the estimate is for the total condition population or just for the reimbursement-eligible population.

In Box 4.3, we show the relationship between uptake of a new drug in the reimbursement-eligible population and in the total condition population.

Box 4.3 Estimating Uptake of New Drug in the Total Condition Population or in the Reimbursement-Eligible Population

A new biologic drug is indicated and reimbursed only for those with severe chronic plaque psoriasis for whom both conventional treatment and tumor necrosis factor-alpha (TNF-α) inhibitor biologic treatment have failed. There are limited treatment alternatives in the reimbursement-eligible population. The expected uptake in the reimbursement-eligible population is 30%. If the reimbursement-eligible population accounts for only 10% of those with moderate or severe disease, then what is the expected uptake in all those with moderate or severe chronic plaque psoriasis?

Expected uptake can be calculated as 30% × 10% = 3%.

Once the estimates of the treatment shares for the new drug have been determined for the chosen population, then the impact of the uptake of the new drug on the shares of the current treatments must be estimated. The clinical data and drug

indication will generally determine whether the new drug will be added to current treatments, substituted for the current treatments, or a mix of both. If the new drug is indicated for add-on therapy, then the researcher has to determine which drugs it will be added to. Entries in the treatment mix will need to be added to represent all the new drug combinations so that their price and clinical efficacy can be appropriately used in the analysis. If the new drug replaces currently used treatments, then estimates from which current drugs the treatment shares for the new drug will be taken will be needed. If there are no clinical or other data to guide these estimates, one possibility is to assume that the treatment share will be taken equi-proportionately from all current treatments. Another possibility, perhaps based on expert opinion, is to assume that it will be taken equi-proportionately from only a subset of current treatments (e.g., only from branded treatments or only from a specific class of drugs in the current treatment mix). Once again, the magnitude of these estimates will vary depending on whether the treatment shares are for the total condition population or for only the reimbursement-eligible population.

In Box 4.4, we present a hypothetical example of the treatment shares needed for a new drug that is indicated for both monotherapy and add-on therapy as well as a hypothetical example of a new drug taking treatment share from only the subset of current drugs in the same class.

Box 4.4 Examples of Impact of New Drug on Current Treatment Shares

New Drug Indicated for Monotherapy or Add-On Therapy

In this hypothetical example, the new drug C is indicated for both monotherapy and for combination therapy with drug A or drug B. The table below indicates the treatment share data required for the budget-impact analysis.

Hypothetical treatment shares for a new drug indicated for both monotherapy and combination therapy

Drug regimen	Current treatment shares without drug C (%)	Treatment shares with drug C (%)
Drug A	50	20
Drug B	50	20
Drug C	0	10
Drug A + Drug C	0	25
Drug B + Drug C	0	25

In this example, both drug A and B composed 50% of the market before the introduction of drug C. Once drug C was added to formulary, it was estimated that the projected uptake of drug C monotherapy would be 10%. The uptake of drug C in combination therapy was estimated at 50% where it was added to

drugs A and B equally. Shares for this new monotherapy and combination therapy were projected to be taken equi-proportionately from drugs A and B.

New Drug in One Drug Class Used to Treat Relapsing-Remitting Multiple Sclerosis

Peginterferon beta-1a is a pegylated interferon indicated for the treatment of relapsing-remitting multiple sclerosis. In this hypothetical budget-impact analysis, we assumed that the treatment share for peginterferon beta-1a would be taken equi-proportionately only from the other interferons currently used to treat relapsing-remitting multiple sclerosis. We assumed that the treatment shares of the drugs in different drug classes indicated for relapsing-remitting multiple sclerosis would not be affected by the addition of peginterferon beta-1a to the treatment mix.

Hypothetical treatment shares over time with and without new interferon indicated for relapsing-remitting multiple sclerosis

Drug	2016 with PEG-IFN (%)	2016 without PEG-IFN (%)
Peginterferon beta-1a	5.00	0.00
Delayed-release dimethyl fumarate	25.00	25.00
IFNβ-1a (intramuscular)	3.33	5.00
IFNβ-1a (subcutaneous) 44 μg	3.33	5.00
IFNβ-1b (generic)	0.67	1.00
IFNβ-1b (branded)	2.67	4.00
Glatiramer acetate 20 mg	5.00	5.00
Glatiramer acetate 40 mg	25.00	25.00
Natalizumab	5.00	5.00
Fingolimod	15.00	15.00
Teriflunomide 14 mg	10.00	10.00
Total	100.00	100.00

IFNβ interferon beta, *PEG-IFN* peginterferon beta-1a

However, the budget impact of a new drug is often quite sensitive to the assumptions about from which drugs the treatment share for the new drug is taken. Alternative assumptions about the source of the new drug's treatment shares should be tested in sensitivity analyses, and the treatment mix should always allow a user to change the default assumptions. Thus, the treatment shares of other drugs for relapsing-remitting multiple sclerosis should be included in the treatment mix to allow for sensitivity analyses where treatment share is taken from multiple drug classes and not only the interferons.

4.3 Which Treatment Shares Should We Include in the Budget-Impact Analysis?

In summary, critical elements of a budget-impact analysis are the estimates of treatment shares over the analysis time horizon both with and without the new drug in the treatment mix. If data for treatment shares with the current treatment mix are available for the reimbursement-eligible population, then the reimbursement-eligible population should be used for estimating the budget impact along with treatment shares for the new drug and redistribution of treatment shares from the current drugs for the reimbursement-eligible population. However, when the only available data for treatment shares with the current treatment mix come from the total condition population, then the total condition population could be used for estimating the budget impact along with treatment shares for the new drug and redistribution of treatment shares from the current drugs for the total condition population. It is very important that the selection of the population included in the budget-impact analysis be consistent with that used for the estimates of treatment shares. In addition, whatever assumptions are made about the current and projected treatment mixes and populations for the base-case estimates in the analysis, the users should be allowed to change those assumptions to apply to their jurisdiction or health plan. Examples of how to structure the computer program for the analysis to allow the user to make these changes are shown in Chap. 10.

Exercises

Exercise 4.1 Identify a new drug that is coming to market soon. What are the potential competitors for this new drug? How might you obtain the current treatment mix estimates for the competitors with which this new drug will compete?

Exercise 4.2 Discuss how off-label use of drugs might affect the current treatment mix that would be considered in a budget-impact analysis for a new drug.

Exercise 4.3 A new drug is being developed to treat patients with diabetes who are not controlled on metformin. How might you identify the new drug's potential competitors and analyze administrative health-care claims data in order to estimate the current treatment mix upon which this new drug will enter?

Exercise 4.4 A new fixed-dosed, triple-therapy combination drug is being developed for treatment of chronic obstructive pulmonary disease. Identify potential competitors for this new drug and discuss how you will estimate the current treatment mix.

Exercise 4.5 Disease X is a rare condition for which there are no currently approved treatments. Discuss what treatments should be considered within the current treatment mix and how might the current treatment shares be estimated?

Exercise 4.6 Discuss how reimbursement restrictions such as prior authorization, prescription from a specialist only, and proof of prior use of two other drugs might influence the current and projected treatment mixes.

Exercise 4.7 Choose a condition in which a new drug may be approved for treatment. Design a worksheet in Excel that can be used within a budget-impact analysis to present current and projected treatment mixes for examining the drug's impact.

Exercise 4.8 How might determining current and projected treatment mixes differ in acute versus chronic conditions? List issues that a developer of a budget-impact analysis might need to consider differently among these two condition types.

Exercise 4.9 A new drug that is highly effective in treating condition X will be approved in the coming months. A budget-impact analysis is being built to understand the impact of this new drug. The current market is crowded with treatments that are going generic in the next year such that before the year is over, all competitor treatments will be generic. Discuss the impact that these generics will have on the uptake of the new drug. Discuss issues to consider and features to be built within the budget-impact analysis.

Exercise 4.10 A new drug is being approved that would be an add-on therapy for treating HIV. Treatments in HIV are typically regimens composed of three to four drugs. Discuss how one would determine the treatment regimens to be considered within a budget-impact analysis for assessing the impact of this new add-on drug. How would the current and projected treatment mixes be estimated? Set up budget scenarios up to 5 years to present the current and projected mixes in an Excel worksheet.

Reference

Mahlich J, Nishi M, Saito Y. Modeling the budget impact of long-acting injectable paliperidone palmitate in the treatment of schizophrenia in Japan. Clinicoecon Outcomes Res. 2015;7:267–72. doi:10.2147/CEOR.S85514.

Chapter 5
Estimating Treatment-Related Costs

Thor-Henrik Brodtkorb, Stephanie Earnshaw, and Josephine Mauskopf

Abstract Estimating treatment-related costs for drugs includes estimating the drug acquisition costs as well as costs for administration, diagnostic testing, monitoring, and treatment of side effects. Acquisition costs may be from published price lists or may be negotiated privately at the national or plan level. In addition, the cost to the budget holder may be modified by patient co-payments, manufacturer discounts or rebates, or patient coinsurance. Costs for administration, diagnostic testing, monitoring, and treatment of side effects can generally be estimated using resource use based on the requirements stated in the drug label and unit costs from standard costing sources. In this chapter, we present a description of each of these types of costs and methods for estimating them.

Keywords Acquisition • Co-payments • Discounts • Rebates • Dispensing fee • Administration • Diagnostic tests • Monitoring • Side effects

Chapter Goal
To show how to estimate acquisition, administration, monitoring, side effect, and other treatment-associated costs, with suggestions about data sources and the type of costs to include.

Once the population and corresponding treatment mix estimates have been determined, the next step in a budget impact analysis is to estimate the treatment-related costs for all treatments in the treatment mix with and without the

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new drug.[1] If other types of treatment such as surgery, psychotherapy, or physical therapy are treatment options for the reimbursement-eligible population, they should be included in the current treatment mix, and their treatment-related costs should also be estimated. Treatment-related costs include not only the acquisition cost of the current and new drugs and the cost of performing other nondrug modalities, but they also may include other types of costs. The following cost categories should be included if applicable:

- Drug acquisition and administration costs or nondrug treatment costs
- Costs of diagnostic tests to determine eligibility for the drug or nondrug treatment
- Costs of monitoring for safety and efficacy while taking the drug or monitoring of nondrug treatment
- Costs of treatment of side effects or complications associated with the drug or nondrug treatment

In this chapter, we describe methods for estimating each cost category, focusing only on drug-related costs.

5.1 Costs for Drug Acquisition

The first and most important cost associated with a drug is its acquisition cost, the cost to the budget holder for the drug. Drug acquisition costs may be obtained from national or regional drug price lists for jurisdictions where these are available. These costs may be representative of the acquisition costs for budget holders. For example, the British National Formulary has a price list of all drugs approved for marketing in the United Kingdom (UK). These costs are the amount that the UK system pays for drugs reimbursed under the National Health Service system. Each province in Canada also has a drug price list for the publicly funded drug benefits program. The Red Book in the USA presents average wholesale prices, which are the equivalent of "list" prices. This is the benchmark price for payers, both government and private. The Red Book also presents the wholesale acquisition costs, which represent the cost of the drug paid by the wholesaler before discounts and rebates for drugs approved for marketing in the USA. Although actual payments by budget holders for drugs vary greatly within the USA, these costs represent a starting point from which many payers within the USA will negotiate their actual payments.

In Box 5.1, we present examples of national or regional drug price lists.

[1] In this chapter we make the simplifying assumption that the budget impact analysis is based on the introduction of a new drug to the current mix of drugs for treatment of a condition. Changes in our recommended approaches to estimate the budget impacts of other types of health-care interventions (i.e., vaccines, diagnostics, surgery, and devices) are discussed in Chap. 13.

Box 5.1. National and Regional Price Lists for the USA, Canada, and the United Kingdom

A budget holder is looking to populate a budget impact analysis with the most current pricing for fluticasone propionate for the USA, Canada, and the United Kingdom. To obtain this pricing, the budget holder has to access the national or regional price lists for these countries. The presentation of drug prices within these countries varies greatly. We provide a brief description of how fluticasone propionate is presented for each country's pricing source.

Red Book for the USA (Micromedex 2015)

For all forms of fluticasone propionate that are available for purchase in the USA, the Red Book presents product name, National Drug Code, active ingredient, manufacturer/distributor, whether the product has been repackaged, whether the product is generic, form, strength, route of administration, package size, wholesale acquisition cost per package, average wholesale price per package, and average wholesale price per unit. The Red Book is maintained by a private holding and is available as a subscription service.

Ontario Drug Benefit Program E-Formulary for Ontario, Canada (2015)

For all forms of fluticasone propionate that are available for purchase in Ontario, Canada, the Ontario Drug Benefit Program presents drug identification number, brand name, strength, dosage form, manufacturer, drug benefit price, amount that Ministry of Health and Long-Term Care pays, whether there is limited use, and additional therapeutic notes. Ontario drug prices are available from the Ontario Drug Benefit (ODB) Program E-Formulary, which is freely available at http://www.health.gov.on.ca/en/pro/programs/drugs/odbf_eformulary.aspx.

British National Formulary for the United Kingdom (2015)

The British National Formulary presents all the fluticasone propionate inhalers that are available for prescription on the National Health Service. They are listed by product name, and for each product, the British National Formulary gives the strength, pharmaceutical form, dosage information, available pack sizes, and associated list price and tariff price (if available). The British National Formulary is available as a subscription service.

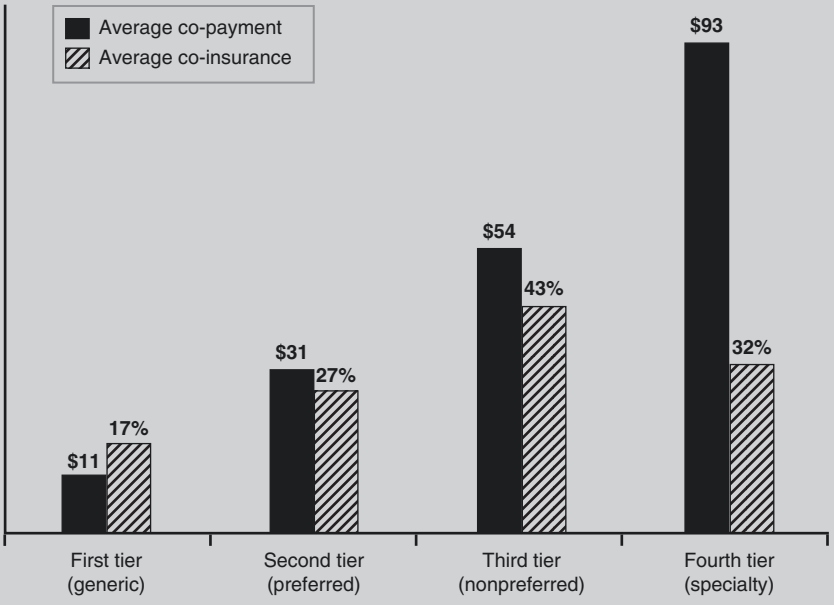
In many jurisdictions, including the UK and Canada, the published prices may not necessarily reflect the actual cost to the budget holder for some or all drugs because of negotiated discounts that are not publicly available. For this reason, the budget impact analysis should be developed to allow users to enter their own drug prices. This could be done by allowing direct entry of the drug price or allowing the model user to enter a discount percentage that is applied by the computer program to the publicly available price.

5.1.1 Co-payments and Coinsurance

Also affecting the budget holders' drug acquisition costs are co-payments that a patient might have to pay for each prescription filled. In the USA, this co-payment is not generally based on the drug cost but may vary from drug to drug, with drugs being assigned to different tiers with different co-payment amounts. Co-payments are typically lower for generic drugs than branded drugs. Alternatively or in addition to the co-payment, patients in some jurisdictions may have to pay a fixed percentage of the total drug costs (coinsurance). In many health plans in the USA as well as in Canada, an annual ceiling amount is applied to the coinsurance payment, above which the patient no longer has to pay any coinsurance. Both the co-payment per prescription and the coinsurance may be set at the national or health plan level. These amounts may or may not be publicly available and may vary among patients. If the computer program is to be used in jurisdictions where partial patient payment is the norm, the computer program may be designed to allow for these amounts to be subtracted from the budget holder payments as they would be monies not expended by the budget holder.

In Box 5.2, we present USA national estimates of the average co-payment and coinsurance amounts for drugs allocated to different tiers.

Box 5.2. USA Health Plans, Average Co-payment, and Coinsurance Amounts for Drugs on Different Prescription Tiers (Kaiser Family Foundation and Health Research & Educational Trust, 2015, Exhibit 9.4)



These averages are computed for all covered workers with three or more tiers of prescription cost sharing. They are the average co-payment and average coinsurance in 2015.

Estimating coinsurance costs to be subtracted from the budget holder costs can be quite complicated given the population approach of the budget impact analysis. Specifically, the amount paid by the patient might be driven by both a deductible, where the patient pays the full price up to a defined out-of-pocket expense in a given year, and a maximum amount that the patient may pay in a given year. The computer program can be designed to include an estimate of the impact on the region or health plan budget accounting for deductibles and coinsurance annual ceilings. However, caution should be taken when including these effects in the budget impact analysis, as these deductibles and maximum ceiling expenditures by a patient might be applied to any drug used by the patient within a specific time horizon and not just to expenditures on drugs for a specific indication. In addition, these amounts may vary by patients' insurance coverage or by their income level.

As an example, a budget impact analysis may be created to understand the impact of a new antibiotic. The budget impact analysis is set up such that it only considers the new antibiotic and other antibiotics whose treatment shares might change with the new antibiotic on the formulary. If a patient also had asthma and was on maintenance treatment with a corticosteroid, the patients' payments for both the asthma drug and the antibiotic might contribute to their annual health-care deductible and/or coinsurance annual ceiling. Thus, it can be challenging to include the effects of deductibles and coinsurance annual ceilings in a budget impact analysis that is examining a population with a specific condition.

One possible approach to account for deductibles or coinsurance annual ceilings due to costs of all drugs or all health-care services used by the patient (e.g., chronically ill patients with considerable medical needs) in the budget impact analysis is to assume that all patients in the reimbursement-eligible population will have already met the deductible and/or the coinsurance ceiling. As a result, there is no deductible or coinsurance paid by the patient for either the new or current treatments. Alternatively, a proportion of patients in the reimbursement-eligible population who have not met their deductible limit and/or their coinsurance ceiling for the health plan can be assumed and included in the model calculations. With either of these approaches, an underestimation of the impact on the budget holder can be avoided. In particular, with the latter approach, the effect on the budget holder of a different proportion of patients not meeting the deductible and/or paying the coinsurance can be explored.

In Box 5.3, we present calculations of the annual acquisition cost for a budget holder for a drug with multiple dosage formulations with co-payments only and for a drug with coinsurance.

Box 5.3. Calculation of Annual Drug Acquisition Costs

Calculation of Annual Methylphenidate Extended-release Acquisition Costs With Co-payment Only

MPH-EX dose level (assume 1 pill per day) (mg)	Co-payment per prescription	Prescription drug pack cost (30 pills)	# Prescriptions per year	Annual cost to budget holder	Percentage of patients using formulation (%)
18	£10	£31	12.167	£255.50	30
27	£10	£37	12.167	£328.50	50
36	£10	£42	12.167	£389.30	20

MPH-EX methylphenidate extended-release

The per prescription cost of MPH-EX 18 mg, 27 mg, and 36 mg is £31, £37, and £42, respectively. Co-payments for each prescription are £10. If patients need 12.167 prescriptions per year assuming one pill per day (365 days per year/30 days per prescription), the annual cost to the budget holder for an annual prescription of each of the MPH-EX dose levels is:

18 mg cost = (£31 - £10) × 12.167 = £255.51
27 mg cost = (£37 - £10) × 12.167 = £328.51
36 mg cost = (£42 - £10) × 12.167 = £389.34

If each drug pack includes 30 pills but more than one pill needs to be taken each day by some patients, then the annual number of prescriptions will need to be increased to supply the correct number of pills.

To calculate the average annual costs for the overall drug, the percentage of patients taking each dosage formulation must be estimated either using market research data or expert opinion. The average annual cost is:

Average annual costs for MPH-EX
= 0.3 × £255.51 + 0.5 × £328.51 + 0.2 × £389.34
= £318.78

Calculation of Annual Costs for Nalmefene or Naltrexone for Alcohol Dependence for Budget Holder with Patient Coinsurance and Annual Ceiling

Patients in a health plan take nalmefene or naltrexone. The cost for each drug is listed below.

Drug (mg)	Cost per tablet	Tablets per year
Nalmefene 18	40.61 kr	127
Naltrexone 50	16.99 kr	356

Coinsurance for patients within the health plan is 2185 kroner (kr) with a coinsurance rate of 38%. If 50% of patients pay coinsurance, what is the annual cost to the budget holder for each drug?

Annual cost to budget holder without coinsurance based on 28 tablets (18 mg) of nalmefene in a pack and wholesale acquisition costs from Statens legemiddelverk (2015):

Annual cost
= per tablet cost (40.61 kr) × # tablets per year (127)
= 5158 kr

Annual cost to budget holder without coinsurance based on 28 tablets (50 mg) of naltrexone in a pack and wholesale acquisition costs from Statens legemiddelverk(2015):

Annual cost
= per tablet cost (16.99 kr) × # tablets per year (356)
= 6048 kr

Given the following information:

Proportion of patients who will pay coinsurance for the full year = 50%
Coinsurance ceiling = 2185 kr
Coinsurance rate (percentage of drug cost) = 38%

Annual cost to budget holder for each drug is calculated as:

Annual cost
= annual cost of drug − {minimum of [(annual drug cost × coinsurance rate) or (the coinsurance ceiling)] × proportion paying coinsurance}

For nalmefene, annual cost to budget holder:

Annual cost
= 5158 kr − {min[(5158 kr × 0.38) or 2185 kr] × 0.5}
= 5158 kr − (1960 kr × 0.5)
= 4178 kr

For naltrexone, annual cost to budget holder:

Annual cost
= 6048 kr − {min[(6049 kr × 0.38) or 2185 kr] × 0.5}
= 6048 kr − (2185 kr × 0.5)
= 4956 kr

5.1.2 Dispensing Fees

Dispensing fees are another type of costs that may be incurred as part of the acquisition cost. Specifically, the budget holder or the patient may be required to pay a dispensing fee for each prescription dispensed. These are much more straightforward and can easily be included in the model if relevant.

5.1.3 Dose Levels

Another factor that needs to be taken into account when estimating the acquisition costs for current and new drugs is the distribution of the possible dosage formulations for each drug that are used by the patients taking that drug as well as the average daily number of tablets for each dosage formulation per patient. Further, the proportion of patients using each dosage level needs to take into account the fact that patients may start at a low dose and then titrate up to a higher dose depending on the efficacy and safety of the initial dose. Market research data will frequently include estimates of these values for currently used drugs. However, these data will not be available for the new drug. As a result, credible assumptions will need to be made, either based on similarity to current drugs, the clinical trial data, the prescribing information, or expert opinion.

5.1.4 Duration of Treatment

Finally, an important factor that needs to be taken into account when estimating the budget holder's annual acquisition costs is the duration of treatment if it varies among the drugs in the treatment mix. This is especially relevant for acute conditions or curative therapy for a chronic condition such as hepatitis C. But it also needs to be considered for chronic conditions such as metastatic cancer or HIV infection. For acute treatment that is resolved within the budget year, the per event drug acquisition costs to the budget holder can be estimated directly for each dosing formulation for each drug in the treatment mix as follows:

Drug cost
= per pack cost net of co-payments × the number of packs needed to complete the treatment regimen,

If the health system has coinsurance, then acquisition costs will need to account for coinsurance and the coinsurance ceiling.

For chronic treatment, changes in the duration of treatment because of better efficacy that is keeping people on treatment longer are best accounted for by changing the size and condition severity distribution of the treated population and/or changing the treatment mix, which, in turn, changes the treatment-related and condition-related costs. Alternatively, the duration of treatment can be estimated directly as described above for acute conditions. However, for chronic conditions with treatment duration for some or all of the patients spanning over multiple years, applying the cost based on the mean treatment duration for all patients in the first treatment period (i.e., first budget year) will inflate the budget impact of the initial periods. In these cases, the use of a disease progression model to estimate the change in size in the incident and prevalent populations alive and being treated will more precisely estimate the budget impact over the budget impact analysis time horizon.

In Box 5.4, we present some examples of conditions where treatment duration will vary for different drug regimens.

Box 5.4. Drugs with Different Duration of Treatment

Drug category and condition	Alternative duration of treatment
Antibiotics for urinary tract infection	Duration of treatment may range from 3 to 10 days
Direct-acting antiviral drugs for chronic hepatitis C	Duration of treatment may range from 8 to 48 weeks
Chemotherapy for metastatic cancer	Treat until disease progression
Antiretroviral therapy for HIV infection	Treat until virologic failure or rebound
Congestive heart failure	Treat until death

5.2 Costs for Administering the Drug

In addition to the cost of acquiring the drug, some drugs may incur an administration cost. Oral medications can be taken directly by the patients. So the cost to administer them is zero. However, injectable drugs or drugs given intravenously may require nurse and/or physician training, oversight, or administration. These costs should be included in the budget impact analysis.

For injectable drugs, a key factor is whether the patient can be trained and allowed to self-administer the injection. The extent to which self-administration occurs will likely vary by jurisdiction and should be considered in the analysis. However, care should be taken when incorporating these costs into the analyses. For example, even when the patient self-administers an injection, nurse resource time and costs should be included for initial training of the patient. It may also be necessary to incorporate subsequent training sessions over time.

If a health professional is required to administer the drug, the additional resource use and unit costs necessary for the administration may include extra visits to the physician or extra time at a scheduled visit to administer the injection, travel costs for the patients when these are covered by the budget holder, etc.

Guidance for the additional resource use needed to administer intravenous formulations can generally be obtained from the product label. This document will specify how the infusion is to be performed, for how long the drug should be infused, and who should infuse the drug. From this information, estimates can be made for staff time, facilities time, and supplies needed for the infusion. Regional or jurisdiction standard unit costs can then be applied to these resources.

In Box 5.5, we present an example for the estimation of administration costs for chemotherapy regimens in the USA.

Box 5.5. Example Estimation of Drug Administration Costs
A budget impact analysis has been constructed for a new chemotherapy drug. It is expected to compete in the same space as the combination chemotherapies paclitaxel + carboplatin and pemetrexed + cisplatin. The administration costs for the current regimens are estimated using the following information:

- Paclitaxel requires intravenous administration over 3 h.
- Carboplatin requires intravenous administration over 1 h.
- Pemetrexed requires intravenous infusion over 10 min.
- Cisplatin requires intravenous infusion over 2 h at least 30 min after pemetrexed with hydration prior to and/or after cisplatin.

Per unit administration costs in the USA are obtained from the resource-based relative value scale (RBRVS) (Ingenix 2015):

- Conversion factor used for RBRVS weights = $35.9335
- Current Procedural Terminology (CPT) 96,413 up to 1 h (single or initial substance drug) nonfacility code = 3.80
- CPT 96415 each additional hour nonfacility code = 0.79
- CPT 96417 additional sequential infusion (different substance/drug) up to 1 h nonfacility code = 1.76
- CPT 96360 hydration, 31 min to 1 h nonfacility code = 1.62
- CPT 96361 hydration, each additional hour nonfacility code = 0.43
- CPT 99215 office or other outpatient visit nonfacility code = 4.09

Administration costs using RBRVS weights and Medicare conversion factor for the USA:

Administration costs for paclitaxel + carboplatin
= [CPT 99215 (one office visit) + CPT 96413 (up to 1 h) + 2 × CPT 96415 (each additional hour) + CPT 96417 (additional sequential infusion up to 1 h)] × RBRVS conversion factor
= (4.09 + 3.80 + 2 × 0.79 + 1.76) × $35.9335
= $403.53

Administration cost for pemetrexed + cisplatin
= [CPT 99215 (one office visit) + CPT 96413 (up to 1 h) + CPT 96360 (hydration, 31 min to 1 h) + 2 × CPT 96417 (additional sequential infusion up to 1 h) + CPT 96361 (hydration, each additional hour)] × RBRVS conversion factor
= (4.09 + 3.80 + 1.62 + 2 × 1.76 + 0.43) × $35.9335
= $483.66

5.3 Costs for Diagnostic Tests to Determine Eligibility for the Drug

When considering a budget impact analysis for a new drug, costs of other health-care resources required to be incurred in order to receive the new drug or other competing drugs or nondrug treatments need to be included. For example, prior to receiving a particular drug, patients may be required to have a diagnostic test. This may include

genetic testing to assess risk of a harmful side effect (e.g., testing for *HLA-B*5701* to prevent hypersensitivity reaction in patients who take abacavir) or likelihood of benefit of the drug (e.g., testing for epidermal growth factor receptor mutation to predict whether a tyrosine kinase inhibitor can help treat a patient). Genetic testing is also used to help optimize drug dosing (e.g., testing for hepatitis C virus genotype to determine how long different treatment regimens should be given in patients with hepatitis C).

Care should be taken when incorporating diagnostic costs into the budget calculations for a chronic condition, as these costs would only be valid for the incident population because they are only incurred once before starting a drug. This is straightforward when the budget impact for the incident and prevalent populations is estimated separately. When a combined incident/prevalent population is used, then the percentage of those in their first year of treatment must be estimated for each drug in the treatment mix based on average duration of treatment.

Other considerations when including diagnostics in budget impact analyses are (1) whether it is mandatory that all patients who receive the particular drug actually receive the test or just a portion of the eligible population receives the test, (2) how the results of the tests change the treatment mix, and (3) how false-positive or false-negative results from diagnostic tests might have cost implications. These should be accounted for in the budget impact model.

In Box 5.6, we present examples of drugs that need diagnostic testing.

Box 5.6. Example List of Drugs Requiring Diagnostic Testing (USA Food and Drug Administration 2015)

Below is a list of drugs by therapeutic area that may require diagnostic testing before administration. The drug, the specific biomarker needing to be identified, patients at risk, and where in the product label a physician may identify the need for diagnostic testing are listed.

List of drugs requiring diagnostic testing (USA Food and Drug Administration 2015)

Therapeutic area	Drug	Biomarker	Patients at risk	Sections of product label referenced
Cardiology	Clopidogrel	*CYP2C19*	*CYP2C19* intermediate or poor metabolizers	Boxed warning, dosage and administration, warnings and precautions, clinical pharmacology
Gastroenterology	Omeprazole	*CYP2C19*	*CYP2C19* poor metabolizers	Drug interactions
Infectious diseases	Abacavir	*HLA-B*	*HLA-B*5701* allele carriers	Boxed warning, contraindications, warnings, and precautions
	Boceprevir	*IFNL3*	*IL28B rs12979860 T* allele carriers (*C/T* and *T/T* genotype)	Clinical pharmacology

Therapeutic area	Drug	Biomarker	Patients at risk	Sections of product label referenced
Neurology	Clobazam	*CYP2C19*	*CYP2C19* poor metabolizers	Dosage and administration, use in specific populations, clinical pharmacology
Oncology	Irinotecan	*UGT1A1*	*UGT1A1*28* allele carriers	Dosage and administration, warnings and precautions, clinical pharmacology
	Letrozole	*ESR1, PGR*	Hormone receptor positive	Indications and usage, adverse reactions, clinical pharmacology, clinical studies
Rheumatology	Celecoxib	*CYP2C9*	*CYP2C9* poor metabolizers	Dosage and administration, use in specific populations, clinical pharmacology
	Azathioprine	*TPMT*	*TPMT* intermediate or poor metabolizers	Clinical pharmacology, warnings, precautions, drug interactions, adverse reactions, dosage and administration
Psychiatry	Clozapine	*CYP2D6*	*CYP2D6* poor metabolizers	Dosage and administration, use in specific populations, clinical pharmacology
	Fluoxetine	*CYP2D6*	*CYP2D6* poor metabolizers	Clinical pharmacology, warnings, precautions
Pulmonary	Indacaterol	*UGT1A1*	*UGT1A1*28* allele homozygotes	Clinical pharmacology

5.4 Costs for Monitoring the Drug for Safety and Efficacy

Monitoring costs may be associated with taking a drug. These costs may be required to track the amount of drug in a patient's system to avoid a potential side effect or to ensure the patient is getting the proper amount of drug for adequate efficacy. For example, patients on warfarin are tested periodically to ensure that their international normalized ratio (INR) levels are appropriate. If INR levels are too high, then patients have too much drug in their system and are at risk for bleeding events. If INR levels are too low, then patients do not have enough drug in their system to be effective at preventing blood clots. Drugs are also monitored for efficacy especially for chronic infectious diseases where resistance might develop over time. For example, in HIV, all drugs are monitored for their effect on viral load and CD4 cell count.

If the viral load is not suppressed or rebounds after an initial period of suppression, a regimen is assumed to have failed and patients are switched to a new regimen. As a result, monitoring a patient's viral load is important for treatment.

However, even though monitoring may be required or may be standard clinical practice, it is also important to understand when it is necessary to include these costs in a budget impact analysis. Typically, if monitoring for drug-related side effects is required as part of the regulatory approval for a drug and the intensity and/or type of monitoring varies for the different drugs in the treatment mix, then these costs should be included in the budget impact analysis. However, in the HIV example, even though monitoring viral load is important, since all antiretroviral treatment regimens are monitored for efficacy in the same way, there may be no need to include these costs in the analysis since they will not change with changes in the mix of drug treatments used.

Monitoring for drug efficacy may or may not be required in different jurisdictions. For example, some jurisdictions have stopping rules with some drugs such that if early indications of efficacy are not observed, the drug is discontinued. In addition, monitoring of efficacy may be performed to allow for titration of the daily dose to a higher value over time. These extra monitoring costs may need to be included in the analysis if they differ among the drugs included in the treatment mix.

For costing the resource use associated with monitoring, developers of budget-impact analyses not only need to include the cost of the test to understand the extent of the drug in the patient's system, but they also may need to include the cost of additional physician or nurse visits in order to perform the tests as well as other reimbursed costs associated with the monitoring when the monitoring required additional visits. Additional resource use may include blood tests and other laboratory tests to ensure that known side effects are not occurring.

The best source for estimating the resource use associated with monitoring for drug-related side effects is the drug labels, since required or recommended monitoring for safety is typically listed in these labels. Estimating the number of additional physician or nurse visits needed for monitoring might not be as easy. For drugs that have been on the market, obtaining the average number of visits from an analysis of health-care claims may be the best source. However, for new drugs not yet on the market or when these data cannot be obtained from health-care claims data, expert opinion might be the best source. Additional testing to ensure that the known side effects are not occurring may be estimated in the same manner. Once the number of resources needed to perform the appropriate level of monitoring is known, standard unit costs can be applied to the resources.

In Box 5.7, we present an example of estimating monitoring costs for current and new treatments.

Box 5.7. Warfarin Versus New Anticoagulant Treatment for Atrial Fibrillation

Patients with atrial fibrillation have historically been treated with warfarin. Treatment with warfarin must be individualized for each patient to ensure that the amount of warfarin in their blood is high enough for efficacy but not so

high that there are safety risks. This is accomplished through international normalized ratio (INR) testing. For adequate treatment with warfarin, physicians should target an INR of 2.5 (range of 2.0–3.0). Patients on warfarin are typically started on 5–10 mg per day and then are tested once a week, adjusting the dosing according to the INR level.

Several new oral anticoagulants have been approved and have come on the market to treat atrial fibrillation. These include dabigatran, apixaban, and rivaroxaban. Although they have different risks, unlike warfarin, these drugs do not require monitoring to ensure that the amount of drug in a patient's system is within the appropriate range.

In estimating the impact of including these new drugs on a payer's budget, the following differences in drug and other related costs associated with treating patients with warfarin and a new oral anticoagulant should be included in the budget impact analysis.

Drug and Other Costs Associated with Patients on Warfarin:

- Initial dosing of warfarin
- Periodic testing of INR
- Titration of warfarin to achieve blood levels with an adequate amount of drug but not too much
- Side effects associated with too much warfarin in a patient's system
- Side effects associated with too little warfarin in a patient's system
- General side effects associated with treating with warfarin

Drug and Other Costs Associated with Patients on New Anticoagulants:

- Dosing of new anticoagulant
- General side effects associated with treating with new anticoagulants

5.5 Costs for Treating Side Effects Associated with the Drug

Despite monitoring, patients taking drugs are likely to experience side effects, some of which may require treatment. There are several factors contributing to the costs for side effects to be included in a budget impact analysis. Not only is it important to estimate the rates at which these events occur, but it is important to determine when these events are likely to occur (i.e., only upon initiation of treatment, as long as the patient takes the treatment, or only after several years on the treatment), severity of the events, and the extent to which these events may lead to discontinuation of the drug.

In order to assign health-care costs to the side effects, side effect rates are needed by level of severity, since severity of the side effect will likely determine the intensity and cost of treatment. At the very least, serious side effects might be separated from nonserious side effects.

The rates and types of side effects expected with the different drugs in the treatment mix can be obtained either from the product labels or from the published clinical trials. If head-to-head studies have not been performed to compare the various drugs within the budget impact analysis, mixed treatment comparison analyses could be used to generate credible estimates of side effect rates for the different drugs in the treatment mix. This type of analysis might have been performed to provide inputs into a cost-effectiveness analysis.

Once the rates of side effects for all the drugs in the treatment mix have been obtained, then resource use for treating each side effect can be taken from published studies, or if these are not available, then treatment algorithms can be developed based on recommendations from treating physicians. The treatment patterns are likely to be different in different jurisdictions. So the treatment algorithms should be easily modifiable in the program. Given the health-care resources required to treat the side effects, unit costs can be applied to the resource use using standard data sources.

It is not uncommon for the list of side effects that may be experienced by patients taking specific drugs to be very long. If this is the case, then we recommend limiting the side effects considered in the budget impact analysis to those that are most resource intensive and that are most likely to change with the new drug added to the formulary.

In Box 5.8, we present the side effect rates and costs that can occur with a new drug for opioid-induced constipation.

Box 5.8. Side Effects in a Budget Impact Analysis for Naloxegol

Naloxegol is a new treatment on the market for treating opioid-induced constipation. Two other drugs are available for treatment, lubiprostone and linaclotide. As these drugs have different side effect profiles that may affect the budget impact, they need to be included in a budget impact analysis for a health plan.

To incorporate the side effects in the budget impact analysis, we first need to obtain the rate of occurrence for the side effects that we feel will most significantly affect the payer's budgets or occur most often. We have obtained these side effects from each treatment's product information label. From the label, we can obtain the side effects from both the treatment and placebo control arms. Obtaining the side effects from both arms allows us to estimate the increased rate of side effects with the drug treatment.

Once the rates for each side effect are obtained, we obtain costs expected to treat those side effects. In this example, all side effects were assumed to be treated via the patients seeking care from a physician. Given these data, we can incorporate them into the budget impact analysis based on the treatment shares for the three drugs to estimate the cost of treating these side effects.

Side effect rates

Side effect	Lubiprostone (LUB) prescribing information (2013)			Linaclotide (LIN) prescribing information (2016)			Movantik (MOV) prescribing information (2015)		
	LUB (%)	Placebo (%)	Δ (%)	LIN (%)	Placebo (%)	Δ (%)	MOV (%)	Placebo (%)	Δ (%)
Abdominal pain[a]	4	1	3	7	6	1	21	7	14
Diarrhea	8	2	6	16	5	11	9	5	4
Flatulence	4	3	1	6	5	1	6	3	3
Nausea	11	5	6	0	0	0	8	5	3

Δ difference from placebo, *LIN* linaclotide, *LUB* lubiprostone, *MOV* Movantik (naloxegol)
[a]Side effects reported for those with chronic idiopathic constipation since linaclotide is not currently approved for treating opioid-induced constipation. Abdominal pain in linaclotide prescribing information (2016) includes abdominal pain and upper and lower abdominal pain.

Side effect costs

Side effects	Costs[a]	Source or assumptions
Abdominal pain	$73.30	One physician visit (RBRVS) (Ingenix 2015)
Diarrhea	$73.30	One physician visit (RBRVS) (Ingenix 2015)
Flatulence	$73.30	One physician visit (RBRVS) (Ingenix 2015)
Nausea	$73.30	One physician visit (RBRVS) (Ingenix 2015)

RBRVS resource-based relative value scale
[a]The physician visit cost was estimated using Current Procedural Terminology code 99213, which is described as "an office or other outpatient visit for the evaluation and management of an established patient".

5.6 Accounting for Differing Treatment Costs in the First and Subsequent Treatment Years

One issue that can arise when estimating drug treatment costs for a population with a chronic condition is that the treatment costs the first year on the drug might differ from those in subsequent years. This could be the case for many reasons:

- Administration costs are higher the first year on therapy for injectable drugs.
- Monitoring for side effects is more intensive the first year on therapy.
- Dosing levels might be different for the first year compared with subsequent years.
- Side effects are likely to be more frequent and more severe the first year on treatment because the body adapts to the medicine and/or because those with severe side effects switch to another drug.

In a budget impact analysis, as stated before, the unit of analysis is the population rather than an individual or cohort of individuals. For a chronic condition, this population includes those who are taking a drug for the first year and those who have been taking the drug for more than 1 year. Thus, an adjustment for costs that are different for the first year compared with subsequent years must be made when estimating drug treatment costs. As described above for estimating the diagnosis costs, if the budget impact for incident and prevalent populations are estimated separately, these differences in first-year treatment costs can be explicitly included in the analysis. But if the treated population in the analysis includes both incident and prevalent patients, the proportion of the population taking a specific drug that are in their first year on therapy can be approximated using estimates of annual discontinuation rates for the drug or estimates of the average duration on treatment with the drug. Thus, a simple way to determine the number of patients who are taking their first year of the current treatment is to divide the total number of people on each treatment by the mean duration on each treatment type.

In Box 5.9, we present an example of how to estimate the number of patients on their first year of therapy in the treatment mix.

Box 5.9. Adjustment for First-Year and Subsequent-Year Costs for Drugs in the Treatment Mix

The current treatment mix in a population of 1000 individuals with the condition of interest includes three drugs, drug A (30%), drug B (30%), and drug C (40%) where:

- Mean duration of treatment on drug A is 3 years
- Mean duration of treatment on drug B is 4 years
- Mean duration of treatment on drug C is 5 years

For drug A, the number in the first year on treatment is calculated as:

Number treated in year 1
= (1000 patients × 30% on drug A) / duration of 3 years
= 100.

For drug B, the number in the first year on treatment is calculated as:

Number treated in year 2
= (1000 patients × 30% on drug B) / duration of 4 years
= 75.

For drug C, the number in the first year on treatment is calculated as:

Number treated in year 3
= (1000 patients × 40% on drug A) / duration of 5 years
= 80.

For a new drug D, in the first year, all patients will be in their first year of treatment. After that, the proportion in their first year will depend on the change in treatment shares each year and the expected discontinuation rates with the new drug estimated from the clinical trial data.

5.7 Accounting for Other Treatment Costs

Although this chapter assumed the new drug would displace or add to other drug treatments among a mix of drug treatments, this might actually not be the case. The new drug might displace another health-care resource such as surgical treatment, psychotherapy, or physical therapy. Thus, the costs associated with this other type of treatment may also need to be included in the budget impact analysis. It is important to include the full costs of these other treatments. For example, the costs of surgical treatments will include the procedure costs as well as presurgical and postsurgical monitoring costs and the costs of treating surgical complications. If these costs are expected to change in use or intensity with the addition of the new drug, the costs for these other types of treatment need to be included in the budget impact analysis.

5.8 Estimating Resource Use Changes with the New Drug

The focus of this chapter has been on estimating treatment-related costs. The changes in treatment-related costs for administration, diagnosis, monitoring, and side effects are estimated based on estimated changes in the use of a variety of health-care resources, including provider time and supplies for administration, provider and laboratory personnel time and supplies for diagnosis and monitoring drug safety and efficacy, and the full range of health-care services needed for the treatment of any drug-related side effects. Treatment-related changes in the use of these resources over the budget impact analysis time horizon can be calculated in addition to their use in estimating the treatment-related costs. They can be presented to budget holders to help them with planning their resource needs (see Chap. 11).

Exercises

Exercise 5.1 Identify a new drug that is about to come to market. With which treatments will this drug compete? List the treatment-related costs associated with this new drug and its competitor treatments. Build an Excel-based workbook to calculate treatment-related costs for this new drug.

Exercise 5.2 Identify a drug that requires the use of a diagnostic test prior to prescribing the drug. List the specific costs associated with the drug and diagnostic to be included in the budget-impact analysis. Describe how these costs would be applied within the analysis. How will you estimate these costs?

Exercise 5.3 How might the sensitivity or specificity of a diagnostic test affect the estimation of treatment-related costs?

Exercise 5.4 Oncology drugs are associated with numerous side effects. Clinical trials for oncology drugs will track side effects of grade 1 (mild) to grade 4 (most severe). In building a budget-impact analysis for a new oncology drug, how would you approach incorporating side effects such that the number of side effects considered is not unwieldly?

Exercise 5.5 Discuss characteristics of a health plan that might affect the estimation of treatment-related costs.

Exercise 5.6 A new inhaled corticosteroid is being approved for treatment of asthma and chronic obstructive pulmonary disease. A health plan is interested in understanding the impact that introducing this new treatment will have on its budgets. Discuss how this new inhaled corticosteroid will affect treatment-related costs.

Exercise 5.7 A new drug is being studied for treatment of HIV/AIDS. This drug will be used as an add-on to other commonly used drugs to make up new drug regimens. Discuss what treatment-related costs should be considered in a budget-impact analysis for this new drug.

Exercise 5.8 The introduction of a new drug comes with a substantial increase in treatment-related costs (i.e., high acquisition costs, increase in administration costs, increased monitoring and diagnostic costs). However, the drug has shown to be highly effective in preventing disease X. Even though the treatment-related costs are high, explain how introducing this drug to a health plan formulary may be beneficial.

Exercise 5.9 A budget-impact analysis is being built to examine annual budgets up to 5 years. Treatment-related costs are variable over a period of 1.5 years and then are constant thereafter. Explain how these costs may be accounted for within the budget-impact analysis.

Exercise 5.10 A new drug is expected to come to market for treating high cholesterol. Identify the reimbursement-eligible population, the treatments with which this new drug will compete, and the treatment-related costs. Build a worksheet in Excel to present this information.

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Chapter 6
Estimating Condition-Related Costs

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Abstract In this chapter, we discuss how to estimate any changes in condition-related costs and outcomes that might be expected to occur as a result of the introduction of the new drug to the formulary. These changes should be included in the budget-impact estimates if they are likely to occur within the analysis time horizon and if there are credible clinical data that indicate that such changes are likely. Condition-related costs and outcomes that occur beyond the analysis time horizon may also be important to consider within an analysis. Consideration of these costs along with condition-related costs and outcomes that might occur for an incident versus a prevalent population are discussed.

Keywords Budget-impact analysis • Condition-related costs • Acute conditions • Chronic conditions

Chapter Goal
To provide guidance on when to include these costs in a budget-impact analysis. To show how to estimate from a population perspective changes in condition-related costs as well as changes in health and health care service use as a result of the new drug being included in the treatment mix.

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6.1 Why the New Drug Might Change Condition-Related Costs

When a new drug[1] is introduced, it is important to present estimates of the impact of the change on immediate treatment-related costs (i.e., drug acquisition costs and the associated costs such as administration, monitoring, diagnostics for targeted therapies, and side effects). However, adding a new drug with differing efficacy to the treatment mix might also change costs associated with managing the symptoms and/or consequences of the condition. For example, introducing a more effective antiplatelet agent may reduce costs associated with rehospitalizations for cardiovascular events after acute coronary syndromes, or a more effective osteoporosis therapy may reduce the overall costs associated with treating fractures. Thus the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines suggest that a budget-impact analysis include estimates of the impact of the new drug on both treatment-related costs and condition-related costs but with the ability to show the results separately for each type of cost. A review of all National Institute for Health and Care Excellence (NICE) costing templates showed that offsetting condition-related costs were included only when data supporting such an effect were strong—that is, from head-to-head clinical trials or from a credible network meta-analysis (Mauskopf et al. 2013). It is thus important that if changes in condition-related costs are included in the budget-impact estimates, care should be taken to develop credible evidence to support these estimates.

In Box 6.1, we present examples of expected changes in condition-related costs that might be attributable to a new drug.

Box 6.1 Examples of Expected Changes in Condition-Related Costs with a New Drug

Condition and drug impact	Expected changes in condition-related costs
Acute coronary syndromes with immediate percutaneous coronary intervention New antiplatelet drug with fewer rehospitalizations for cardiovascular disease events but an increased risk of bleeding events shown in a head-to-head, double-blinded, randomized controlled clinical trial compared with standard of care (Mahoney et al. 2010)	Costs for rehospitalizations each year after introduction of the new drug for cardiovascular disease events and for drug-related bleeding events

[1] In this chapter we make the simplifying assumption that the budget-impact analysis is based on the introduction of a new drug to the current mix of drugs for treatment of a condition. Changes in our recommended approaches to estimate the budget impacts of other types of health-care interventions (i.e., vaccines, diagnostics, surgery, and devices) are discussed in Chap. 13.

Condition and drug impact	Expected changes in condition-related costs
Osteoporosis New drug with lower incidence of vertebral and other fractures shown in a mixed-treatment comparison analysis (Freemantle et al. 2013)	Cost for treating vertebral and other fractures each year after introduction of the new drug
Age-related macular degeneration New drug expected to slow disease progression and thus reduce the incidence of low vision and blindness shown by extrapolation from short-term slowing in vision decline from a head-to-head randomized controlled trial (Colquitt et al. 2008)	Costs for low-vision aids, rehabilitation, community services, and residential care associated with reduced vision and blindness each year after introduction of the new drug

6.2 Estimating Changes in Condition-Related Costs for Incident Populations

Estimating changes in condition-related costs for the population with the condition each year after introduction of a new drug depends on the type of condition (acute or chronic) and the timing of expected changes in condition-related costs. The calculations may be similar to those that would be conducted in a cost-effectiveness analysis where condition-related outcomes are predicted (most often using health states) and the costs associated with each health state are estimated. The primary data sources for estimating the impact on condition-related costs for all treatments in the treatment mix are the same as those for cost-effectiveness analyses. Condition-related outcomes are estimated by using clinical trials directly or by indirect treatment comparisons using all relevant available clinical trial data. Sources of resource use and cost data include published studies for specific condition outcomes and micro-costing using resource use from published studies, treatment guidelines, or treatment algorithms developed by treating physicians. When micro-costing, resource use estimates can be converted to cost estimates using standard unit cost data sources.

6.2.1 Acute Conditions or Chronic Conditions Where Changes Occur Almost Immediately

Calculating outcomes and costs in budget impact analyses in which the use of the new drug causes outcomes to change within a couple of days to a year is fairly straight forward. In most of these cases, we can assume the new outcomes occur immediately (i.e., on the first day of the budget time horizon) for the incident population and for the prevalent population if applicable. For acute conditions, clinical trials may supply data to estimate the changes in condition outcomes as the outcomes may be observed during the trial. This may also be the case for chronic

conditions where the effects of treatment are observed immediately or very rapidly in the clinical trials and do not change as the patient continues to be treated. Given the immediate occurrence of outcomes for each drug in the treatment mix, the overall impact between a budget scenario with the new drug and a budget scenario without the new drug can be estimated by weighting the drug-specific outcomes by the treatment shares in each year of the budget-impact analysis time horizon.

In Box 6.2, we present examples of clinical outcomes data for acute conditions or immediate effects on chronic conditions.

Box 6.2 Example Changes in Clinical Outcomes for Acute Conditions or Chronic Conditions Where the Changes Are Immediate

Condition and drug impact	Sources for data
Influenza New drug reduced the duration of symptoms	Randomized controlled trials comparing the new drug with placebo (Nicholson et al. 2000)
Congestive heart failure New drug reduced the rate of exacerbations requiring hospitalization	Randomized controlled trial comparing the new drug with active treatment (Maggioni et al. 2002)
Acute coronary syndromes needing immediate percutaneous coronary intervention New drug reduced rehospitalizations in the first year after event	Randomized controlled trial comparing the new drug with active treatment (Mahoney et al. 2010)
Attention-deficit/hyperactivity disorder New drug in children and adolescents for whom treatment with stimulants has failed shows increased response rate compared with placebo and another second-line treatment	Mixed-treatment comparison analysis using data from both head-to-head studies and placebo-controlled studies (Roskell et al. 2014)
Relapsing-remitting multiple sclerosis New drug reduced annual relapse rates and rate of disease progression	Mixed-treatment comparison analyses of head-to-head and placebo-controlled trials (Roskell et al. 2012)

6.2.2 Chronic Conditions Where Changes Occur Beyond the Budget-Impact Analysis Time Horizon

For chronic conditions where there is no or very limited impact on condition-related costs during the analysis time horizon, the developer of the budget-impact analysis should consider very carefully whether to include condition-related costs in the analysis. The ISPOR budget-impact analysis guidelines state that these costs should not be included if doing so would make the analysis more complex without changing the estimates of budget impact over the typical 5-year time horizon (Sullivan et al. 2014). The following are examples of such situations in which condition-related costs may not be affected within the time horizon of the budget-impact analysis:

- Curative treatment for chronic hepatitis C in those without cirrhosis or advanced liver disease
- Treatments designed to prevent microvascular or macrovascular complications of diabetes for those early in the disease course
- Disease-modifying treatments for multiple sclerosis in those with relapsing-remitting disease where their Expanded Disability Status Scale score is low and progression is very slow

However, if the budget holder or other decision makers are likely to be interested in cost offsets that may be expected to be realized after their specified analysis time horizon, then the computer model should be designed to estimate the long-term cost offsets and report them separately from the budget-impact estimates. For example, the budget impact in each year over the first 5 years after launch would be presented, and estimates of the cost offsets expected over the lifetimes of the patients treated during the first 5 years after launch could be presented separately to demonstrate the future savings that are expected beyond the analysis time frame.

6.2.3 Chronic Conditions Where Changes Occur Gradually Within the Budget-Impact Analysis Time Horizon

The most complex situation is for a chronic condition where a new drug will affect condition-related outcomes not immediately but gradually over the analysis time horizon, whether this is 5 years or longer. A decision-analytic model such as a Markov model or simulation model might be needed to capture the effects on the condition outcomes over the analysis time horizon through changes in the treated population size and/or changes in condition severity mix. One way to include these types of condition-related outcomes in the budget-impact analysis is to run separate incident cohorts of patients representing those starting treatment in each year of the budget-impact analysis through a disease-progression model and sum, for each year of the budget-impact analysis, the condition-related costs from all of these cohorts in that year. For example, the costs in the third year of the budget-impact analysis will be equal to the sum of the third-year costs for those starting treatment in the first year of the analysis, the second year costs for those starting treatment in the second year of the analysis, and the first-year costs for those starting treatment in the third year of the analysis.

These estimates may be calculated for each of the drugs separately included in the treatment mix by applying a simple disease-progression model for each treatment. Each year's condition-related costs are then weighted by the mix of treatments within the respective budget scenarios. If a cost-effectiveness analysis is being developed as well as the budget-impact analysis, it may be convenient to transfer the predictions of population changes from the cost-effectiveness analysis to the budget impact analysis where condition-related costs for the budget-impact analysis are then calculated for a series of cohorts starting treatment each year. The treatment shares for each incident cohort can be assumed constant or allowed to

change over time. Alternatively, a simpler approach may be followed in which an average treatment efficacy with and without the new drug in the treatment mix could be applied directly to the total population who are reimbursement-eligible with and without the new drug in the treatment mix to estimate changes in condition-related costs.

To calculate the condition-related costs using a Markov/disease progression model that may be constructed for a cost-effectiveness analysis, we recommend the following set of calculations for a situation where three drugs are available. A cost-effectiveness analysis is performed using a Markov modeling approach in which drugs A, B, and C are compared for a chronic condition. Patients progress through the disease/model as seen in Fig. 6.1. Patients on each drug transition through the Markov with a different set of transition probabilities which represents the efficacy of each drug. The resulting percentage of patients in each of the health states when on each drug at the end of each yearly model cycle is presented in Table 6.1. We assume that the annual condition-related costs for monitoring and symptomatic care are £1,000 for those in the preprogression state (C_x), £2,000 for those in the postprogression state (C_y), and £0 for those in the dead state (C_d).

To determine costs for each budget year during the budget-impact analysis time horizon, the annual cost for each budget year is first calculated for each drug. This cost is based on the number of patients in each health state in each year after the start of treatment (as calculated in a Markov model). Specifically, for a new treatment, budget year 1 assumes all patients have been on treatment for 1 year whereas the budget in year 2 includes a portion of patients who have been on treatment for 1 year and a portion of patients who have been on treatment for 2 years. For budget year 3, it continues in that the budget includes a portion of patients who have been on treatment for 1 year, a portion of patients who have been on treatment for 2 years, and a portion of patients who have been on treatment for 3 years.

The estimation of preprogressive disease management costs for each budget year are calculated as follows:

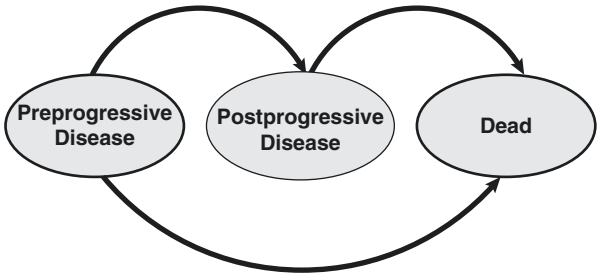

Fig. 6.1 Model structure

Table 6.1 Percentage of Patients in Each Health State

Time from Start of Treatment (Cohort Model)	Drug A (P_{Aj})			Drug B (P_{Bj})			Drug C (P_{Cj})		
	PRP	PP	Dead	PRP	PP	Dead	PRP	PP	Dead
Year 0	100%	0%	0%	100%	0%	0%	100%	0%	0%
Year 1	80%	15%	5%	82%	13%	5%	85%	10%	5%
Year 2	64%	26%	10%	66%	24%	10%	68%	22%	10%
Year 3	51%	34%	15%	52%	33%	15%	54%	31%	15%
Year 4	41%	40%	19%	42%	39%	19%	44%	37%	19%
Year 5	33%	43%	24%	34%	42%	24%	35%	41%	24%

PRP pre-progression, *PP* post progression

Using the percentage of patients in each health state in each cycle derived for each drug from Table 6.1, the calculations are presented in Table 6.2. Assume the number of patients starting treatment in year j with drug i is Pij, where i = A, B, or C *and* j = 1, 2, 3, 4, or 5 calculated based on the eligible population size and the treatment mix among all eligible patients starting treatment in each year of the analysis. In addition, the percentage of patients on each drug i who are in the pre-progression health state each year k after starting treatments where i = A, B, C and k = 1, 2, 3, 4, 5 is PRPik and the percentage of patients on each drug i who are in the post-progression health state each year k after starting treatments where i = A, B, C and k = 1, 2, 3, 4, 5 is PPik (see Table 6.1 for hypothetical estimates). If the cost for a year in the pre-progression health state is C_{PRP} (assumed in our hypothetical example to be £1000) and for a year in the post-progression health state is C_{PP} (assumed in our hypothetical example to be £2000), in year 1 of the budget-impact analysis, the cost of condition management for patients receiving drug A is calculated as follows:

$$\text{Cost of condition management in Year 1 for patients receiving drug A} = P_{A1} \times [(PRP_{A1} \times C_{PRP}) + (PP_{A1} \times C_{PP})]$$

In year 2 of the budget-impact analysis, the group of patients who started treatment in year 1 (P_{A1}) will be in year 2 after treatment initiation. Some of these patients will have died and so incur no further treatment-related costs and some will have progressed from pre-progression to post progression health state. In addition, a new cohort of patients (P_{A2}) will initiate treatment with the year 1 outcomes. Therefore, in year 2 of the budget impact analysis, the cost of disease management for all patients receiving drug A in year 2 is calculated by summing the costs for those initiating treatment in year 1 and those initiating treatment in year 2 as follows:

$$\text{Cost of condition-management in Year 2 for patients receiving drug A} = \{P_{A1} \times [(PRP_{A2} \times C_{PRP}) + (PP_{A2} \times C_{PP})]\} + \{P_{A2} \times [(PRP_{A1} \times C_{PRP}) + (PP_{A1} \times C_{PP})]\}$$

Table 6.2 Condition-related management costs

Drugs	Year 1	Year 2	Year 3	Year 4	Year 5
Drug A	$P_{AI} \times [(PRP_{A1} \times C_{PRP}) + (PP_{A1} \times C_{PP})]$	$P_{AI} \times [(PRP_{A2} \times C_{PRP}) + (PP_{A2} \times C_{PP})] + P_{A2} \times [(PRP_{A1} \times C_{PRP}) + (PP_{A1} \times C_{PP})]$	$P_{AI} \times [(PRP_{A3} \times C_{PRP}) + (PP_{A3} \times C_{PP})] + P_{A2} \times [(PRP_{A2} \times C_{PRP}) + (PP_{A2} \times C_{PP})] + P_{A3} \times [(PRP_{A1} \times C_{PRP}) + (PP_{A1} \times C_{PP})]$	$P_{AI} \times [(PRP_{A4} \times C_{PRP}) + (PP_{A4} \times C_{PP})] + P_{A2} \times [(PRP_{A3} \times C_{PRP}) + (PP_{A3} \times C_{PP})] + P_{A3} \times [(PRP_{A2} \times C_{PRP}) + (PP_{A2} \times C_{PP})] + P_{A4} \times [(PRP_{A1} \times C_{PRP}) + (PP_{A1} \times C_{PP})]$	$P_{AI} \times [(PRP_{A5} \times C_{PRP}) + (PP_{A5} \times C_{PP})] + P_{A2} \times [(PRP_{A4} \times C_{PRP}) + (PP_{A4} \times C_{PP})] + P_{A3} \times [(PRP_{A3} \times C_{PRP}) + (PP_{A3} \times C_{PP})] + P_{A4} \times [(PRP_{A2} \times C_{PRP}) + (PP_{A2} \times C_{PP})] + P_{A5} \times [(PRP_{A1} \times C_{PRP}) + (PP_{A1} \times C_{PP})]$
Drug B	…	…	…	…	…
Drug C	…	…	…	…	…
All Drugs	Sum of condition management costs for drugs A, B and C in year 1	Sum of condition management costs for drugs A, B and C in year 2	Sum of condition management costs for drugs A, B and C in year 3	Sum of condition management costs for drugs A, B and C in year 4	Sum of condition management costs for drugs A, B and C in year 5

P*ij* = number of patients *starting* treatment with drug *i* in year *j* of the budget-impact analysis (calculated using the total population size and the treatment mix data), where *i* = A, B, or C and *j* = 1, 2, 3, 4, or 5 years after the drug is launched. For example, P_{A1} is the number of patients that started treatment A in year 1 of the budget-impact model (the first year after launch)
PRP_{ik} = percentage of patients on drug *i* in the pre-progression health state in the *k*th year after starting treatment, where *k* = 1, 2, 3, 4, or 5; PP_{ik} = percentage of patients on drug *i* in the post-progression health state in the *k*th year after starting treatment, where *k* = 1, 2, 3, 4, or 5; C_{PRP} = annual cost for those in the pre-progression health state; C_{PP} = annual cost for those in the post-progression health state
… = calculations are similar for drugs B and C

Equivalent calculations for years 3–5 in the budget impact analysis for drug A are shown in Table 6.3. The corresponding calculations are performed for drug B and drug C. For each budget year, the costs (in Table 6.2 are summed to estimate the annual total condition-related costs for that year. The impact of changes in condition-related costs is calculated as the difference between these two budget scenarios.

6.3 Estimating Changes in Condition-Related Costs for Prevalent Populations

The approaches described above are straightforward for the incident populations for either acute or chronic conditions. However, as mentioned in Chap. 3, in a chronic condition, a prevalent population, those who became eligible for the new

drug in previous years, might need to be included in the analysis if there is the possibility of individuals in the prevalent population switching from their current treatment to the new drug. There are two alternative approaches for estimating the changes in condition-related costs for the prevalent population if it is included in the analysis. First, the simplest approach is to assume that a certain proportion of the individuals in this population will switch in the first year that the new drug becomes available but none will switch in the following years. With this assumption, the changes in condition-related costs for the prevalent population can be estimated in the same way as those for the year 1 incident population. The second approach recognizes that those in the prevalent population might switch to the new drug in the first or subsequent years as their current treatment ceases to be effective. To estimate changes in condition-related costs for the prevalent population in this case, we could divide the prevalent population into subgroups that would be expected to switch drugs in each year and treat each subgroup as a new incident population that might switch either to the new drug or to another drug in the treatment mix. The prevalent population or its subgroups should be included in the model separately from the incident populations since their condition characteristics and their response to the new drug might be different from those who are newly eligible for the new drug.

6.4 Estimating Changes in Health Outcomes and Resource Use with the New Drug

The focus of this chapter has been on estimating changes in condition-related costs. As we have shown, changes in condition-related costs are estimated based on estimated changes in health outcomes associated with the underlying condition and the associated use of a variety of health-care resources needed for the treatment of the underlying condition. Condition-related changes in these health outcomes and the use of health-care resources that are expected to occur during the budget-impact analysis time horizon can be calculated in addition to their use in estimating the changes in treatment-related costs. For example changes in the number of deaths or symptom days and in the number of physician visits or hospital days for the reimbursement-eligible population can be calculated for each year of the budget-impact analysis. They can be presented to decision makers to help them with assessing their progress toward meeting health targets and/or planning their resource needs (see Chap. 11).

Exercises

Exercise 6.1 Choose 10 conditions for which a new drug has come to market or is entering the market. Assuming that condition-related outcomes and costs are of interest to the audience for the model, determine whether these should be included

in the budget-impact analysis (i.e., whether they are expected to change on introduction of the new for each drug). If so, what condition-related outcomes and/or costs should be considered for each drug?

Exercise 6.2 Consider a new drug coming to market to treat asthma. The primary endpoint within the clinical trials is change in forced expiratory volume in the first second (FEV_1). What condition-related costs might be considered in a budget-impact analysis, and how would you estimate these costs?

Exercise 6.3 A new drug is entering the market to treat a rare condition. There are few treatments in the market to treat this condition, and the endpoints within the clinical trials are based on clinical and laboratory evaluations (they are not clinical events that require resource utilization). How would you estimate condition-related outcomes and/or costs? Would you consider these types of costs and outcomes within a budget-impact analysis? Why or why not?

Exercise 6.4 A drug is being studied to replace surgery. How might a budget-impact analysis be set up, and how would condition-related outcomes and costs be considered?

Exercise 6.5 Another HMG-CoA reductase inhibitor (i.e., a statin) is expected to come to market to treat patients with high cholesterol. This statin is the eighth statin to market, but it has a cleaner side effect profile than existing drugs. How might a budget-impact analysis be set up to assess the impact of this new treatment? Would condition-related outcomes and/or costs be considered? Why or why not?

Exercise 6.6 A new treatment is coming to market. The manufacturer believes the treatment will reduce the length of stay in the hospital, but there is no good evidence of this compared with the other competing treatments. How might a study be designed to collect these condition-related outcomes and/or costs?

Exercise 6.7 Choose a condition for which a new treatment has come to market. Determine the condition-related costs that the new treatment might affect and collect the evidence for a budget-impact analysis.

Exercise 6.8 For the treatment in Exercise 6.7, design an Excel worksheet to present the condition-related outcomes and costs.

Exercise 6.9 Identify a condition for which a micro-costing approach might be necessary for presenting the impact on condition-related costs. Create an Excel worksheet to present this micro-costing.

Exercise 6.10 A budget-impact analysis is being built to examine annual budgets up to 5 years for a chronic condition in which the impact on resource use and costs is not expected until after the analysis time horizon. Explain why condition-related outcomes and costs might/might not be important to consider.

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Chapter 7
The Computing Framework and Calculations

Anita Brogan, Stephanie Earnshaw, and Josephine Mauskopf

Abstract The process of developing the computing framework for a budget-impact analysis includes making decisions about the computer model structure while accounting for available input data, necessary assumptions, and other model design requirements. The computing framework can be developed once the analytic framework for the budget-impact analysis has been determined, a detailed flow diagram has been created, and the methods for estimating input parameter values including population size, treatment mix, treatment-related costs, and condition-related costs have been determined. In general, a static cost-calculator model structure should be used whenever such a model can credibly capture the impact of the new drug on the decision maker's budget. However, there are circumstances when accurately estimating budget impact requires the use of more complex calculations, such as the use of formal decision-analytic modeling techniques. These circumstances generally occur when a dynamic accounting of the treated population is necessary.

Keywords Computing framework • Budget-impact analysis • Cost calculator • Decision-analytic model • Static • Dynamic

Chapter Goal
To show, with examples, that once the researcher has developed the analytic framework and determined the availability of data for estimating population size and relevant descriptors, treatment mix and costs, and condition-related outcomes and costs, decisions can be made about the computing framework.

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The process of developing the computing framework for a budget-impact analysis for a new drug[1] includes making decisions about the model structure while accounting for available input data, necessary assumptions, and other model design requirements. The computing framework can be developed once the analytic framework for the budget-impact analysis has been determined, a detailed flow diagram has been created, and the methods for estimating input parameter values including population size, treatment mix, treatment-related costs, and condition-related costs have been determined.

Since the primary purpose of a budget-impact analysis is to help health care budget holders plan their budgets over their typical planning time horizons, it is critical that the computing framework be kept as simple as possible. Simplicity helps ensure that the analysis is transparent and can be readily adapted to the environment specific to each budget holder. The National Institute for Health and Care Excellence (NICE) costing templates are good examples of budget-impact analyses that use simple cost-calculator computing frameworks. However, more complex computing frameworks that include disease progression models are sometimes preferred when a combined model is desired to assess both the budget impact and the cost-effectiveness of the new intervention or when a cost-calculator computing framework cannot credibly capture the changes in population size, treatment patterns, or condition outcomes over the appropriate time horizon.

Developing the computing framework may feel like putting together a puzzle. The pieces of the puzzle have been identified, and now it is time to put them together to form one cohesive picture. Through this process, the overall size of the puzzle will be determined, and it may become apparent that a few additional pieces are needed or that a few extra pieces can be left out. When the puzzle is complete, the final version should provide a clear picture of the impact of the new drug on annual budgets as well as on annual resource use and/or health outcomes.

When making decisions about the computing framework for the budget-impact analysis, the target user should always be the driving factor. Decision makers can only use information from a budget-impact analysis if they find the analysis and results to be credible. This concept is critical to keep in mind because if any aspect of the analysis does not align with the decision maker's expectations, the analysis may be rejected without further consideration. Therefore, all decisions should be made while carefully considering the decision maker's perspective. Ideally, the planned computing framework and all assumptions and input parameter values can be shared with appropriate stakeholders early in the process to obtain feedback and assess credibility (see Chap. 9 on face validity).

The computing framework should be developed to allow the analysis to capture the relevant population(s), costs, and resource use and/or health outcomes while remaining as simple as possible. In this chapter, we provide an overview of budget-impact calculations, discuss static versus dynamic approaches to these calculations, and provide simple examples.

[1] In this chapter, we make the simplifying assumption that the budget-impact analysis is based on the introduction of a new drug to the current mix of drugs for the treatment of a condition. Changes in our recommended approaches to estimate the budget impacts of other types of health care interventions (i.e., vaccines, diagnostics, surgery, and devices) are discussed in Chap. 13.

7.1 Budget-Impact Calculations

The calculations are the basis of the computing framework of any budget-impact analysis. Revisiting the conceptual diagram for budget-impact analyses shown in Chap. 1 helps provide a clear picture of the components that go into the calculation. In Fig. 7.1, we show this conceptual diagram for completing a budget-impact analysis.

In general, the calculations used to estimate the budgets, resource use, and health outcomes for each year can be described as the product of the eligible population (see Chap. 3), treatment mix (see Chap. 4), and per-person total treatment-related costs (see Chap. 5) and associated condition-related costs, resource use, and health outcomes (see Chap. 6) for each drug. These estimates can be calculated for each year of the analysis time horizon for a budget scenario with the new drug and for a budget scenario without the new drug. The differences between these estimates represent the annual budget impact of the new drug as well as the new drug's impact on annual resource use (e.g., physician visits, hospital days, laboratory tests) and/or health outcomes (e.g., symptom days, exacerbations, deaths).

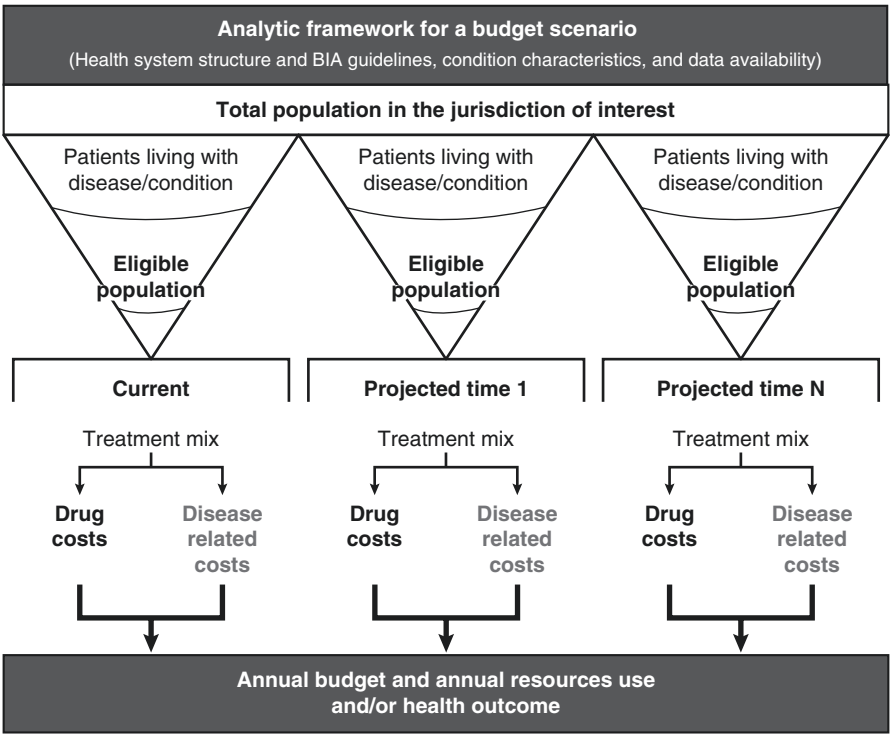

Fig. 7.1 Conceptual diagram for estimating a budget scenario with the current or new treatment mix

The steps for calculating the annual budget and annual resource use and/or health outcomes for each projected budget year are as follows:

- Calculate the size of the population receiving treatment. This population size may or may not differ for the budget scenario with the new drug and the budget scenario without the new drug.
- For the budget scenario with the new drug and for the budget scenario without the new drug, estimate the projected mix of treatments.
- For each drug, calculate total costs (i.e., drug and condition-related costs) and associated resource use and/or health outcomes on a per-person basis.
- Within each budget scenario (with or without the new drug), multiply the per-person costs and resource use and/or health outcomes for each drug by the population size.
- Multiply the population-level costs and resource use and/or health outcomes from the previous step by the proportion of individuals on each treatment within each budget scenario.

Once these values are calculated for each budget scenario, the differences between the budget scenario with the new drug and the budget scenario without the new drug represent the budget impact and resource use and/or health outcomes impact of the new drug.

As an example, consider a condition for which drugs X and Y are currently available. Suppose drug Z is likely to be introduced in the near future, and we would like to estimate the impact on budgets, resource use, and health outcomes associated with the introduction of drug Z. In this example, suppose there are 1000 individuals in the population eligible for treatment and that resource use is represented by physician visits and health outcomes are represented by exacerbations of a chronic illness. In Fig. 7.2, we present the calculations as a flow diagram, where the branches represent the treatment options and the resulting annual budgets, resource use, and health outcomes are calculated as the product of the size of the population, the treatment mix, and the costs, physician visits, and exacerbations for each comparator.

To illustrate the calculations for this hypothetical example, the equations for the 1-year budget impact and resource use and health outcomes impact of drug Z in this example are as follows:

- *Scenario 1: with drugs X and Y (without drug Z)*

  Budget
  = total population × % on drug X × per-person 1-year cost (treatment related + condition related) on drug X + total population × % on drug Y × per-person 1-year cost (treatment related + condition related) on drug Y
  = 1000 × 80% × $100 + 1000 × 20% × $75
  = $95,000

  Number of physician visits
  = total population × % on drug X × per-person 1-year physician visits for drug X + total population × % on drug Y × per-person 1-year physician visits for drug Y
  = 1000 × 80% × 2 visits + 1000 × 20% × 2.2 visits
  = 2040 visits

Number of exacerbations
= total population × % on drug X × per-person 1-year exacerbations on drug X + total population × % on drug Y × per-person 1-year exacerbations on drug Y
= 1000 × 80% × 1.5 exacerbations + 1000 × 20% × 1.8 exacerbations
= 1560 exacerbations

- *Scenario 2: with drugs X, Y, and Z*

Budget
= total population × % on drug X × per-person 1-year cost (treatment related + condition related) on drug X + total population × % on drug Y × per-person 1-year cost (treatment related + condition related) on drug Y+ total population × % on drug Z × per-person 1-year cost (treatment related + condition related) on drug Z
= 1000 × 75% × $100 + 1000 × 20% × $75 + 1000 × 5% × $125
= $96,250

Number of physician visits
= total population × % on drug X × per-person 1-year physician visits for drug X + total population × % on drug Y × per-person 1-year physician visits for drug Y + total population × % on drug Z × per-person 1-year physician visits for drug Z
= 1000 × 75% × 2 + 1000 × 20% × 2.2 + 1000 × 5% × 1
= 1990

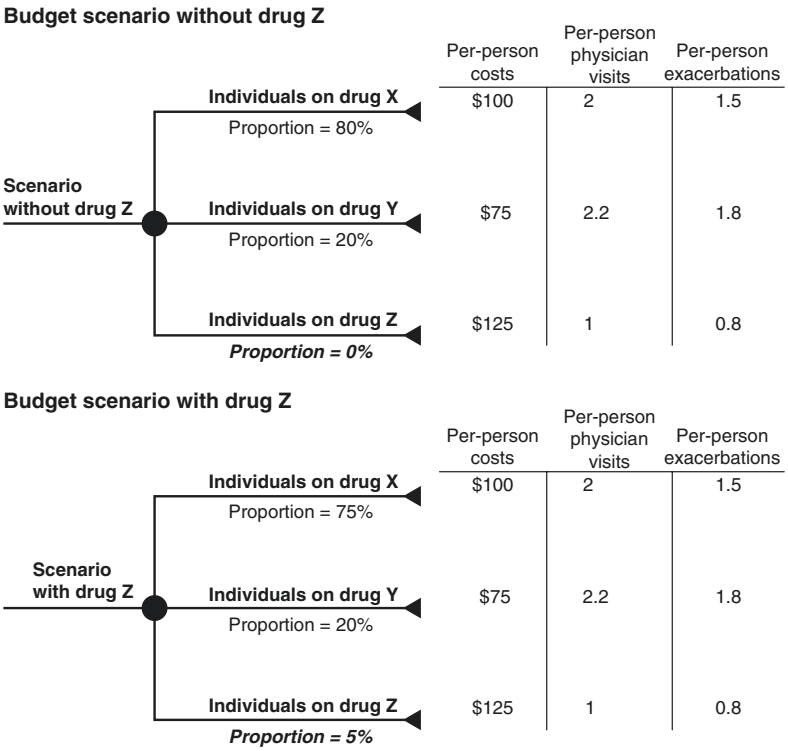

Fig. 7.2 Flow diagram for budget-impact analysis calculations for each year of the time horizon for the reimbursement-eligible population

Number of exacerbations
= total population × % on drug X × per-person 1-year exacerbations on drug X + total population × % on drug Y × per-person 1-year exacerbations on drug Y + total population × % on drug Z × per-person 1-year exacerbations on drug Z
= 1000 × 75% × 1.5 + 1000 × 20% × 1.8 + 1000 × 5% × 0.8
= 1525

- *Budget impact and resource use and health outcomes impact of the introduction of drug Z (for 1 year)*

Budget impact
= scenario 2 budget − scenario 1 budget
= $96,250 − $95,000
= $1250

Physician visits impact
= scenario 2 physician visits − scenario 1 physician visits
= 1990 − 2040
= −50

Exacerbations impact
= scenario 2 exacerbations – scenario 1 exacerbations
= 1525 − 1560
= −35

Interpretation: Within a 1000-person population eligible for treatment, the introduction of drug Z is expected to increase the 1-year payer budget by $1250 while reducing the number of physician visits in the population by 50 and reducing the number of exacerbations by 35.

These equations illustrate calculations for budget impact and resource use and health outcome impacts for 1 year. In a full budget-impact analysis, it is important to calculate the budget impact and resource use and health outcome impacts over a time horizon that is relevant to the budget holder. Therefore, the calculations simply need to be repeated for each year of the time horizon using the relevant input parameter values for each year.

7.2 Static Versus Dynamic Approach

Within the general budget-impact computing framework presented above, the size of the treated population and total per-person annual costs, resource use, and health outcomes are estimated. The computing framework is typically designed to ensure that the estimates of these model components are both simple and accurate. Depending on the impact of the new drug on the population characteristics and other input parameter values, these calculations can be designed using a cost

calculator (as illustrated above) or using a formal decision-analytic approach. The recent International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force on budget-impact analysis recommends that, where possible, simple cost-calculator models programmed in a spreadsheet format should be used to produce budget-impact estimates for new drugs (Sullivan et al. 2014). This recommendation is intended to ensure that budget-impact analyses can be easily understood by budget holders and can be readily adapted by them to provide information relevant to their jurisdictions.

In Box 7.1, we present an overview of NICE costing templates using the cost-calculator approach.

Box 7.1. NICE Costing Templates

NICE develops costing templates for use by regional authorities in England and Wales to estimate the budget impact of NICE recommendations for reimbursement of new drugs. The guidelines for these templates recommend a simple approach, focusing on changes in treatment patterns and on accounting costs during a model time horizon of 5 years (NICE 2013). This simplicity is in contrast to the NICE guidance for cost-effectiveness analyses, which request the use of formal decision-analytic modeling techniques, opportunity costs, and systematic literature reviews to estimate input parameter values. The same agency that has particularly rigorous requirements for cost-effectiveness analysis recognizes that simple budget-impact analyses are more appropriate for budget-planning purposes.

In general, a cost-calculator model structure should be used whenever such a model can credibly capture the impact of the new drug on the decision maker's budget. However, there are circumstances when accurately estimating budget impact requires the use of more complex calculations. For example, the use of formal decision-analytic modeling techniques may be needed to generate estimates of population size and treatment-related and condition-related costs when a dynamic accounting of the treated population is necessary. A dynamic accounting may be necessary when the availability of the new drug is expected to affect the size of the total treated population or the distribution of patients across condition severity levels within the total treated population. If these changes are expected to occur gradually during the model time horizon (e.g., 5 years), credible estimates of the budget impact of the new drug may require a dynamic approach to capture these changes.

In Box 7.2, we contrast the static and dynamic approaches used to estimate the budget impact of a new drug.

Box 7.2. Static and Dynamic Computing Structures

In a *static approach*, the size of the treated population and the distribution of patients across condition severity levels attributable to the introduction of the new drug either do not change over the time horizon of the analysis, or the change can credibly be assumed to occur immediately. Therefore, the patient population defined at the beginning of the analysis time horizon does not change, regardless of the number of future years analyzed. However, even with a static approach, the starting size and/or condition severity distribution of the population can differ between the scenario with the new drug and the scenario without the new drug. Within each scenario, however, the population is stable (with the simple exception that overall population growth rates in the jurisdiction of interest can be included within a static approach). Calculations for costs, resource use, and health outcomes for each drug in the treatment mix are typically fairly simple to program and do not generally require formal decision-analytic modeling techniques.

In a *dynamic approach*, the size of the population and/or the distribution of patients across condition severity levels may change over the time horizon of the model due to the introduction of the new drug. The patient population is defined at the beginning of the analysis time horizon but can change over the budget years analyzed. The treated population can grow or shrink, and the condition severity of the patient population can improve or worsen over time. Calculations for costs, resource use, and health outcomes for each drug in the treatment mix are typically more complex to program in a dynamic approach than in a static approach and often require formal decision-analytic modeling techniques (e.g., a decision tree or a Markov or patient-level simulation model). These techniques allow tracking of annual cohorts and disease progression over the analysis time horizon. Typically, a decision tree structure can be used if disease progression tracking is required only for the first year of treatment (e.g., for an acute condition). Disease progression tracking over the full analysis time horizon may require a Markov or a patient-level simulation structure (e.g., for a chronic condition).

In Box 7.3, we present a summary of the differences between static and dynamic frameworks.

Box 7.3. Static Versus Dynamic Budget-Impact Analyses

Structural component	Static approach	Dynamic approach
Population size	Remains constant over the analysis time horizon: • Population size can differ between the budget scenario with the new drug and the budget scenario without the new drug • Population changes due to general demographic shifts can be included	Changes over the analysis time horizon as a result of the new drug: • Additional patients presenting for treatment results in more treated patients • Curative treatment results in fewer patients requiring treatment • Reduced condition-related mortality results in more treated patients
Condition severity mix	Remains fixed over the analysis time horizon: • Condition severity mix can differ between the budget scenario with the new drug and the budget scenario without the new drug	Changes over the analysis time horizon as a result of the new drug: • Reduced rate of disease progression results in a healthier mix
Treatment patterns	Remains fixed over the analysis time horizon: • Treatment patterns accounting for titration, discontinuation, and switching can differ between the budget scenario with the new drug and the budget scenario without the new drug	Changes over the analysis time horizon as a result of the new drug: • Reduced need for treatment titration or switching results in a healthier mix or delayed treatment progression • Reduced rates of discontinuation from treatment result in more treated patients
Underlying calculations	Simple calculations for the incident or prevalent population(s)	Annual population cohorts with disease progression model, if needed: • Start with prevalent cohort • Add newly eligible incident cohort each year • Individuals can exit the model due to death or end of treatment • Structure could be a simple decision tree or a Markov or patient-level simulation for disease progression tracking

To program a static model, the model developer begins with an incident cohort (for an acute condition) or a prevalent cohort (for a chronic condition) with a stable set of demographic and condition severity characteristics. These characteristics may differ between the budget scenarios with and without the new drug in the treatment mix. Within each scenario, the population size and relevant descriptors are then assumed to remain constant over the analysis time horizon.

To program a dynamic model, the model developer typically begins with a prevalent cohort of patients with a specific set of characteristics (i.e., the cohort that became eligible for treatment with the new drug in previous years). Then, in each budget year, an incident cohort of newly eligible patients enters the model. In Fig. 7.3, we show that each cohort remains in the model over the full analysis time horizon (with some individuals exiting due to death or end of treatment), and a new cohort enters each year.

Costs, resource use, and health outcomes are tracked for each cohort. Since individuals in any of the cohorts can exit the model due to death or the end of their treatment, the model has both inflow and outflow of patients. These flows can be programmed using a simple decision tree model structure in some cases. However, if disease progression must be tracked over several years in order to capture the benefit of the new drug, a Markov or patient-level simulation model structure may be needed.

Most new drugs are intended to improve condition severity levels in the treated population, but fortunately not all new drugs require a dynamic approach. If all of the improvement is observed relatively quickly, it is generally possible to assume that the improvement happens immediately (i.e., at the beginning of the analysis time horizon) in the budget scenario with the new drug. This assumption then avoids

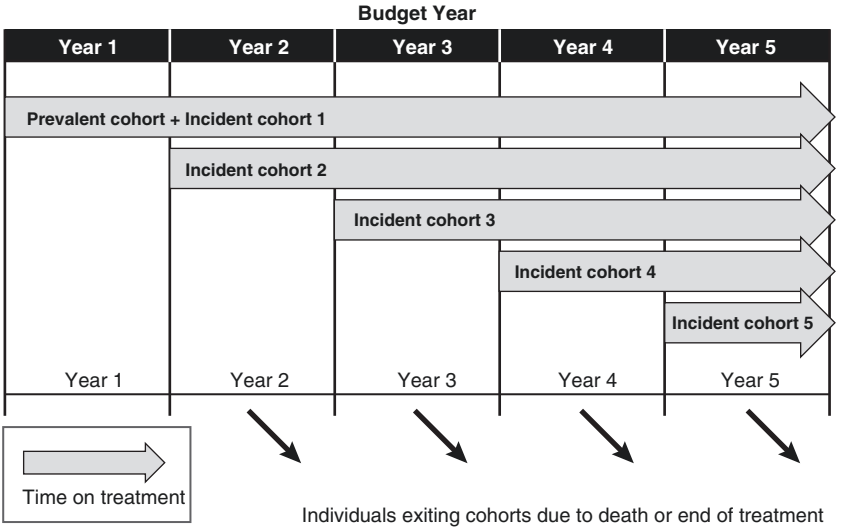

Fig. 7.3 Prevalent and incident cohorts in a 5-year dynamic model

the need for a model structure to track disease progression for individual cohorts over the analysis time horizon and allows for the use of a static model.

Even beyond this exception, the choice between a static and dynamic model is not always clear. The model developer must decide if the potential improvement in accuracy that may be achieved with a dynamic model is worth the added complexity. If the new drug is expected to result in only minor changes to the patient population size or relevant descriptors, the best decision may be to use a static analysis, unless ignoring these changes will reduce the credibility of the analysis to the budget holder.

In Box 7.4, we present examples of recommended model types for specific treatment/condition scenarios.

Box 7.4. Recommended Model Structure for Sample Condition/Treatment Scenarios

Condition area	Hypothetical new drug	Choice of model structure
Influenza	Shows significant reduction in duration of symptoms Shows significant reduction in duration of symptoms	Model choice: static model • The size of the treated population each year will not change as a result of the new treatment, though it will vary from year to year depending on the strength of the epidemic • The disease occurs over a very short time, so there is no need for the model to incorporate disease progression
Psoriasis	Shows superior results in skin clearance (e.g., significantly greater percentages of individuals achieving PASI 90 and PASI 75)	Model choice: static model • The new drug does not affect disease progression or mortality. Therefore, population size is unlikely to change. However, new patients might present for treatment with a better treatment choice available. As a result, the population size with the new drug might differ from that without the new drug • The distribution of patients across disease severity levels may change (e.g., more individuals with clear skin), but this change could be assumed to happen immediately
Pain during and after outpatient procedures	Shows significant improvement in mean pain scores during and after procedure	Model choice: static model • The size of the treated population each year will not change as a result of the new drug • The pain occurs over a very short time. Therefore, there is no need for the model to incorporate disease progression

Condition area	Hypothetical new drug	Choice of model structure
Relapsing/ remitting multiple sclerosis	Shows reduction in annualized relapse rates and slower progression measured using the Expanded Disability Status Scale	Model choice: static model • The new drug will not change the size of the treated population since the disease progresses slowly, and mortality will not be affected within the model time horizon • Changes in the number of patients with relapses will occur within the model time horizon, but this can be assumed to occur immediately • Slower disease progression for those with relapsing-remitting multiple sclerosis initiating treatment will have a very small impact on condition-related costs within the model time horizon and so can be omitted from the budget-impact analysis
Hepatitis C	Shows significant improvement in the percentage of patients achieving sustained virologic response (i.e., cure) and exhibits a better safety profile	Model choice: static model • The size of the treated population may increase if people who were waiting for a better treatment decide to seek treatment. Thus, the population size with the new drug might differ from that without the new drug • Disease progression is slow. Changes in the distribution of patients across the liver disease stages, and hence in condition-related costs, are unlikely to occur within the time horizon of the analysis • Treatment could reduce the size of the population with hepatitis C and thereby reduce onward transmission, but new cases avoided are probably beyond the time horizon of the analysis
Early-stage oncology	Shows significantly improved cure rates	Model choice: dynamic model • The new drug is likely to decrease the size of the treated population because cured patients require no further treatment (i.e., they leave the treated population), whereas patients not achieving cure may require further treatment • Relapses among cured patients should be included in the model if they occur within the time horizon of the analysis

Condition area	Hypothetical new drug	Choice of model structure
HIV	Shows superior results in highly treatment-experienced patients in immune function recovery and in the percentage of patients both achieving virologic suppression and remaining suppressed over time	Model choice: dynamic model • Better immune function recovery may improve the condition severity mix over a number of years. The improved and extended virologic efficacy may delay the need for treatment switching and thus may delay disease progression • Delayed disease progression may indirectly reduce disease-related mortality, which could increase the number of people receiving treatment (though this increase might not be substantial within the time horizon of the analysis)

HIV human immunodeficiency virus, *PASI* Psoriasis Area and Severity Index

Even in examples shown above in which a dynamic approach is recommended, it is sometimes possible to be creative, keep it simple, and use a cost-calculator model. In Box 7.5, we present an example of the use of a static approach for a budget-impact analysis for a new combination regimen for the treatment of HIV infection.

Box 7.5. HIV Budget-Impact Analysis

In 2012, Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) prepared to launch. In treatment-naive individuals with HIV-1 infection, Stribild exhibited higher rates and longer durations of virologic suppression and better immune function recovery over time than previous treatments. Another key advantage was its single-tablet, once-daily formulation. Simpler regimens are known to improve adherence, which is critical in HIV to avoid resistance.

The use of a dynamic approach to track disease progression for new incident cohorts starting treatment each year would have been very reasonable. Over the time horizon of the analysis, the use of the new drug, with its simpler regimen and better efficacy, would likely slow transition to costlier later-line therapies, shift people to healthier disease states, reduce the use of health care services, and reduce mortality. A dynamic approach could capture the likely contributions of these components to changes in costs and health outcomes within the treated population. However, such a model would be complex.

After considering the audience for the budget-impact analysis, a simpler, more direct approach was sought. A published retrospective database analysis of USA managed care claims had shown that individuals using a previously launched single-tablet regimen had substantially lower hospitalization rates than individuals using comparable multitablet regimens (Sax et al. 2012). A cost-calculator model was developed to leverage the results of this study; it included drug costs and linked pill burden for Stribild and the comparator regimens to hospitalization costs, using the results of the database analysis. The analysis projected that the introduction of Stribild was expected to result in fewer hospitalizations and modest reductions in payer budgets due to lower pharmacy and hospitalization costs (Brogan et al. 2013).

7.3 Examples of Static and Dynamic Budget-Impact Calculations

In this section, we present examples of the computing framework using both a static and a dynamic approach.

7.3.1 Static Approach

Drugs A, B, C, and D are currently available on the market to treat an acute condition that resolves within a year. A new treatment, drug E, is entering the market. Drug E is more expensive than the other treatments, but patients receiving drug E are expected to require fewer physician visits and therefore have lower condition-related costs over the course of treatment. Each year, 1000 patients seek treatment for this acute condition. If drug E is introduced into the marketplace, the number of patients seeking treatment is not expected to change. Uptake of drug E is expected to be 5% in the first year. The use of the other four available treatments is expected to decline slightly as a result. In Table 7.1, we present the current mix of treatments used by patients as well as the projected treatment mix with drug E on the market. In Table 7.1, we also show average per-patient treatment costs, condition-related costs, number of physician visits, and symptom days associated with each comparator drug.

In this example, a static approach to the computing framework is recommended because introducing drug E will not change the size of the population. Further, per-person costs, physician visits, and symptom days can be calculated each year without tracking disease progression. Given this static approach, a simple decision tree or cost calculator can be constructed to estimate total costs and health outcomes for two budget scenarios: the budget scenario without drug E and the budget scenario with drug E. The budget and health impact of drug E is simply the difference between these two budget scenarios. We present these calculations in Fig. 7.4 and Table 7.2 below.

Table 7.1 Treatment mix and per-person outcomes for each comparator (1 year)

Comparator	Treatment mix without drug E (%)	Treatment mix with drug E (%)	Per-patient treatment costs	Per-patient condition-related costs	Per-patient physician visits	Per-patient symptom days
Drug A	30	28	$100	$250	3	21
Drug B	30	29	$200	$200	2.5	15
Drug C	20	19	$300	$150	2.2	12
Drug D	20	19	$400	$100	1.5	8
Drug E	0	5	$500	$50	1	3

A. Decision tree for budget scenario without drug E

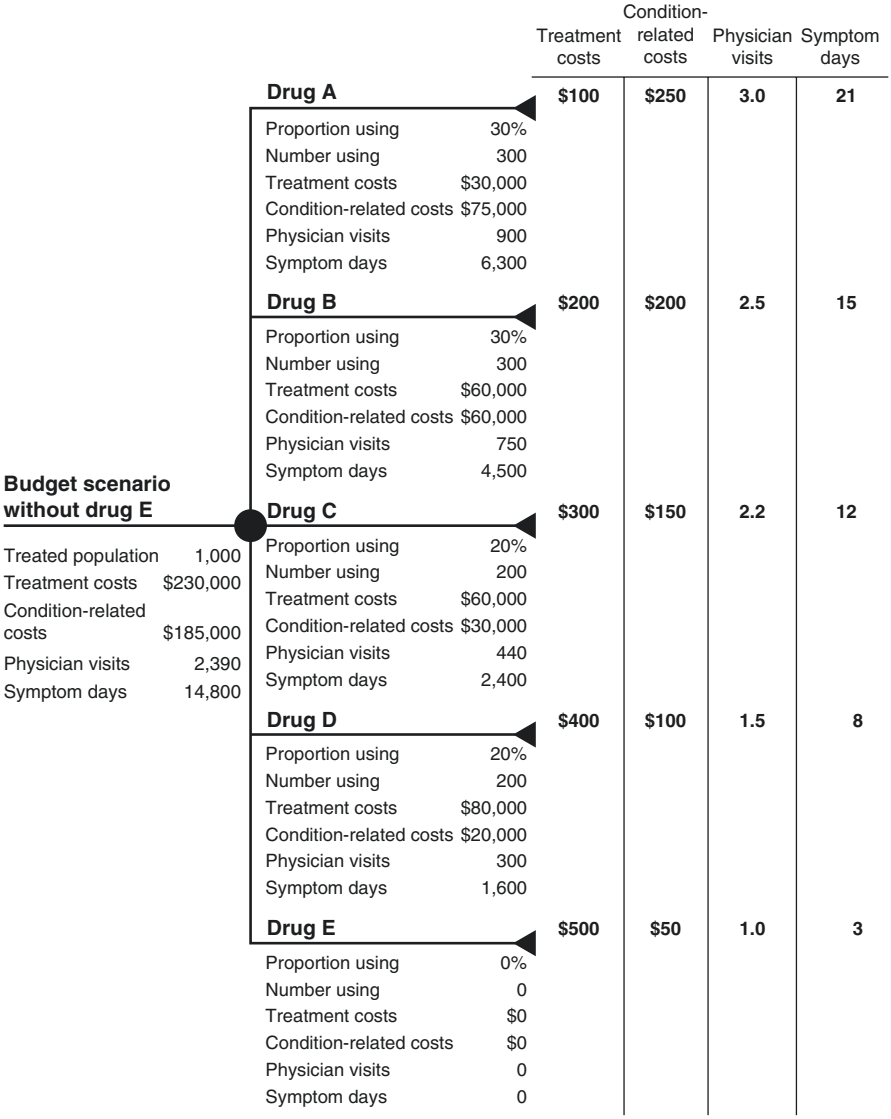

Fig. 7.4 Static decision tree or cost-calculator computing framework

B. Decision tree for budget scenario with drug E

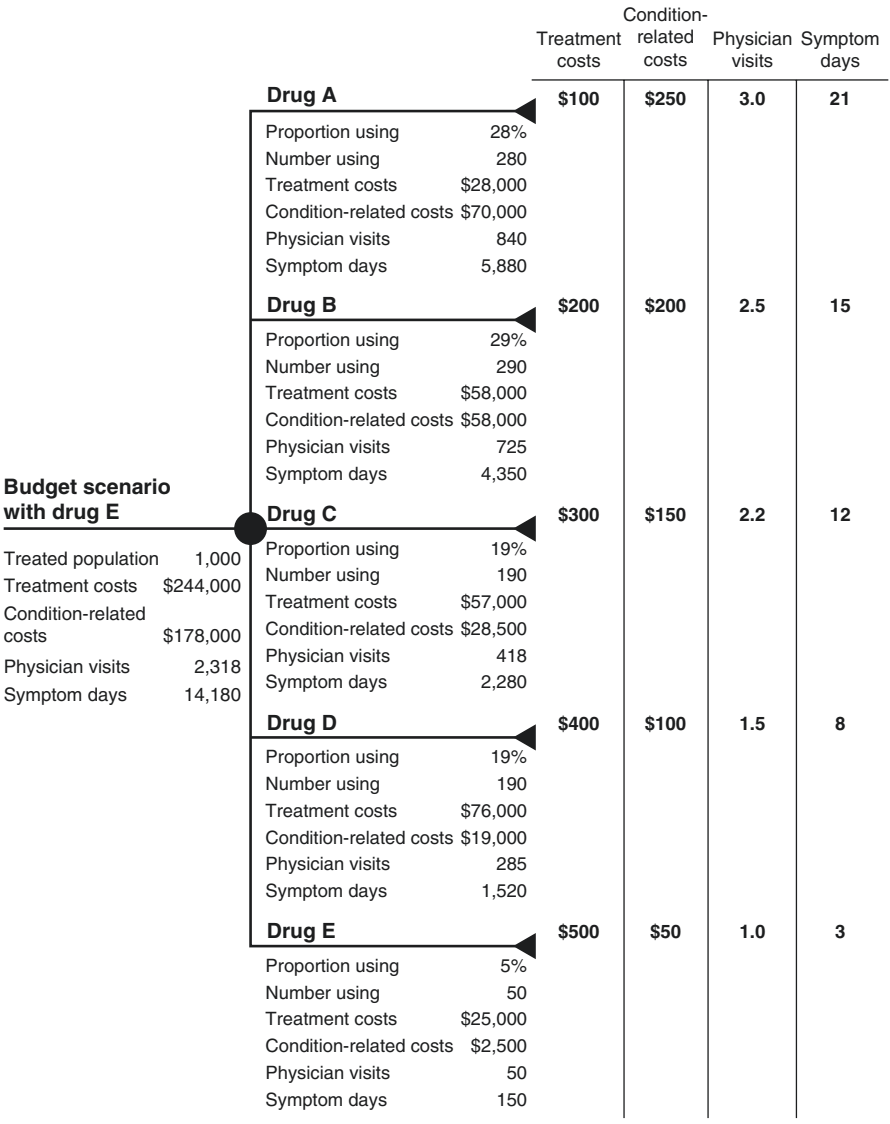

Fig. 7.4 (continued)

The budget scenario without drug E and the budget scenario with drug E are constructed as two decision trees or cost calculators. The comparator drugs are represented by the branches of the tree. Starting to the far right of each tree, the columns display the per-person treatment costs, condition-related costs, physician visits, and symptom days for each comparator from Table 7.1. Just to the left, each branch shows the percentage of the population and the total number of people (assuming a total treated population size of 1000) receiving each of the comparator treatments.

Table 7.2 Budget-impact calculation

Outcome	Budget scenario without drug E	Budget scenario with drug E	Budget/health impact
Treatment costs	$230,000	$244,000	$14,000
Condition-related costs	$185,000	$178,000	−$7000
Total costs	$415,000	$422,000	$7000
Physician visits	2390	2318	−72
Symptom days	14,800	14,180	−620

Each branch also shows total treatment costs, condition-related costs, physician visits, and symptom days for the corresponding comparator, as calculated from the per-person values. To the far left, totals for each budget scenario are calculated by summing the values listed for each drug. In Table 7.2, we present these totals and the calculation of the budget and health impact of the introduction of drug E.

As shown in Table 7.2, the total 1-year cost without drug E is $415,000, and the total 1-year cost with drug E is $422,000. The budget impact of the introduction of drug E is the difference between these two totals, or $7000. The corresponding resource use impact is a reduction of 72 physician visits per year, and the health outcomes impact is a reduction of 620 symptom days per year.

7.3.2 Dynamic Approach

Drugs A, B, C, and D are currently available on the market to treat a chronic condition with a high mortality rate. A new drug, drug E, is entering the market. Drug E is more expensive than the other drugs, but patients receiving drug E are expected to experience improved survival. Drug E is not expected to affect any other health outcomes or per-patient condition-related costs. Patients with this chronic condition remain on treatment for the remainder of their lifetimes. Therefore, improved survival with drug E is likely to lead to more patients on treatment each year. In Table 7.3, we present the per-person annual treatment-related and condition-related costs for each drug as well as the annual probability of death.

Each year, 1000 new patients seek treatment for this chronic condition. Existing patients are not eligible for drug E. If drug E is introduced into the marketplace, the number of patients seeking treatment is not expected to change. Uptake of drug E is expected to be 5% in the first year, 10% in the second year, and 15% in the third year. The use of the other four available drugs is expected to decline slightly each year as a result. In Table 7.4, we present the current mix of treatments used by patients as well as the projected treatment mix with drug E on the market.

In this example, a dynamic approach to the computing framework is recommended because introducing drug E will improve survival and therefore change the size of the population each year. Because patients remain on treatment for their remaining lifetimes and because there is a risk of death each year, the change in the population size cannot be assumed to occur immediately at the beginning of the analysis.

Table 7.3 Per-person outcomes for each comparator treatment

Comparator	Per-patient annual treatment costs	Per-patient annual condition-related costs	Annual probability of death (%)
Drug A	$100	$150	5
Drug B	$200	$150	4
Drug C	$300	$150	3
Drug D	$400	$150	2
Drug E	$500	$150	1

Table 7.4 Treatment mix[a] without drug E and with drug E

Comparator	Treatment mix without drug E (years 1–3) (%)	Treatment mix with drug E (year 1) (%)	Treatment mix with drug E (year 2) (%)	Treatment mix with drug E (year 3) (%)
Drug A	30	28	26	24
Drug B	30	29	28	27
Drug C	20	19	18	17
Drug D	20	19	18	17
Drug E	0	5	10	15

[a]Represents mix of treatments used by all individuals in the model (i.e., all cohorts combined).

In the static example, it was possible to use a simple decision tree or cost calculator to calculate costs and health outcomes for each budget scenario. The population using each treatment in the decision tree was simply calculated by multiplying the 1000 new patients each year by the expected treatment mix. In this dynamic example, however, we will first need to calculate the size of the treated population each year. This population will differ each year and will differ depending on the treatment mix, because each comparator has a different 1-year probability of death. The simplest way to carry out the necessary calculation is to first determine the size of the population each year for each comparator separately and then apply the treatment mix. We show these calculations below. To keep the exposition simple, we round calculated values to the nearest person or to the nearest dollar. Any apparent discrepancies in the calculations are simply due to rounding.

In Table 7.5, we present the first part of the population calculation. For each drug, we assume that 1000 new patients enter the model each year and that these annual cohorts are tracked separately over the analysis time horizon, which is 3 years in our hypothetical example. We will later show the second part of the population calculation, in which we apply the treatment mix.

Using the drug A calculations as an example, we track the three entering cohorts as follows:

- Cohort 1 enters the model in year 1. Everyone in cohort 1 who survives in the model remains on treatment for 3 years. For simplicity, we assume that all deaths occur at the end of each year. At the end of the first year, 5% of the cohort dies (50 people), and 95% survive (950 people). Among the individuals who survive (950 people), another 5% die at the end of the second year (47 people) and 95% survive (903 people).
- Cohort 2 enters the model in year 2. These individuals begin treatment at the beginning of year 2. At the end of the second year of the model (which is the first

Table 7.5 Population calculations for each comparator treatment

Comparator/cohort	Year 1	Year 2	Year 3
Drug A		Annual mortality = 5%	
Cohort 1	1000	950	903
Cohort 2		1000	950
Cohort 3			1000
Total	1000	1950	2853
Drug B		Annual mortality = 4%	
Cohort 1	1000	960	922
Cohort 2		1000	960
Cohort 3			1000
Total	1000	1960	2882
Drug C		Annual mortality = 3%	
Cohort 1	1000	970	941
Cohort 2		1000	970
Cohort 3			1000
Total	1000	1970	2911
Drug D		Annual mortality = 2%	
Cohort 1	1000	980	960
Cohort 2		1000	980
Cohort 3			1000
Total	1000	1980	2940
Drug E		Annual mortality = 1%	
Cohort 1	1000	990	980
Cohort 2		1000	990
Cohort 3			1000
Total	1000	1990	2970

year for this cohort), 5% of the cohort dies, and 95% survive. The individuals who survive receive a second year of treatment in the third year of the analysis.

- Cohort 3 enters the model in year 3. These individuals begin treatment at the beginning of year 3. We do not calculate the number of deaths for this cohort since the analysis time horizon ends at the end of their first year of treatment.

In Table 7.5, we present the tracking of the individual cohorts as well as the total number of individuals in the model each year for each comparator. For drug A, we have 1000 individuals in the model in year 1, 1950 in the model in year 2, and 2853 in the model in year 3.

Now that we know the size of the treated population in each year for each comparator drug separately, we apply the treatment mix to complete the second part of the population calculation. This calculation will allow us to estimate the actual size of the treated population given that only a fraction of the population uses each drug. In Table 7.6, we first summarize the annual totals calculated in Table 7.5 for each comparator. In the second half of the table, we show these totals weighted by the treatment mixes shown in Table 7.3.

Table 7.6 Population calculations for each scenario

Population: if all patients receive each comparator						
Comparator	Year 1		Year 2	Year 3		
Drug A	1000		1950	2853		
Drug B	1000		1960	2882		
Drug C	1000		1970	2911		
Drug D	1000		1980	2940		
Drug E	1000		1990	2970		
Population: weighted by treatment mix						
	Without drug E			With drug E		
Comparator	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Drug A	300	585	856	280	507	685
Drug B	300	588	864	290	549	778
Drug C	200	394	582	190	355	495
Drug D	200	396	588	190	356	500
Drug E	0	0	0	*50*	*199*	*446*
Total	1000	1963	2890	1000	1966	2903

Note: Example calculations for italicized values are shown in the text.

As an example, consider drug E. In the budget scenario without drug E, the use of drug E in the treatment mix is 0%, and therefore zero individuals use drug E for all 3 years of the analysis time horizon. In the budget scenario with drug E, we have the following calculations:

Year 1: Number individuals
= 5% use of drug E × 1000 individuals in the model if everyone used drug E
= *50 individuals* actually using drug E

Year 2: Number individuals
= 10% use of drug E × 1990 individuals in the model if everyone used drug E
= *199 individuals* actually using drug E

Year 3: Number individuals
= 15% use of drug E × 2970 individuals in the model if everyone used drug E
= *446 individuals* actually using drug E

Note that the treatment mix in this example applies to all of the cohorts included in the model in each year of the analysis time horizon. Ideally, we would like to know the treatment mix within each cohort separately. However, this information is rarely available. Therefore, we generally make the simplifying assumption that the treatment mix represents an average across the cohorts and does not vary according to when the cohort started treatment.

Note also that in the budget scenario without drug E, we assumed the same treatment mix all 3 years. In reality, the projected treatment mix without the new drug may actually shift over the time horizon of the model as described in Chap. 4. Such shifting can be handled by simply assuming a different treatment mix in each year of the analysis time horizon.

Now that we have the number of individuals receiving each drug in each year of the model for the budget scenario without drug E and the budget scenario with

drug E, we could draw simple decision trees or cost calculators to perform the calculations like those shown in the static example. We would need one tree for each budget scenario (two scenarios) in each year (3 years) and would thus need six trees. To save space, we have shown the treatment-related and condition-related costs in Table 7.7. These costs are calculated by multiplying the number of individuals receiving each comparator (Table 7.6) by the treatment-related and condition-related costs specific to those comparators (Table 7.4).

As an example, consider the treatment costs for drug E in the budget scenario with drug E:

Year 1: Treatment costs
= 50 individuals receive drug E × $500 per year
= *$25,000*

Year 2: Treatment costs
= 199 individuals receive drug E × $500 per year
= *$99,500*

Year 3: Treatment costs
= 446 individuals receive drug E × $500 per year
= *$222,758*
(Note that 446 was previously rounded from 445.515)

Once we have calculated the costs for each comparator in each budget scenario and each year, we can calculate totals by year for each budget scenario. Calculating total treatment costs and total condition-related costs separately can help payers see

Table 7.7 Cost and budget-impact calculations

	Without drug E			With drug E		
Comparator	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Treatment costs						
Drug A	$30,000	$58,500	$85,575	$28,000	$50,700	$68,460
Drug B	$60,000	$117,600	$172,896	$58,000	$109,760	$155,606
Drug C	$60,000	$118,200	$174,654	$57,000	$106,380	$148,456
Drug D	$80,000	$158,400	$235,232	$76,000	$142,560	$199,947
Drug E	$0	$0	$0	*$25,000*	*$99,500*	*$222,758*
Total	$230,000	$452,700	$668,357	$244,000	$508,900	$795,227
Condition-related costs						
Drug A	$45,000	$87,750	$128,363	$42,000	$76,050	$102,690
Drug B	$45,000	$88,200	$129,672	$43,500	$82,320	$116,705
Drug C	$30,000	$59,100	$87,327	$28,500	$53,190	$74,228
Drug D	$30,000	$59,400	$88,212	$28,500	$53,460	$74,980
Drug E	$0	$0	$0	$7500	$29,850	$66,827
Total	$150,000	$294,450	$433,574	$150,000	$294,870	$435,430
Total costs	$380,000	$747,150	$1,101,931	$394,000	$803,770	$1,230,657
Budget impact				*$14,000*	*$56,620*	*$128,727*

Note: Example calculations for italicized values are shown in the text.

how the introduction of a new drug might affect different parts of their budget. Overall total costs are then calculated to allow for calculation of budget impact (Table 7.7). Budget impact is calculated as the difference between the total costs in each budget scenario:

Year 1: Budget impact
= $394,000 (with drug E) − $380,000 (without drug E)
= *$14,000*

Year 2: Budget impact
= $803,770 (with drug E) − $747,150 (without drug E)
= *$56,620*

Year 3: Budget impact
= $1,230,657 (with drug E) − $1,101,931 (without drug E)
= *$128,727*

These results indicate that the introduction of drug E could result in a $128,727 increase in payer budgets by year 3.

As a reminder, the health outcome in this example is improved survival. Thus, the health impact is simply the difference between the number of individuals alive in each budget scenario (Table 7.6):

Year 1: Budget impact
= 1000 individuals (with drug E) − 1000 individuals (without drug E)
= 0

Year 2: Budget impact
= 1966 individuals (with drug E) − 1963 individuals (without drug E)
= 3

Year 3: Budget impact
= 2903 individuals (with drug E) − 2890 individuals (without drug E)
= 13

These results indicate that the introduction of drug E could result in 13 additional individuals surviving through the third year. In other examples, the health impact may be measured by exacerbations avoided, hospitalizations avoided, the percentage of the population in the best health state, or any other relevant outcome. Resource use impacts can also be estimated in the same way for outcomes such as number of physician visits or number of hospital days.

The dynamic model we have described in this example is very simple. However, when a dynamic model is needed for a realistic budget-impact analysis, the approach of using simple tabular calculations to track the model cohorts, costs, and outcomes may not be sufficient to capture the expected treatment patterns (including switching, titration, and discontinuation) or changes in resource use and health outcomes corresponding to alternative treatments or different treatment durations. In these cases, a Markov model or discrete event simulation model may be more appropriate to accurately capture the required complexities of the condition and its treatment. As described in more detail in Sect. 7.4, the model calculations would need to track the initial prevalent cohort as well as annual incident cohorts. This cohort tracking, in addition to the Markov model or discrete event simulation model calculations, may yield a model that is quite complex.

Chap. 10 provides an example of such a model, including a link to a working sample model in Excel.

7.4 Computing Framework for Combined Cost-Effectiveness and Budget-Impact Model

The choice of computing framework might be influenced by the decision to use the same computer model to estimate the cost-effectiveness and budget impact of a new drug. Of course, the purposes of these two analyses are very different. Cost-effectiveness analysis is designed to estimate the value of a new drug compared with a standard-of-care comparator. The time horizon of a cost-effectiveness analysis is generally long enough to capture the full costs and benefits of the new drug, and costs and outcomes are typically discounted if they occur over multiple years. A budget-impact analysis is designed to provide information for budget planning within the planning time horizon comparing the treatment mix with and without the new drug included on the formulary. For budget-impact analyses, costs and outcomes are not discounted. Cost-effectiveness analyses may be reviewed by those with modeling expertise, while budget-impact analyses are intended for adaptation and use for budget planning by those who are not expert modelers. Therefore, the complexity appropriate for a cost-effectiveness analysis may not be appropriate for a budget-impact analysis.

If a static approach will suffice for the budget-impact analysis, the preferred approach may be to keep the budget-impact analysis separate from the cost-effectiveness analysis while ensuring that consistent input parameter values are used in both analyses. However, if a dynamic approach is necessary for the budget-impact analysis, it may be convenient to leverage the calculations in the cost-effectiveness analysis. These calculations may include disease progression, treatment switching, titration, discontinuation, mortality, or other health outcomes calculations.

If a combined model is desired, the model will need to be programmed with two different modes:

- Single cohort mode: This mode is appropriate for the cost-effectiveness analysis. In this mode, the model tracks the costs and health outcomes of a single initial cohort over a fixed time horizon, often over the remaining lifetime of the cohort. Results are typically presented as discounted totals over the full time horizon.
- Open population mode: This mode is appropriate for the budget-impact analysis. In this mode, an initial prevalent cohort enters the model in the first year and is tracked for the duration of the budget-impact analysis time horizon. In each year, a newly incident cohort enters the model and is also tracked until the end of the budget-impact analysis time horizon. Each cohort is typically tracked separately in the model. Results are calculated as annual undiscounted totals across all the cohorts included in each year of the budget-impact analysis time horizon.

Programming a combined model with both of these modes may be efficient, but the model calculations will be more complex than if the cost-effectiveness and budget-impact analyses are kept separate. It is important to consider whether the efficiency gained is worth the additional complexity.

In general, when developing the computing framework for a budget-impact analysis, it is critical to maintain focus on the target user. Since the primary purpose of a budget-impact analysis is to help health care budget holders plan their budgets over their typical planning time horizons, it is critical that the computing framework be kept as simple as possible while including enough detail about the condition and treatment process to ensure credibility. Simplicity helps ensure that the analysis is transparent and can be readily adapted to the environment specific to each budget holder.

Exercises

Exercise 7.1 Explain when it is better to use a static computing framework rather than a dynamic computing framework. What are the advantages of using a dynamic computing framework?

Exercise 7.2 Identify a condition for which a static computing framework would be appropriate. Outline the components of the computing approach that need to be considered when developing the underlying calculations for this model. Why is the static approach appropriate for this condition?

Exercise 7.3 Identify a condition for which a dynamic computing framework would be appropriate. Outline the components of the computing approach that need to be considered when developing the underlying calculations for this model. Why is the dynamic approach appropriate for this condition?

Exercise 7.4 Describe the differences in the computing frameworks that result from using a static versus a dynamic approach for the conditions identified in Exercises 7.2 and 7.3.

Exercise 7.5 For the condition that requires a dynamic approach in Exercise 7.3, how could the computing framework be revised to transform it into a static approach? How might the results be affected if a static approach is used instead of a dynamic approach?

Exercise 7.6 A typical assumption within a dynamic computing framework is that the treatment mix for a given budget year is the same for each of the cohorts that has entered the model. How could you account for different cohorts having different treatment mixes? Explain or show an example.

Exercise 7.7 Drug C is getting ready to go to market to treat condition X. One hundred people are treated for condition X every year. Patients are cured after 1 year of treatment. Condition X is currently treated with drugs A and B. These existing drugs and drug C must be administered by a physician, and one administration is required for each prescription. It is common for patients with condition X to seek additional physician care while being treated. Drug C has been shown to reduce the

number of additional physician visits patients sought while being treated. Using the table below, calculate the budget and health outcomes impact of introducing drug C to the market for three budget years. What computing framework did you use and why? What key values messages should the manufacturer of drug C project?

	Treatment mix without drug C			Treatment mix with drug C		
Drug	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)
Drug A	80	75	70	75	70	65
Drug B	20	25	30	20	23	25
Drug C	0	0	0	5	7	10

Drug	Drug cost per prescription	Number of administrations per year	Cost per administration	Number of physician visits per year	Cost per physician visit
Drug A	$100	15	$50	20	$300
Drug B	$150	12	$50	18	$300
Drug C	$200	12	$50	10	$300

Exercise 7.8 Condition Y is similar to condition X in Exercise 7.7 except that condition Y is treated for the remainder of the patient's lifetime. In the first year, 100 people are treated for condition Y. Each subsequent year, five new patients begin treatment for condition Y. Annual mortality if treated with drug A or B is 5%. Drug C reduces annual mortality to 1%. As with condition X, these drugs must be administered by a physician, and one administration is required for each prescription. It is common for patients with condition Y to seek additional physician care while being treated. Drug C has been shown to reduce the number of additional physician visits sought while being treated. Using the tables below, estimate the budget and health outcomes' impact of introducing drug C to the market for three budget years. What computing framework did you use and why? What key values messages should the manufacturer of drug C project?

	Treatment mix without drug C			Treatment mix with drug C		
Drug	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)
Drug A	80	75	70	75	70	65
Drug B	20	25	30	20	23	25
Drug C	0	0	0	5	7	10

Drug	Annual mortality (%)	Drug cost per prescription	Number of administrations per year	Cost per administration	Number of physician visits per year	Cost per physician visit
Drug A	5	$100	15	$50	20	$300
Drug B	5	$150	12	$50	18	$300
Drug C	1	$200	12	$50	10	$300

Exercise 7.9 Exercises 7.7 and 7.8 are very similar. However, there are differences in how the population changes over time. For each budget year, compare the costs, health outcomes, and budget impact between the exercises. What differences do you observe? Are the differences significant? Why or why not? How did the dynamic approach affect the results?

Exercise 7.10 What are the advantages and disadvantages of combining a cost-effectiveness analysis and a budget-impact analysis into a single Excel-based model? Discuss the implications of the choice of computing framework when combining these analyses into a single model.

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Chapter 8
Uncertainty Analysis

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Abstract The purpose of budget-impact analysis is to project the potential future impact of the introduction of a new drug or other intervention on payer or provider budgets. Because estimates of current input values as well as assumptions about the structural model elements and changes in many input values over the analysis time horizon are needed, the results are estimated with uncertainty. Therefore, it is important for the model to include a method for performing uncertainty analyses. Uncertainty analyses allow the user to test the impact of different structural elements, assumptions, and input parameter values on the outcomes of the budget-impact analysis. In this chapter, methods for testing the impact on the results are presented (1) for alternative scenarios created using data and assumptions known to the budget holder and (2) for estimated ranges of input parameter values using uncertain data estimates and assumptions.

Keywords Budget-impact analysis • Uncertainty • Sensitivity analysis • Scenario analysis • One-way sensitivity analysis • Probabilistic sensitivity analysis

Chapter Goal
To describe the sources of uncertainty within budget-impact analyses for new drugs and to provide recommendations for demonstrating the impact of this uncertainty on the analysis results.

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The results of any budget-impact analysis contain inherent uncertainty. The purpose of budget-impact analysis is to project the potential impact on payer or provider budgets of the introduction of a new drug.[1] Because estimates of current input values, assumptions, and predictions about the future form the basis for the analysis, the results are estimated with uncertainty. Therefore, it is important for the analysis to include a method for performing both scenario and sensitivity analyses. These analyses allow the user to test the impact of different structural elements, assumptions, and input parameter values on the outcomes of the budget-impact analysis.

8.1 Sources of Uncertainty

There are generally two primary sources of uncertainty associated with any budget-impact analysis. The first source of uncertainty is for parameter values and assumptions that vary by jurisdiction or by health plan. These analysis inputs may be known with certainty by the individual jurisdictions and health plans, but not by the model developer. These include patient characteristics, condition incidence and prevalence, current costs for drug acquisition and other health services, and treatment guidelines and practice patterns for the jurisdiction or health plan. The second source of uncertainty is for parameter values and structural and other assumptions that are estimated with uncertainty to both the analysis developer and the jurisdiction or health plan. These may include condition natural history, drug efficacy and safety, changing drug costs over the analysis time horizon, changes in treatment shares over the analysis time horizon, and other future events. Scenario analyses are generally the most useful for the first source of uncertainty (i.e., input parameters that are known by the jurisdiction or health plan), while both scenario analyses and one-way sensitivity analyses are useful for the second source of uncertainty. These two sources of uncertainty are discussed in the following sections, and alternative methods for assessing this uncertainty are presented.

8.2 Analyses for Plan-Specific Parameters and Assumptions Known with Certainty

A model developed to assess the impact of a new drug on payer budgets is likely to include a number of parameters and assumptions that may be known with certainty by the jurisdiction or health plan, but not by the model developer. Rather than leave inputs for such parameters as blank placeholders, we recommend that any

[1] In this chapter we make the simplifying assumption that the budget-impact analysis is based on the introduction of a new drug to the current mix of drugs for treatment of a condition. Changes in our recommended approaches to estimate the budget impacts of other types of healthcare interventions (i.e., vaccines, diagnostics, surgery, and devices) are discussed in Chap. 13.

budget-impact analysis be populated with default data so that the analysis displays results for a reasonable base-case scenario. However, this scenario may be hypothetical and not particularly relevant to any actual jurisdiction or health plan, which may have very different inputs.

Examples of input parameters and assumptions that may vary by jurisdiction or by health plan, but may be known with certainty by the plan, include the following:

- Number of participants enrolled in the health plan
- Age and sex distribution of the health plan population
- Incidence and prevalence of the condition in the health plan population
- Condition-related management patterns in the health plan
- Current mix of treatments used to manage the condition in the health plan population
- Acquisition costs of the existing drugs in the treatment mix
- Planned restrictions, if any, on prescribing the new drug (e.g., restricted to those for whom the previous drug failed or to those with a specific condition severity)
- Costs of other resources currently used to manage the condition in the health plan

Because all of these inputs to the model may vary across health plans, budget-impact results based on a specific set of default values may not be very informative for a particular health plan budget holder. For this reason, the computer program that generates the estimates of the budget impact should be designed to allow the user to input values for these parameters and assumptions, and the computer program should be made available to budget holders whenever possible. Budget holders can then enter their own values for all these input parameters to create a scenario that best matches their specific situation. In general, availability of a flexible computer program to the budget holder is the recommended approach for dealing with uncertainty that arises from differences between jurisdictions and health plans.

However, there are some circumstances in which budget-impact results must be presented in a written format. Specifically, publications, reports, and dossiers will need to show results that are calculated using a specific set of base-case parameters. In these cases, plausible alternative scenarios should be included in the publication or reports to help make the presented results as relevant to the intended audience as possible. These plausible scenarios could include different patient characteristics and current treatment patterns, for example, and should be developed in collaboration with representatives of those likely to read the publication and reports. The impact on the results of alternative input values for the plan-specific parameters and assumptions can be presented in table format and/or illustrated using a tornado diagram that might typically be used to present one-way sensitivity analyses.

In Box 8.1, we present an example of alternative scenarios that might be adopted for providing treatment with bisphosphonates to various at-risk populations.

Box 8.1 Budget-Impact Analysis for Alternative Scenarios for Expanding the Use of Bisphosphonates in Women with Low Bone Mineral Density: Cumulative Three-Year Budget Impact (Tosteson et al. 2008)

Scenarios	Current practice	All untreated receive bisphosphonates	Difference
Scenario 1: All women aged 65–84 years with low bone mineral density			
Total societal cost	$25,957 million	$31,520 million	$5563 million
Total number of fractures	1,118,670	728,621	−390,049
Scenario 2: Women aged 75+ years with low bone mineral density and previous fracture			
Total societal cost	$8154 million	$8136 million	−$18 million
Total number of fractures	350,245	253,459	−96,786

In this analysis, two scenarios are presented: a scenario in which all women aged 65–84 years have low bone mineral density and a scenario in which women aged 75+ years have low bone mineral density and previous fracture. Running these two scenarios helps the budget holder understand the budget implication of implementing policies using bisphosphonates to treat all eligible women or just those over the age of 75 years with previous fracture.

8.3 Analyses for Uncertain Input Parameter Values

The second primary source of uncertainty is the uncertainty around values for parameters that are not known for certain by the modeler or the health plan. These include the efficacy and safety of current and new drugs as well as condition natural history, changing drug costs over the analysis time horizon, changing treatment shares over the analysis time horizon, and other future events over the analysis time horizon. These parameters will be uncertain to both the modeler and the health plan. In particular, the following input parameters are estimated with uncertainty:

- Changes in treated incidence or prevalence over the analysis time horizon
- Efficacy and safety of current and new drugs in the treated population over the analysis time horizon
- Condition outcomes over the analysis time horizon with the current treatment mix and with the new treatment mix

- Treatment shares of the new drug over the analysis time horizon and redistribution to the new drug from the current drugs
- Changes in the prices of current and new drugs over the analysis time horizon
- Impact of entry of other new branded or generic drugs during the analysis time horizon on all inputs
- Costs of providing other condition-related services and changes over the analysis time horizon

One way to present this uncertainty is to perform a one-way sensitivity analysis, varying each uncertain input parameter one at a time. This is the method recommended in the National Institute for Health and Care Excellence (NICE) guidance on estimating financial impact (NICE 2013) and in the updated International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Budget Impact Task Force guidelines (Sullivan et al. 2014). To the extent possible, the ranges or alternative values used for these sensitivity analyses should be based on the observed variability in each data element, and the methods used to derive these ranges should be provided. For example, the ranges used for efficacy could be the 95% confidence limits from the clinical trial data. However, for many of the uncertain variables, there are no observed data. Therefore, expert opinion on likely ranges may be needed for the one-way sensitivity analyses. If possible, ranges such as ± 20% for all input parameters should not be used, because the feasible variability in input parameter values is likely to be different for different types of parameters. For example, the percentage range in costs might be much higher than the percentage range in treatment share estimates. For all alternative values tested in sensitivity or scenario analyses, it is necessary to provide the data source and rationale for the alternative values tested.

Scenario analyses or multiway sensitivity analyses may also be used to examine the impact of parameter uncertainty. This approach can be used when there is uncertainty around a set of values. For example, an alternative set of values might be plausible for examining changes in the treatment shares of all drugs in the treatment mix over the analysis time horizon. In this case, alternative scenarios might be tested based on inputs from budget holders or physicians. Scenario analyses or multiway sensitivity analyses may also include variation in multiple types of parameters, including characteristics of the new drug such as its efficacy, safety, price, and dosing formulation, as well as the extent to which the current drugs are providing effective relief.

In presenting these one-way sensitivity analyses and scenario analyses, we typically present the base-case analysis results using a single set of default values for both the inputs known to the budget holder and the inputs for which there is structural or parameter uncertainty. We then also present the alternative sets of results by changing the uncertain input parameter values one at a time or by changing a group of parameter values. One-way sensitivity analyses and scenario analyses can also be presented for alternative base-case scenarios that include alternative feasible values for those inputs whose values are known to the budget holder.

In Box 8.2, we present an example of uncertainty analyses where the authors have presented the derivations for the data-driven ranges or alternative scenarios included in the analysis.

Box 8.2 One-Way Sensitivity Analysis: Total Per-Patient Budget Impact of a Drug for Treatment of Chemotherapy-Induced Anemia (Rubin et al. 2008, Table 2)

Input parameter	DA Q3W total cost	EA QW total cost	EA QW – DA Q3W
Drug price			
Base case: AWP – 20%	$8544	$8667	$123
AWP	$10,606	$10,614	$8
ASP + 6%	$6087	$7101	$1014
Mean dose per injection			
Base case: DA Q3W 375.6 μg; EA QW 43,187 U	$8544	$8667	$123
DA Q3W 283.8 μg[a]; EA QW 43,187 U	$6527	$8667	$2140
DA Q3W 467.2 μg[a]; EA QW 43,187 U	$10,555	$8667	−$1888
DA Q3W 375.6 μg; EA QW 38,044[b] U	$8544	$7740	−$804
DA Q3W 375.6 μg; EA QW 46,307[c] U	$8544	$9230	$686
Visit costs			
Base case: $58.75 (CPT 99212 + CPT90772)	$8544	$8667	$123
Visit cost + CBC panel ($58.75 + CPT 85027)	$8589	$8803	$214
Visit cost for injection only $20.09 (CPT 90722)	$8350	$8087	−$263
Frequency of administration visit			
Base case (DA three times per week, EA once a week)	$8544	$8667	$123
DA weekly office visit; EA weekly visit[d]	$8930	$8667	−$263
Time horizon			
Base case: 16 weeks	$8544	$8667	$123
12 weeks	$5126	$6356	$1230
24 weeks	$11,961	$13,290	$1329

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ASP average sales price, *AWP* average wholesale price, *CBC* complete blood count, *CPT* Current Procedural Terminology codes, *DA* darbepoetin alfa, *EA* epoetin alfa, *Q3W* every 3 weeks, *QW* every week

[a]The minimum mean dose per infection for darbepoetin alfa Q3W was 283.8 μg Q3W based on an efficacy study of the Q3W 200 μg regimen (Taylor et al. 2005) (representing a 24.4% reduction in dose from the base case), and the maximum mean dose per injection was varied to 467.2 μg Q3W, representing a 24.4% increase from the base case (Canon et al. 2006)

[b]Mean dose per infection was calculated based on values reported in Waltzman et al. (2005) using the following equation: mean weekly dose = mean cumulative dose/mean duration of treatment

[c]Mean dose per injection was calculated based on values reported in Witzig et al. (2005). A weighted average dose per injection was calculated based on dose (i.e., starting, escalated, and reduced dose), number of injections administered, and the number of patients on each regimen

[d]It was assumed that during a 16-week duration of treatment, a patient on a QW regimen will receive 15 injections

In this analysis, the budget holder is able to observe the impact that changes in the drug price, mean dose per injection, visit costs, frequency of administration visits, and time horizon have on the results. It is observed that changes in drug price, mean dose per injection, and time horizon could have a substantial impact, whereas visit costs and frequency of visits hardly affect the costs.

8.4 Probabilistic Sensitivity Analysis?

In cost-effectiveness analyses, an additional sensitivity analysis where all the uncertain input parameters are varied simultaneously through taking a random draw from their probability distributions (probabilistic sensitivity analysis) is typically performed. A similar type of probabilistic sensitivity analysis could be performed for a budget-impact analysis. For example, Purmonen et al. (2010) present the result of such an analysis as the probability of an increased budget above different threshold values, analogous to the cost-effectiveness acceptability curve. However, budget-impact analysis guidelines published by organizations such as ISPOR, NICE, and the Canadian Agency for Drugs and Technologies in Health (CADTH) do not recommend performing a probabilistic sensitivity analysis for budget-impact analyses, though this is recommended in the Belgian guidelines (Neyt et al. 2015).

If considering probabilistic sensitivity analysis, one needs to be careful and ensure a clear understanding of what the results of the probabilistic sensitivity analysis is really saying. In budget-impact analyses, the analysis needs to be adapted to reflect the perspective of the budget holder and the characteristics of the covered population. Thus, the budget impact is dependent on inputs that are both specific to the budget holder and uncertain in general. As a result, probabilistic sensitivity analyses for budget-impact analyses would be scenario-specific (i.e., it is not appropriate to allow variability of all parameters within a probabilistic sensitivity analysis in a budget-impact analysis). Further, with the exception of the efficacy estimates and possibly the current costs of treating the condition, a probability distribution for the values of the other input parameters based on sampling data is not typically available since uncertainty about the values of the inputs that will occur in the future is a reflection of different possible assumptions about the future rather than based on sampling data.

A secondary reason for not performing a probabilistic sensitivity analysis is that the sensitivity of the budget-impact analysis results to measured parameter uncertainty may be less than the sensitivity to variation in the healthcare budget holder's population characteristics and treatment patterns (Mauskopf 2014) or to variation in estimates about the future or to structural uncertainty of the budget-impact model. Therefore, the information provided by performing a probabilistic sensitivity analysis that only includes the parameters with measured uncertainty may not be very useful for a budget holder.

Finally, probabilistic sensitivity analyses are perceived as complex. As such, inclusion of a probabilistic sensitivity analysis may be perceived to reduce the transparency of the analysis and thus may reduce the credibility and usefulness of its results for the budget holder.

Exercises

Exercise 8.1 Discuss various methods that can be used to examine parameter uncertainty within a budget-impact analysis. Discuss methods that can be used to examine structural uncertainty with a budget-impact analysis.

Exercise 8.2 Define one-way sensitivity, scenario, and probabilistic sensitivity analyses. Explain the differences between these types of analyses and when you would use each analysis type.

Exercise 8.3 A budget-impact analysis was created for a health plan in which no condition-related cost offsets were considered. The parameters, their values, and sources included in the analysis are presented in the table below. What type of uncertainty analysis would you consider including within this budget-impact analysis? Which parameters would you vary, how would you vary them, and why?

Parameter	Value	Source
Health plan population	1 million lives	Known with certainty by health plan
Incidence of condition	1%	Published literature
Percentage of patients with condition who are treated	90%	Known with certainty by health plan
Current market share		
Drug 1	50%	Manufacturer estimate
Drug 2	50%	Manufacturer estimate
New drug	0%	Manufacturer estimate
Projected market share: year 1		
Drug 1	45%	Manufacturer estimate
Drug 2	45%	Manufacturer estimate
New drug	10%	Manufacturer estimate
Drug cost		
Drug 1	$100	Known with certainty by health plan
Drug 2	$125	Known with certainty by health plan
New drug	$150	Known with certainty by health plan

Exercise 8.4 For the budget-impact analysis outlined in Exercise 8.3, explain how each parameter should vary and how the analysis developer should derive or obtain the range over which these parameters should vary.

Exercise 8.5 For the budget-impact analysis outlined in Exercise 8.3, list up to five specific scenario analyses that could be performed. Outline specific values for specific parameters that would be used in each scenario analysis and explain why this scenario was chosen.

Exercise 8.6 A budget-impact analysis was created using the data in Exercise 8.3. The results are presented in the table below. Discuss what these analyses show.

Costs/outcomes	Budget scenario without new drug	Budget scenario with new drug
Drug costs	$1,012,500	$1,046,250
Other medical costs	$16,875,000	$16,537,500

Costs/outcomes	Budget scenario without new drug	Budget scenario with new drug
Total costs	$17,887,500	$17,583,750
Hospitalizations	16,875.00	16,537.50

Perform a one-way sensitivity analysis using the data in the table below. Present the results for each run.

Parameter	Current value	New value
Health plan population	1 million lives	2 million lives
Incidence of condition	1%	0.5%
Percentage of patients with condition who are treated	90%	85%
Current market share		
Drug 1	50%	45%
Drug 2	50%	55%
New drug	0%	0%
Projected market share: year 1		
Drug 1	45%	40%
Drug 2	45%	40%
New drug	10%	20%
Drug cost		
Drug 1	$100	$125
Drug 2	$125	$150
New drug	$150	$150

Exercise 8.7 Using the data in Exercise 8.6, identify three scenario analyses that might be interesting to the budget holder. Perform these scenario analyses and present the results. Interpret the results of each analysis.

Exercise 8.8 Condition-related outcomes and costs were examined in the budget-impact analysis above. The baseline and alternative values for the condition-related outcome and cost parameters are presented in the table below. What happens to the results (see results in Exercise 8.6 above) when each parameter changes one at a time?

Parameter	Baseline value	Alternative value
Hospitalization costs	$1000	$2000
Hospitalizations per year		
Drug 1	2.00	1.75
Drug 2	1.75	1.70
New drug	1.50	1.65

Exercise 8.9 Using the data in Exercise 8.8, describe what happens to the results if the following alternative scenarios occur: Scenario 1: hospitalizations per year for each drug are at their alternative values. Scenario 2: hospitalizations per year for drug 1 and the new drug are at their alternative values.

Exercise 8.10 Identify a situation in which it might make sense to perform a probabilistic sensitivity analysis for a budget-impact analysis. What types of parameters might vary or not vary in this analysis?

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Chapter 9
Validation

Josephine Mauskopf and Stephanie Earnshaw

Abstract A budget impact analysis that is validated will be more credible to healthcare budget holders. In this chapter, we present methods and examples for three types of validation: face validity, internal validity, and external validity. All three are equally important and should be included in every budget impact analysis. Validity should be assessed for all components of the analysis, including the model structure, assumptions, input parameter values, and results.

Keywords Validity • Face validity • Internal validity • External validity

Chapter Goal
To demonstrate the importance to the budget holder of validation of the analysis and to provide guidance and examples for validation of the structure, assumptions, input parameter values, and results of the budget impact analysis

9.1 Introduction to Validation of Budget Impact Analyses

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society of Medical Decision Making (SMDM) appointed a task force to create recommendations for good modeling research practices. One of the task force's charges was to make recommendations on transparency and validation of decision models (Eddy et al. 2012). Since BIA is typically performed using decision-analytic techniques or modeling, these research practices are applicable here.

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In Box 9.1, we present the ISPOR-SMDM cost-effectiveness task force's justification for transparency and ensuring the validity of economic models. We believe that their justification for transparency and validation is also applicable to models designed for performing budget impact analyses.

Box 9.1. ISPOR Task Force: Rationale for Validation of Economic Models ((Eddy et al. 2012), page 844)

> The purpose of health care models is to provide decision makers with quantitative information about the consequences of the options being considered. For a model to be useful for this purpose, decision makers need confidence in the model's results. Specifically, they need to know how accurately the model predicts the outcomes of interest and account for that information when deciding how to use the model results.
>
> Modelers can impart such confidence and enhance model credibility in two main ways: 1) transparency—clearly describing the model structure, equations, parameter values, and assumptions to enable interested parties to understand the model and 2) validation—subjecting the model to tests such as comparing the model's results with events observed in reality.

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The task force identified five main types of validation: face validity, verification (or internal validity), cross validity, external validity, and predictive validity (Eddy et al. 2012). In this chapter, we describe these methods as they can be used for validating a budget impact model for a new drug[1] in three sections:

- Establishing face validity for the model structure, structural assumptions, parameter values, and results including sensitivity analyses
- Establishing internal validity/verification of the computer program used to estimate the budget impact
- Establishing external validity of the results of the analysis by cross validity with other models, observed validity by comparing the results of the analysis with observed data, and predictive validity in which an opportunity arises to compare and contrast the results with actual budget impacts observed over the analysis time horizon

We should note that, in practice, budget impact analyses usually undergo internal validation/verification through quality checking of the computer program used to generate the model estimates. They also are frequently checked for face validity through review by clinicians and other budget holders familiar with the condition

[1] In this chapter we make the simplifying assumption that the budget impact analysis is based on the introduction of a new drug to the current mix of drugs for treatment of a condition. Changes in our recommended approaches to estimate the budget impacts of other types of health care interventions (i.e., vaccines, diagnostics, surgery, and devices) are discussed in Chap. 13.

being modeled. However, cross validity, external validity, and predictive validity of these models through comparison of the model structure, assumptions, inputs, and estimates with other costing or budget impact models or comparison of the model estimates with observed cost data or with costs after introduction of the new product are not generally included and are only briefly mentioned in published guidelines for performing budget impact analyses. Nevertheless, such validation is important to the budget holders.

In Box 9.2, we present statements on validity by the ISPOR Budget Impact Task Force and by those commenting on the Task Force report.

Box 9.2. ISPOR Budget Impact Task Force Comments on Validation ((Sullivan et al. 2014), abstract, and page 9; (Watkins and Danielson 2014), page 3)

In the ISPOR budget impact analysis guidelines, the following statements are included relating to model validation (Sullivan et al. 2014):

> The validation of the model should include at least face validity with decision makers and verification of the calculations.
>
> The computing framework and input data used for a BIA [budget-impact analysis] must be sufficiently valid to credibly inform the budget holder's decisions. Two of the standard steps in validation should be applied in the BIA: 1) determine face validity through agreement with relevant decision makers on the computing framework, aspects included, and how they are addressed (e.g., access restrictions and time horizon); and 2) verification of the cost calculator or model implementation, including all formulas (Eddy et al. 2012). In addition, where possible, the observed costs in a health plan with the current interventions should be compared with the initial-year estimates from a BIA. For research purposes, after the new intervention is introduced, data could be collected and compared with the estimates from a BIA. Although this would not be relevant for the decision already taken, if the results are close then it would provide confidence in the approach for future interventions.

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A statement in an editorial (Watkins and Danielson 2014) commenting on the ISPOR Budget Impact Analysis Task Force report:

> It cannot be overemphasized that the usefulness of an economic model to a user is limited by the accuracy with which it represents the realities of clinical practice in that user's setting. Common threats to validity include unrealistic assumptions about clinical care pathways, frequency of certain diagnostic tests, and patient adherence outside of controlled trials. Models based on unrealistic clinical assumptions have little or no value to us.

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9.2 Establishing Face Validity

Face validity can be established by review of the model structure, key structural assumptions, default input parameter values, and results both by clinicians who treat patients with the condition of interest and by health care budget holders who are likely to use the results of the budget impact analysis. This review can be done through individual interviews or by convening an expert panel to review and discuss the model structure, assumptions, and inputs. It is important to have an assessment of face validity both before and after the model is programmed. The assessment of face validity before the model is programmed and results are available ensures that the reactions to the model components by the clinicians or budget holders are not influenced by the results. It also allows for the development of an analysis that captures the components deemed of importance to these decision-makers. However, it is only after the computer program is developed that the face validity of the results and the changes in the results with different scenarios or input parameter values can be assessed by the clinicians and budget holders.

In Box 9.3, we present the statement about face validity testing both during model development and of the results for a hospital budget impact model comparing stem cell mobilization strategies.

Box 9.3. Example of Face Validity Testing of a Hospital Budget Impact Model Comparing Stem Cell Mobilization Strategies ((Jensen et al. 2015), pages 145–6, 148)

> Published values from the targeted literature search were used, as described previously, to prepopulate the models for a base case estimate. Owing to the complexity of the mobilisation process and lack of head-to-head data for the mobilisation strategies, several assumptions were informed by primary interviews with transplant physicians and further validated by experts in ASCT [autologous stem cell transplant]. The final model structure and evidence used within the model was subject to testing and quality control by a health economist not part of the study team, and both evidence and results were further validated by subject matter experts and key opinion leaders.
>
> The model results have received validation by ASCT experts across the EU and the USA; however, additional research is required to validate the model using data from transplant centres.

9.3 Establishing Internal Validity

Establishing internal validity, or otherwise called verification of the model, is checking that the model is correct and performing as it was intended. This form of validation is important for any analysis and should be of primary importance to ensuring credibility of the analysis.

Although budget impact models are frequently simpler than cost-effectiveness models, it is critically important to ensure that the model programming has correctly implemented the planned calculations as well as correctly entered the values for the input parameters. There are multiple components of the budget impact analysis program that should be checked as part of the verification process:

- Ensure that the text within the analysis file is clear and concise. Ensure that misspellings do not occur.
- Ensure that all input data are properly sourced and that the input values have been extracted from their sources properly.
- Ensure that calculations to transform inputs for the underlying model are correct and presented transparently.
- Ensure that all model calculations are presented transparently and are correct.
- Ensure that any programming code for tasks such as restore defaults, simulations, etc. is correct, functioning properly, and documented.
- Ensure that the model results go in the expected direction when inputs are set at specific values and that results are as expected when inputs are set at their extreme values.

When performing these checks, it is valuable that they be performed at various points in the program development and by different people working on the analysis. Specifically, it is important for the model programmers to double check all their program code, formulas, and input values as they develop the program. Once they have completed the program, they should also perform model runs by changing the allowed model settings and using alternative and extreme values to ensure that the results change in the expected direction.

It can also be useful to have these same checks performed by both other project team members and other experienced budget impact analysis programmers. Because these individuals are not as close to the programming for this analysis, they may be in a better position to ensure instructions for the user are clear and make sense to someone new to the model. They may also be able to ensure that the navigation options included in the model (e.g., restore default, choose model settings, jump to results) are easy to use and error-free.

In Box 9.4, we present an example set of guidelines for the final internal validation program check of an Excel program by someone not part of the model development team.

Box 9.4. Guidelines for Internal Validation of an Excel Budget Impact Analysis Program

Item categories to be checked	Checking instructions
Model description and flow diagram	• Check completeness of the model description and flow diagram such that a user unfamiliar with the model can understand the model flow and included calculations
Inputs default data	• Check references for all data sources • Check input values taken directly from published or other sources • Check derivation of input values when not taken directly from the published source (e.g., inflation rates used to adjust costs to current year)
Workbook text	• Check for spelling errors or typos • Check for clarity of instructions for users unfamiliar with the model • Check for clarity of presentation of each worksheet's content and calculations • Check for use of correct currency
Embedded user manuals	• Check for ability to access the file • Check for ability to close the file and then reaccess • Check for completeness and clarity for users not familiar with the model • Check user instructions for correctness • Check embedded screen shots that they represent the current version of the budget impact model
Calculations	• Check that formulas are correct • Check for accuracy based on text presentation of model calculations • When formulas are repeated for multiple cells, check that they are correctly copied from cell to cell • Check that all input values included in all the macros change to the proper values when the user changes the input values or when default input values are changed by the programmer in any part of the program • Check that results of each calculation are as expected
Macros	• Check that the macro callouts from the Excel program occur at all relevant points in the model calculations • Check that the Visual Basic program statements are correctly performing the required calculations • Check that subroutines are used correctly within the macros • Check that all programming code is documented
Navigation buttons	• Check that navigation buttons are provided for all important program segments • Check that navigation buttons are provided that allow the user to return to the previous program segment • Check to ensure that all navigation buttons work correctly and take the user to the indicated program section

Item categories to be checked	Checking instructions
Restore default function	• Check the code behind the restore defaults function to ensure that it is performing correctly • Check the functionality of all the choices given to the user to restore default input values in the model, including restore defaults only on a single spreadsheet or throughout the workbook • Check that changes made by the user are overridden by the default values when the restore default buttons are used • Check that changes made to the default data are distributed to all relevant Excel program cells when the restore default buttons are used
Alternative input values	• Check that all model calculations use the user-defined input values rather than the default values when appropriate • Check that results make sense when inputs are set at their extreme values
Alternative scenarios	• If alternative scenarios are prepopulated in the model such that the user selects a scenario to run, check all alternative scenario choices to ensure that the model calculations change appropriately based on the scenario(s) selected by the user
Alternative results presentation	• If the model is set up such that tables of results toggle between different results, check all alternative results settings to ensure that the presentation of the model results changes appropriately based on the results settings selected by the user
User runs of sensitivity and scenario analyses	• Check all sensitivity analysis runs included in the program to ensure that results make sense • Check that all user-defined sensitivity analysis runs included in the program use the user-defined input data and that the results make sense • Check the sensitivity run buttons to ensure that they function correctly

An important part of the verification process is documentation. Not only is it important to document what reviews were performed, but it is also important to outline what was checked and what the outcome was, when applicable. For example, when testing that model calculations perform as expected when changing each parameter one at a time at their extreme values, it can be valuable to document in a table each input that was tested, the values to which each input was set, the results that occurred, and whether the outcome was expected. This documentation can be delivered as a separate document, or it can be embedded at the back end of the model such as in the last few worksheets of a workbook if the budget impact analysis is programmed in a software that can incorporate this additional documentation.

9.4 Establishing External Validity

Establishing external validity of a budget impact analysis is a process designed to check that the results of the analysis are likely to be accurate. This is established through comparing the analysis estimates of current costs and/or budget impact with results reported by other models or by retrospective or prospective observational database analyses. Although establishing external validity is rarely done for either cost-effectiveness or budget impact analyses, it can be critically important for demonstrating the accuracy of the model for the decision-maker. For a budget impact analysis, the simplest type of external validity would be to compare the estimates of the current-year costs for the eligible population when using the current treatment mix and site-specific inputs with the observed costs from that site. Other forms of validation using current observed data may compare selected intermediate analysis outcomes for the current-year costs from the analysis with observed outcomes in the specific health plan.

In Box 9.5, we present the external validation of a model estimating the budget impact for Medicaid in the USA of buprenorphine/naloxone sublingual film and

Box 9.5. External Validation of a Budget Impact Analysis for a Drug to Treat Opioid Dependence in the Medicaid Population Using a Markov Model ((Asche et al. 2015), page 609)

> As a test of validity, the total costs per patient predicted by the model were compared to estimates previously obtained from statistical analyses of the MarketScan Medicaid database. Total costs over 6 months were previously estimated at $7356 per patient treated with buprenorphine/naloxone film formulation. According to the model, the total cost in the first year, for the scenario with 100% film, was $673 million for 45,854 treated patients, i.e., around $14,700 per patient over 12 months. Thus it appears that the costs predicted by our model are consistent with results of retrospective studies using Medicaid claims data. However, using another administrative claims database, Baser et al. (2011) estimated total health care costs among patients treated with buprenorphine (with or without naloxone) at $10,710 over 6 months. Previously, a study based on Veterans Health Administration (VHA) data estimated healthcare costs over 6 months after initiation of buprenorphine at $11,597 (Barnett 2009). Two hypotheses may be proposed to explain the lower costs predicted by our model compared to those estimates from the literature: first, buprenorphine/naloxone may be associated with lower costs than buprenorphine mono formulation because the combination reduces the risk of abuse and diversion and therefore may require less intensive medical supervision as well as lower health care service costs since patients stay in treatment; second, costs incurred by Medicaid patients may be lower than those incurred by private health plans or VHA.

Note: The MarketScan Medicaid database was used to derive the inputs for the Markov model in this analysis.

Quoted from Asche et al. (Asche et al. 2015) with permission from Taylor & Francis Ltd. http://www.tandfonline.com

tablet for treatment of opioid dependency (Asche et al. 2015). In Box 9.6, we present the model validation that was completed for a discrete-event simulation budget impact analysis for a new drug for thrombolysis in patients with ischemic stroke (Mar et al. 2010).

Box 9.6. External Validation of Discrete-Event Simulation Budget Impact Analysis of Thrombolysis for Ischemic Stroke in Spain

External Validation Methods and Outcome

Mar et al. (Mar et al. 2010) built a discrete-event simulation model to examine the impact to the Spanish health system budget of the use of thrombolysis in stroke patients. They validated this model by comparing life expectancy of stroke patients generated by the model with data in the published literature. Specifically, they compared their estimates with data from the Auckland Stroke Studies (Bonita et al. 1997) and a study designed to estimate prevalence data via a Markov model analysis (Mar et al. 2008). Life expectancy by age and sex was compared.

They also compared the age-specific prevalence of stroke to the results of these two studies. Their model calculated results similar to the Markov model (Mar et al. 2008). Comparison with the Auckland study showed some discrepancy, but they were able to explain the differences.

In this analysis, they also compared the calculation of the number of recurrent events and first-ever stroke cumulative incidence.

Budget impact analyses are typically performed to help with planning for a new drug in the treatment mix. Given this, a comparison of the year 3 or year 5 costs estimated by the budget impact model with the observed costs in those years would provide the most rigorous validation of a budget impact analysis. A comparison of the actual costs for years 3–5 with those estimated in the budget impact analysis could also be used to recalibrate the model to develop estimates of the continuing costs over the next 3–5 years.

Exercises

Exercise 9.1 Validating a decision model involves checking face validity, internal validity, and external validity. Discuss why it is important to perform all three aspects of this validation for a budget-impact analysis.

Exercise 9.2 Consider a budget-impact analysis built for a novel drug to treat diabetes. Describe several ways in which the face validity of the model built to perform the analysis might be checked. Who might be the budget holders for whom face validity would be important?

Exercise 9.3 Consider a budget-impact analysis built for a new drug to treat a complicated urinary tract infection. Compile a comprehensive plan to test the internal validity.

Exercise 9.4 A budget-impact analysis has been built to examine the impact to a health plan's formulary of a new drug to treat psoriasis. Budget scenarios up to 5 years have been projected. Describe how the external validity of the model would be examined.

Exercise 9.5 A budget-impact analysis was constructed for pimecrolimus for the treatment of atopic dermatitis or eczema. A key component of this analysis was analyzing administrative health-care claims to understand the market before and after the introduction of pimecrolimus (Chang and Sung, 2005). Develop a validation/verification plan for this budget-impact analysis.

Chang J, Sung J. Health plan budget-impact analysis for pimecrolimus. *J Manag Care Pharm*. 2005;11(1):66–73.

Exercise 9.6 A budget-impact analysis was created for a health plan. The parameters, their values, and sources included in the analysis and results are presented in the tables below. Develop a plan for examining internal validity. Discuss how documentation of this testing could be presented. Present an example of that documentation.

Inputs

Parameter	Value	Source
Health plan population	1 million lives	Known with certainty by health plan
Incidence of condition	1%	Published literature
Percentage of patients with condition who are treated	90%	Known with certainty by health plan
Current market share		
Drug 1	50%	Manufacturer estimate
Drug 2	50%	Manufacturer estimate
New drug	0%	Manufacturer estimate
Projected market share: year 1		
Drug 1	45%	Manufacturer estimate
Drug 2	45%	Manufacturer estimate
New drug	10%	Manufacturer estimate
Drug cost		
Drug 1	$100	Known with certainty by health plan
Drug 2	$125	Known with certainty by health plan
New drug	$150	Known with certainty by health plan

Parameter	Value	Source
Hospitalization costs	$1000	Published literature
Hospitalizations per year		
Drug 1	2.00	Published literature
Drug 2	1.75	Published literature
New drug	1.50	Published literature

Results

Costs/outcomes	Budget scenario without new drug	Budget scenario with new drug
Drug costs	$1,012,500	$1,046,250
Other medical costs	$16,875,000	$16,537,500
Total costs	$17,887,500	$17,583,750
Hospitalizations	16,875.00	16,537.50

Exercise 9.7 For the budget-impact analysis presented in Exercise 9.6, discuss how the face validity of this analysis could be tested. How would you document this?

Exercise 9.8 For the budget-impact analysis in Exercise 9.6, discuss how the external validity of this analysis could be tested. How would you document this?

Exercise 9.9 A manufacturer needs a budget-impact analysis for a new drug to treat condition Y. There are currently no treatments in the market for this condition. Compile a comprehensive validation plan for this budget-impact analysis considering face validity, internal validity, and external validity. How would you perform this validation given that no other treatments are currently on the market for this condition?

Exercise 9.10 A budget-impact analysis contains calculation for the underlying analysis along with programming code to restore default values. Why is it important to perform validation/verification on the programming code when the underlying code does not directly affect the base-case analysis?

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Chapter 10
Software and Computer Interface

Anita Brogan, Stephanie Earnshaw, and Josephine Mauskopf

Abstract In this chapter, we provide guidance on the choice of computer software for the budget-impact analysis calculations. In general, we recommend the use of simple spreadsheet software so that the model is readily accessible to budget holders and other decision-makers. We also discuss user interfaces and the importance of transparency and ease of use. A typical budget-impact analysis interface includes introductory information, input parameters, results, and background calculations. The introductory information should describe the model structure and provide instructions on using the model. The input parameters should be clearly laid out, documented, and easy to customize. The model calculations and results should be transparent and simply presented. We recommend selecting a visually appealing layout and color scheme, opting for worksheet equations rather than Visual Basic for Applications code to perform model calculations, and using Microsoft Excel's available features, such as buttons and drop-down boxes, to help simplify user interactions with the model. Screenshots of a sample budget-impact model programmed in Excel are presented, and a link to the full Excel model is provided.

Keywords Software • Microsoft Excel • Interface • Screenshots

Chapter Goals
To provide guidance on the choice of software and on the design of the user interface for budget-impact analyses and to provide an example of a Microsoft Excel-based budget-impact analysis.

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10.1 Software

The choice of software is a critical element of designing the computing framework of any budget-impact analysis. The requirements for the analysis will largely dictate the ideal software choice. In general, basic spreadsheet software has many advantages. While a variety of spreadsheet software packages are available, Microsoft Excel (Excel) is by far the most commonly used. Therefore, the rest of this section will refer to Excel rather than spreadsheet software generally. Most model types appropriate for budget-impact analysis can be programmed in Excel. This includes basic cost calculators as well as analyses with underlying decision tree or Markov structures. More complex model types including individual patient simulation can also be programmed in Excel, but file size and run times may become an issue. In Box 10.1, we present the advantages of programming budget-impact analyses in Excel.

In general, we recommend the use of Excel unless the planned model structure cannot be accommodated. The typical reason for selection of a different type of software is run time. Depending on the audience, run times in excess of a few hours (or even a few minutes) can make a model too difficult to use. Most common model structures (e.g., decision trees and Markov models) can be programmed in Excel so that the base-case analysis requires no run time. Individual patient simulation models generally require time to run, and Excel is not necessarily built to handle the very efficient computations needed to keep run times short. However, these types of models should rarely be needed for budget-impact analysis.

Software packages other than Excel include simulation software packages such as Arena (Rockwell Automation, Wexford, PA), packages specifically designed for health economic models such as TreeAge (TreeAge Software Inc., Williamstown, MA), and basic programming languages such as R, C++, or Java. Some of these packages have their own user interfaces or can be linked with an Excel interface. In using any of these alternate packages, the developer should always keep in mind transparency, familiarity, and user-friendliness. In Box 10.2, we present a list of packages that may be useful in specific instances.

Box 10.1. Advantages of Programming Budget-Impact Analyses in Excel

- Excel is extremely flexible and allows the model developer to design customized, transparent, and interactive models.
- Excel is familiar software, which should maximize the accessibility of the model to the widest possible audience. While versions of Excel change over time, compatibility between versions is generally good.
- Excel's built-in macro language, Visual Basic for Applications, can be used to automate various aspects of the model, including navigation and sensitivity analysis. This automation can help make the model user-friendly but should be used with caution to avoid loss of transparency.

Box 10.2. Selected Available Software Packages

Software package	Advantages	Disadvantages
Excel	• Familiar to most users • Allows development of customized, transparent, and interactive • Most users have license	• Long computation times for some sophisticated analyses • Entire model must be built by developer
Arena	• Appropriate for simulation models • Contains modules of code to expedite model development	• Black-box programming limitations • User must have license
TreeAge	• Developer-friendly interface • Can quickly develop simple models in a visual format	• Black-box programming limitations • Difficult for developer to annotate data • User must have license
MATLAB	• Appropriate for dynamic disease transmission models • Capable of solving complex analyses (e.g., simultaneous differential equations)	• Software learning curve • Difficult for user to interact with MATLAB directly (developer should create an Excel interface) • User must have license
R	• Data analysis capabilities • Statistical robustness • Freeware	• Software learning curve • No user-friendly interface

In general, we strongly recommend that any budget-impact analysis use a model structure that is as simple as possible and programmed in a commonly used software platform such as Excel. If a simple model will not be credible to a budget holder, a more complex model may need to be considered. However, the developer should weigh the trade-offs in terms of need for specialized software, need for additional data and assumptions, and loss of transparency and user-friendliness. If these trade-offs make the model difficult to use or understand, no real credibility will be gained, and a simpler structure may still be preferred.

10.2 User Interface

Budget-impact analyses should be programmed with a transparent interface that allows the user to easily understand the model structure, inputs, calculations, and results. The user should be able to easily progress through the model and customize input values for their own circumstances. In this section, we discuss user interfaces created using Excel. However, we recommend development of a user interface regardless of the software used to calculate the budget impact. In fact, an interface created in Excel can be linked to many of the available software packages.

User interfaces should include more than just tables of inputs, calculations, and results. Inclusion of text and figures to describe the various features of the model can help ensure the user has all the information they need to understand and interpret the model and its results. We recommend including all of the following features into any user interface:

- Introductory information
  - Description of the background and objective of the model
  - Instructions for using the model
  - Description of the model structure and assumptions, with accompanying diagram
- Input parameters
  - Clearly laid out input worksheets, with parameters grouped in an organized fashion. Input parameters should be described so that the user knows how they are being used in the model calculations.
  - Ability to customize values for all or selected inputs. To help the budget holder quickly arrive at relevant results, it may help to point out the inputs that are most important to review and customize. Default values should be provided for each input so that the user has a starting point. However, one set of default values may not be relevant for all budget holders. To handle different perspectives, it may be necessary to allow the user to choose among more than one set of default values.
  - Clear reference information for each default value.
  - Description or actual calculation (shown on the input worksheet or on a background worksheet) of any adjustment or conversion performed on the published or publicly available data to arrive at the default value. For example, costs presented in previous year currency may need to be inflated, or a monthly cost may need to be converted to an annual cost. The step of documenting calculations used to arrive at default values must be taken to ensure users can confirm the model's input values against the source information.
  - List of full references for each source cited in the model.
- Results and model calculations
  - Visible model calculations that are clearly laid out, easy to decipher, and transparent.
  - Simply presented model results, without too many outcomes. Key model settings, such as the time horizon, total population, or treated population, can be shown with the results to help provide context. Graphical display of results can assist with interpretation, and the model can be programmed to allow users to toggle between graphical and tabular results. If graphical results are included, be sure to set appropriate axis limits.

When designing the user interface, we recommend selecting a visually appealing layout and color scheme. The model can be laid out using a series of worksheets to

group related information. Use of multiple worksheets also helps break up the model's content into smaller sections and helps avoid the need for excessive scrolling. For example, the user interface may contain one or two introductory worksheets showing background, objectives, model structure, and instructions for using the model. Then, the user interface may contain a number of input worksheets, a worksheet showing sources for the input data, and a worksheet displaying the model's results. Finally, the user interface may contain background worksheets containing tables that display all of the calculations needed to estimate the model's outcomes.

In general, we highly recommend showing all of the model's calculations as equations in worksheet cells. While Excel contains the Visual Basic for Applications (VBA) programming language, we generally do not recommend using VBA to perform the calculations of the model unless absolutely necessary. A basic model user is more likely to be able to understand worksheet equations than VBA programming code. If any of the model calculations are long and difficult to decipher, breaking them up and showing interim components can help increase transparency. Transparency should always take precedence over squeezing too many mathematical operations into single worksheet cells. The obvious reason is that a budget holder may have only a short period of time to review a model, and simple equations are easier to understand than complex equations. Another reason is that it is much easier to quality check a model whose worksheet equations are simple rather than long and complex.

While we do not recommend the use of VBA to handle model calculations, VBA does allow the model developer to create buttons and other features to simplify use of the model. For example, navigation buttons can help users move through the model. Buttons can also be programmed to restore input parameters to their original default values. Another useful device in Excel that does not require VBA programming is the drop-down box, which can help users make simple selections, such as the following:

- Choosing between two drug cost schemes (e.g., average wholesale price vs. wholesale acquisition cost, list prices vs. negotiated discounted prices)
- Choosing between two alternate sources of data
- Choosing between payer perspectives (e.g., commercial vs. government payer, national vs. regional payer)
- Turning on/off particular modeling assumptions (e.g., whether or not partial responders are allowed to escalate their dose)
- Selecting preferred display of results (e.g., graphical vs. tabular, annual costs vs. per-member–per-month costs)

Overall, the user interface of any budget-impact analysis should allow the user to easily understand the model structure, inputs, calculations, and results. The model will be most useful if budget holders can easily move through the model, check input values and sources, customize input values for their own circumstances, and view results relevant to their decision-making process. Transparency throughout will help add to the credibility of the model and its results.

10.3 Sample User Interface

The sections above have discussed appropriate software and our recommendations for building clear and transparent budget-impact analyses, particularly in Excel. This section presents a visual example to help illustrate the key concepts. Below, we describe a hypothetical budget-impact analysis for a new drug for chronic obstructive pulmonary disease (COPD) and provide screenshots of various aspects of the analysis.

Background

The analysis described in this example assesses the budget and health impact of the introduction of a hypothetical new treatment (Drug C) for moderate-to-severe COPD. The analysis takes the perspective of a USA payer whose formulary currently includes Drug A and Drug B in the same indication. A dynamic approach using a Markov model is used to ensure that the analysis captures the impact of the alternative therapies on disease progression and the size of the treated population. Drug costs and COPD care costs, along with disease severity outcomes, are assessed and used to estimate the total budget and health impact of Drug C.

The figures below show screenshots of an introductory worksheet, several input worksheets, and a result worksheet. The background calculation worksheets are too large to show in this section, but the full model is available as electronic supplementary material associated with this chapter.

Introduction Worksheet

The introduction worksheet (Figure 10.1) of the sample COPD model describes the budget-impact analysis and includes a descriptive figure. The worksheet also includes a figure of the Markov model health states and further describes the underlying model structure. Finally, the worksheet provides instructions for using the model. Depending on the disease area and the audience, additional background and detail could be included, as needed.

Input Parameter Worksheets

The input parameters of the sample COPD model are grouped by type onto several separate worksheets. This grouping allows the user to consider one set of inputs at a time. The screenshots below illustrate several key features we recommend for input parameter worksheets generally:

- Input parameters are clearly described, so the user knows how they are being used in the model calculations.
- Input cells are clearly marked with gray shading so that the user can easily see where to test alternative parameter values.
- Default values are provided for all inputs so that users can quickly arrive at reasonable results without entering data for every input. Depending on the audience, default values can be shown on the worksheet next to each input cell, as shown in the screenshots below, or the user input cell can simply display the default value.

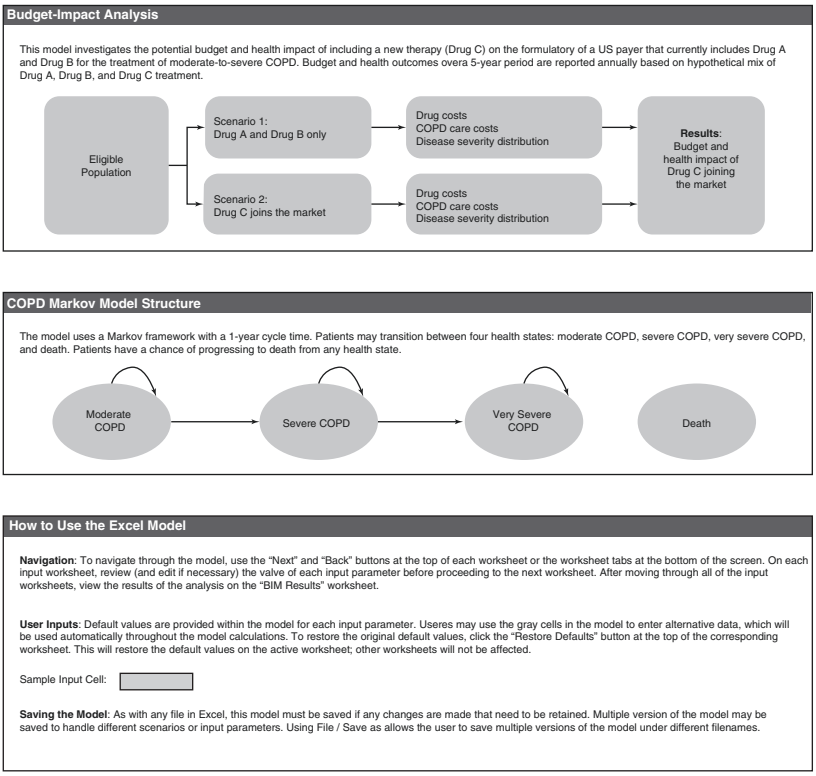

Fig. 10.1 Introduction worksheet

In addition to these features, a button to restore the inputs to their original default values should be provided on each input worksheet. Also, reference information should be provided for each default value. The model shown in the screenshots below uses hypothetical data. For a real model, clear and specific reference information should be shown individually for each parameter.

In the sample model, the order of the worksheets follows the six-step process for developing budget-impact analyses. The population worksheet (Figure 10.2) first details the calculations used to arrive at the size of the eligible population. Because this sample analysis is dynamic, the sizes of both the prevalent cohort and the yearly incident cohorts are estimated. The distribution of modeled individuals across the health states is allowed to differ for these cohorts as well, since incident cohorts may be healthier, on average, than the prevalent cohort. Finally, a few simple calculations are shown to help the user easily see how the number of people in the eligible cohorts is calculated from the size of the health plan and the prevalence and incidence data.

Patients Living with Condition

To arrive at the size of the modeled population, this table begins with the population in the overall health plan. Then, filters are applied to estimate the size of the currently treated population and the number of people initiating treatment each year.

Parameter	Default	User Input				Number of people
Total number of persons in the population of the health plan	1,000,000	1,000,000				1,000,000
Percent of individuals receiving COPD maintenance treatment within health plan	3.70%	3.70%	x	1,000,000	=	37,000
Percent of individuals in the health plan who begin COPD treatment each year	0.20%	0.20%	x	1,000,000	=	2,000

	Existing Patients		New Patients	
	Default	User Input	Default	User Input
Distribution of individuals by health state				
Moderate COPD	50.0%	50.0%	75.0%	75.0%
Severe COPD	40.0%	40.0%	20.0%	20.0%
Very severe COPD	10.0%	10.0%	5.0%	5.0%

Assumption: The model assumes all COPD patients are eligible for Drug A, Drug B, and Drug C.

Source: Hypothetical COPD Population Facts, 2016

Fig. 10.2 Population worksheet

The treatment mix worksheet (Figure 10.3) first provides simple input cells to allow the user to project the uptake of Drug C in each of the five budget years modeled. The table that follows summarizes the treatment mix for all three drugs in the five budget years for the two key scenarios: a scenario with Drug A and Drug B only (i.e., the world without Drug C) and a scenario in which Drug C also joins the market. The text provided with this table describes the assumption about how increased usage of Drug C is projected to affect usage of Drug A and Drug B. To ensure transparency, it is critical to clearly describe assumptions and calculations throughout the budget-impact analysis. Note that in this example, the user is only allowed to enter uptake of Drug C. Depending on the audience, it may be appropriate to allow the user to also enter projected usage of Drug A and Drug B in each future budget year for both scenarios. The benefit of this additional flexibility should be weighed against the benefits of keeping the input worksheet simple.

The cost worksheet (Figure 10.4) provides inputs for monthly drug costs and annual COPD care costs, by health state. The inputs shown for this hypothetical sample model are very simple. Depending on the audience or disease area, additional detail may be needed. For example, budget holders may wish to see drug costs further disaggregated to show drug acquisition costs, available dosages, patient co-payments, rebates, or dispensing fees, along with calculations showing total monthly or annual drug costs. Similarly, health state costs could be disaggregated to show resource use and unit costs. The trade-off between simplicity and detail should be carefully considered in light of budget-holder preferences.

This sample model includes a transition probability worksheet (Figure 10.5), though other budget-impact analyses may estimate disease-related costs directly or from a different type of efficacy data. In this sample model, the transition probability worksheet provides inputs for annual probabilities of transitioning between health states and annual probabilities of death. These probabilities are allowed to vary by treatment, and in this hypothetical example, a dynamic modeling approach was used to capture the impact of differing disease progression on population size over time.

Uptake of Drug C Over Time

This table displays the uptake of Drug C for COPD treatment for the next 5 years.

Year	Default	User Input
Year 1	10.0%	10.0%
Year 2	20.0%	20.0%
Year 3	30.0%	30.0%
Year 4	40.0%	40.0%
Year 5	50.0%	50.0%

Source: Hypothetical COPD Treatment Mix, 2016

Treatment Mix

The budget-impact model compares two scenarios: (1) a scenario in which only Drug A and Drug B treatments are available, and (2) a scenario in which Drug C treatment also becomes available. This table displays the treatment mix for each senario in the current year and for the first 5 years after Drug C becomes available. In Scenario 2, Drug C uptake is assumed to impact the usage of Drug A and Drug B treatments equally.

Comparator	Current Year	Year 1	Year 2	Year 3	Year 4	Year 5
Scenario 1: Drug A and Drug B only						
Drug A	40.0%	40.0%	40.0%	40.0%	40.0%	40.0%
Drug B	60.0%	60.0%	60.0%	60.0%	60.0%	60.0%
Drug C	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Scenario 2: Drug C joins the market						
Drug A	40.0%	36.0%	32.0%	28.0%	24.0%	20.0%
Drug B	60.0%	54.0%	48.0%	42.0%	36.0%	30.0%
Drug C	0.0%	10.0%	20.0%	30.0%	40.0%	50.0%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Fig. 10.3 Treatment mix worksheet

Costs

This table provides monthly COPD treament costs and annual other COPD care costs.

Parameters	Default	User Input
Monthly drug costs		
Drug A	$200	$200
Drug B	$225	$225
Drug C	$240	$240
Annual COPD care costs, by health state		
Moderate COPD	$3,000	$3,000
Severe COPD	$10,000	$10,000
Very severe COPD	$20,000	$20,000

Source: Hypothetical COPD Costs, 2016

Fig. 10.4 Costs worksheet

Annual Transitions Between Health States

The table below displays the annual probabilities of transitioning between the model health states.

Transition	Drug A		Drug B		Drug C	
	Default	User Input	Default	User Input	Default	User Input
Transitions between health states						
Moderate to severe COPD	0.10	0.10	0.09	0.09	0.08	0.08
Severe to very severe COPD	0.10	0.10	0.09	0.09	0.08	0.08
Transitions to death state						
Mortality from moderate COPD	0.02	0.02	0.02	0.02	0.02	0.02
Mortality from severe COPD	0.04	0.04	0.04	0.04	0.04	0.04
Mortality from very severe COPD	0.10	0.10	0.10	0.10	0.10	0.10

Source: Hypothetical COPD Health State Transitions, 2016

Fig. 10.5 Transition probability worksheet

Results Worksheet

The result worksheet (Figure 10.6) displays the cost and health outcomes of the model for each scenario in each budget year. The primary outcome of the model is the difference in costs between the scenarios, which is displayed in the budget-impact rows. A few key settings (i.e., plan and treated population sizes) are also presented to provide context for the user.

In this sample model, all cost outcomes are presented in tabular form as annual totals. Graphical presentation of results can help budget holders quickly visualize results and see trends. Also, for some countries, it may be helpful to include a drop-down box allowing the user to view per-member–per-month or per-treated-member–per-month costs as well.

The hypothetical sample analysis presented in this section highlights many of the key features that should be included in the user interface of any budget-impact analysis. User interfaces should also include a list of full references for each source cited in the model. Our sample analysis used hypothetical data and therefore does not include a worksheet of full references. The sample analysis does include several background sheets clearly displaying all of the calculations used to arrive at the analysis results, but these sheets are too large to show here. However, the full model is available as electronic supplementary material associated with this chapter. The online version can be used to view the full set of worksheets, the equations used to throughout the model, and the VBA code used for navigation and restoration of default values on the input worksheets.

Model Settings

Setting	Value
Total number of persons in the health plan:	1,000,000
Total number in plan receiving COPD treatment (existing patients):	37,000
Total number beginning COPD treatment each year (new patients):	2,000

Budget-Impact Analysis Results

Outcome	Current Year	Year 1	Year 2	Year 3	Year 4	Year 5
Annual Cost Outcomes						
Scenario 1: Drug A and Drug B only						
Drug costs: Drug A	$35,520,000	$36,161,280	$36,693,389	$37,128,296	$37,477,259	$37,750,746
Drug costs: Drug B	$59,940,000	$61,022,160	$61,940,473	$62,712,489	$63,354,519	$63,881,618
Drug costs: Drug C	$0	$0	$0	$0	$0	$0
Total drug costs	$95,460,000	$97,183,440	$98,633,862	$99,840,786	$100,831,778	$100,632,364
COPD care costs	$277,500,000	$299,655,000	$319,285,330	$336,584,802	$351,747,329	$364,962,943
Total costs	$372,960,000	$396,838,440	$417,919,192	$436,425,588	$452,579,107	$466,595,308
Scenario 2: Drug C joins the market						
Drug costs: Drug A	$35,520,000	$32,545,152	$29,354,711	$25,989,808	$22,486,355	$18,875,373
Drug costs: Drug B	$59,940,000	$54,919,944	$49,552,379	$43,898,743	$38,012,712	$31,940,809
Drug costs: Drug C	$0	$10,848,384	$22,030,525	$33,477,881	$45,131,680	$56,941,900
Total drug costs	$95,460,000	$98,313,480	$100,937,615	$103,366,431	$105,630,747	$107,758,082
COPD care costs	$277,500,000	$299,266,500	$317,843,984	$333,587,342	$346,837,456	$357,914,488
Total costs	$372,960,000	$397,579,980	$418,781,599	$436,953,773	$452,468,203	$465,672,570
Budget impact						
Pharmacy budget impact	$0	$1,130,040	$2,303,753	$3,525,645	$4,798,969	$6,125,718
COPD care budget impact	$0	-$388,500	-$1,441,346	-$2,997,460	-$4,909,873	-$7,048,455
Total budget impact	**$0**	**$741,540**	**$862,407**	**$528,185**	**-$110,905**	**-$922,737**
Health Outcomes						
Scenario 1: Drug A and Drug B only						
Number Alive	37,000	37,668	38,230	38,697	39,080	39,389
% with Moderate COPD	50.0%	47.5%	45.4%	43.6%	42.1%	40.8%
% with Severe COPD	40.0%	39.7%	39.3%	38.9%	38.4%	38.0%
% with Very severe COPD	10.0%	12.8%	15.3%	17.5%	19.5%	21.2%
Scenario 2: Drug C joins the market						
Number Alive	37,000	37,668	38,233	38,712	39,119	39,466
% with Moderate COPD	50.0%	47.6%	45.6%	44.1%	42.9%	42.0%
% with Severe COPD	40.0%	39.7%	39.3%	38.8%	38.4%	37.9%
% with Very severe COPD	10.0%	12.7%	15.1%	17.1%	18.7%	20.1%

All outcomes presented are undiscounted, in alignment with the recommendations for budget-impact analysis.

Fig. 10.6 Budget-impact results worksheet

Exercises

Exercise 10.1 Choose two types of software that may be used to program a budget-impact analysis. Compare and contrast the advantages and disadvantages of the two software packages. When would you use one software over the other to program the budget-impact analysis?

Exercise 10.2 A new antibiotic has recently been approved as a first-line treatment for sinusitis. This new antibiotic is unique in that it is anticipated that bacteria will not develop resistance to it. Think about the modeling approach that would be developed for examining the budget impact of this new antibiotic. What type of software would you use to develop a budget-impact model and why?

Exercise 10.3 A new drug getting ready to launch for treating rheumatoid arthritis is expected to be a blockbuster, and a lot of new patients are expected to seek out this treatment because it has been shown to eliminate all symptoms with very few adverse effects. To examine the value for money (i.e., cost-effectiveness) of this new drug, the manufacturer developed a patient-level simulation model. What type of software would you use to develop a budget-impact model and why?

Exercise 10.4 A budget-impact analysis was created for a health plan. The input parameters, their values and sources, and the results of the analysis are presented in the tables below. Create and present introductory information about the budget-impact analysis such that it is easy for the user to understand the structure of the budget-impact analysis, its objective, and how to use the model. Develop this introductory information in software of your choosing. Discuss what features were created and why.

Inputs

Parameter	Value	Source
Health plan population	1 million lives	Known with certainty by health plan
Incidence of condition	1%	Published literature
Percentage of patients with condition who are treated	90%	Known with certainty by health plan
Current market share		
Drug 1	50%	Manufacturer estimate
Drug 2	50%	Manufacturer estimate
New drug	0%	Manufacturer estimate
Projected market share: year 1		
Drug 1	45%	Manufacturer estimate
Drug 2	45%	Manufacturer estimate
New drug	10%	Manufacturer estimate
Drug costs		
Drug 1	$100	Known with certainty by health plan
Drug 2	$125	Known with certainty by health plan
New drug	$150	Known with certainty by health plan
Cost per hospitalization	$1000	Published literature
Hospitalizations per year		
Drug 1	2.00	Published literature
Drug 2	1.75	Published literature
New drug	1.50	Published literature

Results

Costs/outcomes	Budget scenario without new drug	Budget scenario with new drug
Drug costs	$1,012,500	$1,046,250
Other medical costs	$16,875,000	$16,537,500
Total costs	$17,887,500	$17,583,750
Hospitalizations	16,875.0	16,537.5

Exercise 10.5 Consider the example in Exercise 10.4 and the six-step process for developing a budget-impact analysis. In software of your choosing, create a presentation of the derivation of the eligible population. Ensure users can enter their own values with ease. Discuss what features were created and why.

Exercise 10.6 Consider the example in Exercise 10.4 and the six-step process for developing a budget-impact analysis. In software of your choosing, create a presentation of the current and future treatment mix. Ensure users can enter their own values with ease. Discuss what features were created and why.

Exercise 10.7 Consider the example in Exercise 10.4 and the six-step process for developing a budget-impact analysis. In software of your choosing, create a presentation of the drug and condition-related costs, along with corresponding resource use. Ensure users can enter their own values with ease. Discuss what features were created and why.

Exercise 10.8 Consider the example in Exercise 10.4 and the six-step process for developing a budget-impact analysis. In software of your choosing, create a presentation of the base-case results. Discuss what features were created and why.

Exercise 10.9 Given the budget-impact analysis presented in Exercise 10.4 and an alternative set of values for various parameters as outlined below, create a presentation of scenario and sensitivity analyses and their results in software of your choosing. Discuss what features were created and why.

Parameter	Current value	New value
Health plan population	1 million lives	2 million lives
Incidence of condition	1%	0.5%
Percentage of patients with condition who are treated	90%	85%
Current market share		
Drug 1	50%	45%
Drug 2	50%	55%
New drug	0%	0%
Projected market share: year 1		
Drug 1	45%	40%
Drug 2	45%	40%
New drug	10%	20%
Drug costs		

Parameter	Current value	New value
Drug 1	$100	$125
Drug 2	$125	$150
New drug	$150	$150

Exercise 10.10 A manufacturer is developing a budget-impact analysis for a new drug that will be launching in the next few months. As a budget holder, you have received budget-impact analyses from this manufacturer before and have found the models to be thorough, appropriate for the problem, and well-constructed. As a result, what are some of the features that you will be looking for with respect to the budget-impact analysis that the manufacturer will present to you this time? Discuss how the choice of software used to program this budget-impact analysis might affect these issues.

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Chapter 11
Reporting Budget-Impact Analyses

Josephine Mauskopf and Stephanie Earnshaw

Abstract Budget-impact analyses can be presented in reports, articles published in peer-reviewed journals, or interactive models programmed in software such as Microsoft Excel. For all types of presentations, reporting of the budget-impact analysis should follow the general standards from the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) for economic evaluation analysis (Husereau et al. Value Health 16(2):e1–e5, 2013). These standards suggest that an economic evaluation be presented with sufficient detail that an interested researcher could reproduce the computer program and replicate the results of the analysis when using the described approach and input data provided. From this guidance, the following elements should be included for reporting budget-impact analyses: a complete method summary including the modeling approach; assumptions, values, and data sources (including derivations where relevant) for all input parameter values; comprehensive results comprising base-case aggregated and disaggregated results presented in tables or figures for the treatment mix with and without the new drug and the difference between them; extensive scenario and sensitivity analyses; and a discussion presenting conclusions along with strengths and limitations of the analysis.

Keywords Budget-impact analysis • Model reporting • Model structure diagram • Model assumptions • Input parameter values • Results

Chapter Goal
To show how to present the budget-impact analysis methods and results to budget holders as an interactive computer model or in a written report or in a published article in a format that allows budget holders to estimate the likely budget impact for their own jurisdiction.

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11.1 Introduction to Reporting Economic Evaluations

The results of the budget-impact analysis for a new drug[1] can be presented in a variety of formats, such as models, reports, or publications. For example, the National Institute for Health and Care Excellence (NICE) costing templates are generally available to budget holders and to the general public as interactive Excel-based files with worksheets presenting the model results using national or regional input parameter values. The Excel files also include worksheets explaining the model structure, sources, and derivation of the input parameter values and assumptions. These models are designed so that regional users can enter their own data to generate estimates for their own region.

An interactive Excel-based model can be made available to budget holders with an embedded technical report or user manual in Microsoft Word or PDF formats. These embedded documents may present a detailed description of the model structure, sources, and derivation of the default input parameter values and assumptions as well as the results using default input values. The user manual should also present instructions for users to navigate through the model and enter alternative inputs or assumptions to generate budget-impact estimates for their health plan or jurisdiction.

The budget-impact analysis model structure, inputs and their values, assumptions, and results may also be presented in a dossier for submission to budget holders or in an article for submission to a peer-reviewed journal.

For all types of presentations, reporting of the budget-impact analysis should follow the general standards from the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) for economic evaluations (Husereau et al. 2013). These standards suggest that an economic evaluation be presented with sufficient detail that an interested researcher could reproduce the computer program and replicate the results of the analysis when using the model structure, assumptions, and input values provided.

In order to achieve this level of transparency for the budget-impact analysis, the following elements should be included in all the different presentation formats listed above:

- Objective of the analysis
- Description of the analytic approach (i.e., model structure) along with a model structure diagram
- List of all structural assumptions made within the analysis
- Values and data sources (including derivations where relevant) or rationale for assumptions for all input values used for deriving the following:
  - Eligible population size and relevant descriptors
  - Treatment shares
  - Drug safety and efficacy outcomes
  - Drug-related and disease-related costs

[1] In this chapter, we make the simplifying assumption that the budget-impact analysis is based on the introduction of a new drug to the current mix of drugs for treatment of a condition. Changes in our recommended approaches to estimate the budget impacts of other types of healthcare interventions (i.e., vaccines, diagnostics, surgery, and devices) are discussed in Chap. 13.

- Base-case results presented in tables and figures for the treatment mix with and without the new drug and the difference between them:
  - Annual disaggregated costs (e.g., drug acquisition, diagnostic testing, administration, monitoring and side effects, and other condition-related costs) per person and for the reimbursement-eligible or total condition population
  - Annual total costs for the reimbursement-eligible or total condition population
  - Cumulative total costs for the reimbursement-eligible or total condition population over the analysis time horizon (optional)
  - Per-health-plan-member aggregated and disaggregated costs (if applicable)
  - Annual health outcomes and healthcare and other resource uses (optional)
- Results of extensive scenario analyses and one-way sensitivity analyses for the treatment mix with and without the new drug and the difference between them:
  - Annual total and disaggregated costs for the reimbursement-eligible or total condition population
- Study findings
  - Summary of findings and conclusions
  - Strengths and limitations of the analysis, including extent to which the analysis is validated (face validity and internal and external validity)

In Box 11.1, we present a statement made by two budget holders about their desired presentation of the results of budget-impact analyses.

Box 11.1 Statement of Budget Holder Needs for Economic Modeling Reports (Watkins and Danielson 2014, Page 3)

An excellent summary of a budget holder's reporting needs for a budget-impact analysis is the statement by Watkins and Danielson (2014) in their editorial commenting on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Budget Impact Task Force report (Sullivan et al. 2014):

> Modeling reports should clearly and succinctly describe methods, epidemiology, disease burden, and clinical impact. An interactive easily understood version of the model should be provided by using common spreadsheet software, rather than requiring the user to purchase special software. Graphs and figures facilitate user understanding and support presentation of the results by the user to others. Tornado diagrams are very useful to identify key model drivers, and users can focus on accurate estimate of these inputs. We recommend that users reject [budget-impact analyses] lacking such documentation because such omissions directly call into question the overall transparency and validity of the model. (Watkins and Danielson 2014)

11.2 Reporting the Budget-Impact Analysis

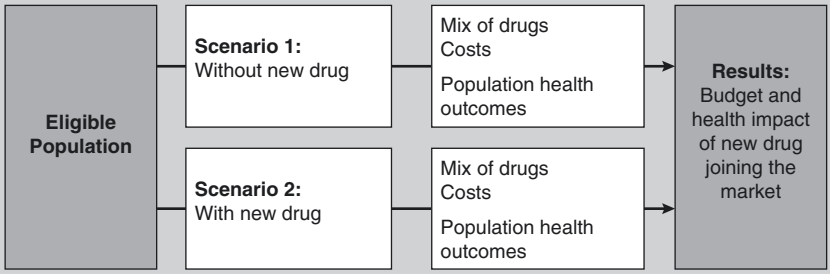
11.2.1 Model Structure Description

A description of the modeling approach is a very important part of the budget-impact analysis report. Frequently, the modeling approach can best be presented through the development of a model structure diagram to provide a simple representation of the analysis calculations. In a report, this diagram can then be accompanied by a brief overview of the key structural features of the model and the flow of patients through the model.

In Box 11.2, we present one general and three condition-specific examples of model structure diagrams.

Box 11.2 Examples of Model Structure Diagrams

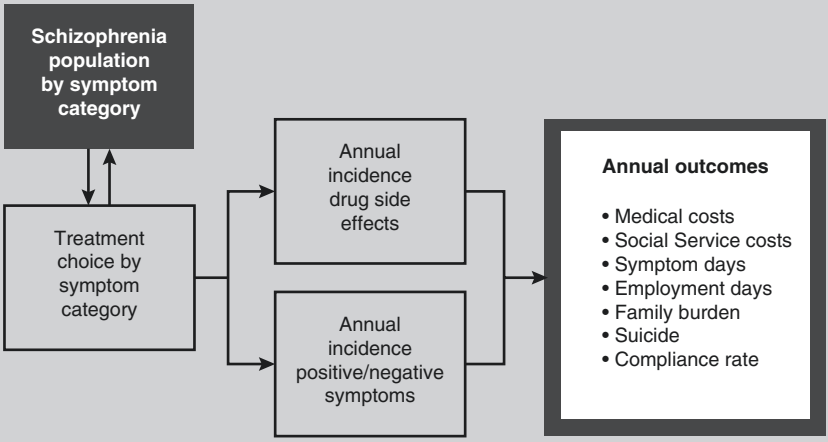
Generic model structure diagram for a budget-impact analysis



A generic approach to a budget-impact analysis is presented above. In this model, we start with a population of patients who are eligible for treatment. With this eligible population, we compare two budget scenarios: one without the new drug and one with the new drug. Each budget scenario will have its own mix of drugs in which costs and population-based health outcomes will be applied. These costs and outcomes will be compiled and compared so that the budget and health impact can be presented.

In a budget impact analysis for schizophrenia illustrated below, Mauskopf et al. (2002) starts with a population of patients with schizophrenia within different symptom categories who seek treatment during a 1-year period. Patients are given different treatments based on their symptom category. This combination of treatments dictates the incidence of side effects and incidence of positive or negative symptoms. These in turn dictate the annual outcomes for costs, symptom and employment days, family burden, suicide, and compliance rates. These costs and outcomes are presented for a 3-year period in which only typical antipsychotic drugs are given and for years 1, 2, and 3 in which atypical antipsychotic drugs enter the market.

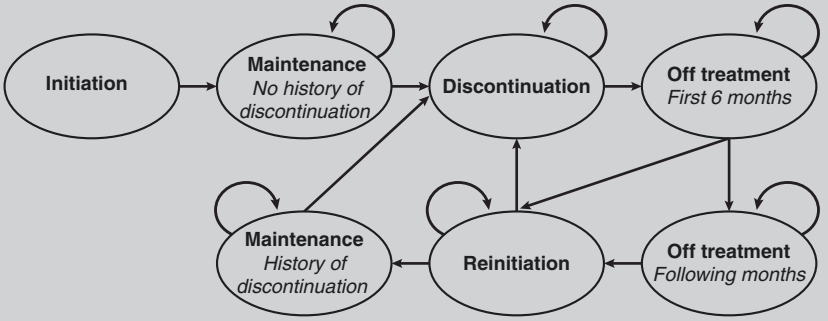
Model structure diagram for a budget-impact analysis using a cost-calculator model for new drugs for the treatment of schizophrenia (Mauskopf et al. 2002, Fig. 1).



Mauskopf et al. 2002, by permission of Oxford University Press

Asche et al. (2015) present a budget-impact analysis of buprenorphine/naloxone sublingual film compared with buprenorphine/naloxone tablets. To derive the drug costs and clinical outcomes over time for the budget-impact calculations, the Markov model as shown in the figure below was used.

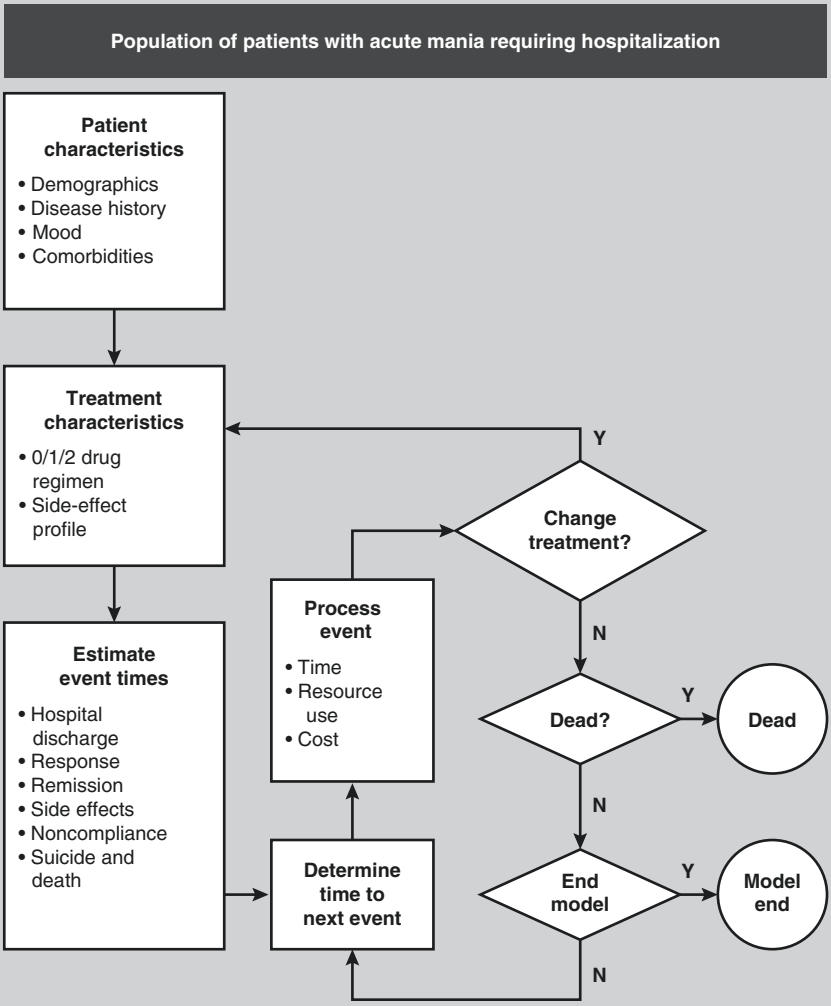
Model structure diagram for a budget-impact analysis using a Markov model for a drug treating opioid dependence (Asche et al. 2015, Fig. 1)



(Reproduced from Asche et al. (2015) with permission from Taylor & Francis Ltd. http://www.tandfonline.com)

Caro et al. (2006) present a budget-impact analysis of quetiapine monotherapy or combination therapy compared with other drug treatments for acute mania. To derive the drug costs and clinical outcomes over time for the budget-impact calculations, the discrete-event simulation model as shown in the figure below was used.

Model structure diagram for a discrete-event simulation budget-impact analysis for a new drug for treatment of mania (Caro et al. 2006, Fig. 1)



(Reproduced from Caro et al. (2006) with permission from Taylor & Francis Ltd. http://www.tandfonline.com)

11.2.2 Structural Assumptions

All budget-impact analyses make some structural assumptions about how the budget will be affected by adding the new drug to the health plan's formulary. These assumptions might be about the model structure or about specific input values.

Below are some examples of assumptions that are commonly needed for budget-impact analyses that can have a major impact on the results of the analysis.

- Populations included in the budget-impact analysis could be made up of different combinations of the following:
  - Reimbursement-eligible population
  - Total condition population
  - Incident population
  - Prevalent population
  - Both incident and prevalent populations

  Depending on the assumptions made, the included populations will be of different sizes, and the impact on the budget-impact estimates could be substantial.
- Changes in population size when the new drug is added to the treatment mix:
  - No change.
  - One-time change and the change occur immediately.
  - Changes occur each budget cycle over the analysis time horizon.

  Changes in the population size should be realistic given the impact of the new drug. The assumptions made could affect the budget-impact estimates.
- Changes in the population condition severity mix when the new drug is added to the treatment mix:
  - No change.
  - One-time change and the change occur immediately.
  - Changes occur every budget cycle over the analysis time horizon.

  Different assumptions about condition severity mix will affect the estimates of condition-related costs.
- Treatment share for the new drug over the analysis time horizon:
  - All patients switch to the new drug.
  - Treatment shares stay constant over time.
  - Treatment shares increase over time.

  The assumptions made about treatment shares for the new drug will significantly affect its budget impact.
- Changes in the treatment shares of current treatments when the new drug is added to the treatment mix:
  - Changes occur every budget cycle over the analysis time horizon, taking treatment shares equi-proportionately from all current treatments.
  - Changes occur every budget cycle over the analysis time horizon, taking treatment shares equi-proportionately only from drugs in a specific class.
  - Changes occur every budget cycle over the analysis time horizon, taking treatment shares equi-proportionately from branded drugs.

  - Changes occur every budget cycle over the analysis time horizon, taking treatment shares from one specific drug.

  The results of a budget-impact analysis are typically very sensitive to the assumptions made about from which current treatments the new drug's treatment share is taken.

- Percentage of reimbursement-eligible or total condition population who are receiving treatment at any time. An assumed higher percentage than that which actually occurs will overestimate the budget impact and vice versa.

These assumptions, preferably including a rationale for them, should be presented clearly in the interactive computer program as well as in a table in a report or publication.

In Box 11.3, we present a hypothetical set of structural assumptions with an associated rationale for each assumption as well as an example in a published budget-impact analysis of immunotherapy for allergy to grass pollen.

Box 11.3 Examples of Structural Assumptions and Rationale

The table below provides a hypothetical set of assumptions along with their rationale.

Hypothetical set of assumptions and rationale

Structural element	Assumption	Rationale
Population incidence rate	Constant each year	Based on national data for the last 5 years
Population prevalence rate	Changes with introduction of new drug because of better efficacy leading to longer time on treatment	Based on clinical trial data for the new drug
Proportion of eligible population being treated	Constant each year but higher with new drug in the treatment mix because of increased options or perceived more effective treatment	Assumption based on expert opinion
Treatment mix without new drug	Constant over analysis time horizon	No other new drugs anticipated and no generic drug entry during analysis time horizon
Treatment share for new drug over analysis time horizon	Increasing each year	Due to both increasing uptake rates for new patients and increasing number of patients in their second, third, etc. year on therapy because of increased efficacy and/or safety with the new drug; uptake rate estimates based on treatment share changes for new drugs introduced in previous years

Structural element	Assumption	Rationale
Source from which treatment share will be taken for new drug	Equi-proportional from all currently used drugs or only from branded drugs or only from specified class of drugs	Assumption based on expert opinion and drug class of the new drug
Drug costs	Constant over analysis time horizon	No generic entry or other new drugs anticipated
Dosing for new drug	As stated in the label or observed in the clinical trials	No real-world data available
Condition-related costs included	Only those likely to change within the analysis time horizon	Based on clinical trial data

The table below presents the structural and input assumptions used for a new drug treatment along with a description of their source or rationale.

Structural assumptions for immunotherapy products for treatment of grass pollen-induced allergic rhinoconjunctivitis (Rønborg et al. 2012, Table 1)

Overall assumptions	Details
Duration of treatment	Patients are treated for 3 years according to the summary of product characteristics
Immunotherapy treatment and visits	Year 1: Treatment is initiated by two consultations (i.e., administration of first tablet in the clinic and investigation of desired treatment effect approximately 1 month later). Initial consultations are followed by an additional follow-up consultation
	Years 2 and 3: Two follow-up consultations per year
	In total, seven consultations per treatment course (3 years)
Treatment setting	Initiation of treatment takes place either at the general practitioner's office, at medical specialist in a private clinic, or at medical specialist in a hospital setting. All follow-up consultations take place at the general practitioner's office
Additional medical supervision	No peak flow measurements are performed.
Compliance	Compliance is set to 80%[a]
Package size	Treatment is based on packs with 100 tablets and packs with 30 tablets

Reprinted from Rønborg et al. (2012) with permission from Dove Medical Press, Ltd.
[a]Based on experiences from daily practice in Denmark

11.2.3 Input Parameters and Their Values

In addition to the structural assumptions, a report, publication, or interactive budget-impact analysis computer program should include the full set of default input values. These values can be subdivided into three categories:

- Those that are assumed values for the jurisdiction, including patient characteristics and other inputs such as age distribution, that are likely to be known with certainty for each jurisdiction
- Those that are based on observed data, such as event rates and costs for condition-related outcomes and side effects
- Those that are based on general assumptions, such as current and/or future values for costs, outcomes, treatment mix, and reimbursement-eligible population size, that are not likely to be known with certainty for each jurisdiction

All inputs should be presented within the interactive Excel program as well as within the analysis report or publication with a reference to the source or rationale for the values presented. Mean (not median) values should be used for base-case estimates. Plausible ranges or alternative values should be used for sensitivity or scenario analyses. When the input value is not taken directly from a cited source but derived using a calculation, the calculation should be presented in sufficient detail that the user could reproduce that calculation using the original data source.

The inputs for which values may be assumed for health plan and patient characteristics include the following that are likely to vary among the budget holders but may also be known with certainty by the health plans:

- Age and sex distribution of their covered population and expected changes to the age and sex distribution over the analysis time horizon independent of changes in the treatment mix
- Incidence and prevalence of the condition in the region of interest
- Condition severity or treatment history (e.g., number of treatment failures) mix of their covered population currently and historically (this information may not be readily accessible for the budget holder)
- Current treatment mix and drug acquisition, administration, and monitoring costs
- Planned restrictions on the use of the new drug

In Box 11.4, we present an example of health plan demographic and condition epidemiology input values for a new drug for advanced non-small cell lung cancer.

Box 11.4 Health Plan Demographics and Condition Epidemiology
In the Bajaj et al. (2014) budget-impact analysis for alternative treatments for advanced treatment of advanced non-small cell lung cancer (NSCLC), estimates of the expected annual number of new patients with advanced NSCLC eligible for the new drug were calculated for a hypothetical health plan with 500,000 members (see table below). The age and sex distributions were used

and assumed to be the same as the USA population with the exception of those over age 65 years, where only 25% were assumed to be enrolled in the plan. Surveillance, Epidemiology, and End Results (SEER) incidence rates were used to estimate the incidence of advanced NSCLC, and published studies were used to estimate the proportion of those with advanced NSCLC eligible for the new drug.

Advanced NSCLC patient population estimation (Bajaj et al. 2014, Table 1)

	Health plan age and sex distribution	Number of patients by age and sex in health plan	Incidence of advanced NSCLC (per 100,000 persons)	Expected annual new advanced NSCLC patients		
				All patients	Treatment eligible: EGFR+, squamous	Treatment eligible: EGFR+, nonsquamous
Men						
≤44 years	33.85%	169,259	1.02	1.73	0.01	0.20
45–54 years	7.85%	39,244	23.03	9.04	0.06	1.06
55–64 years	6.54%	32,719	77.60	25.39	0.17	2.97
65+ years	1.60%	7995	208.33	16.66	0.11	1.95
Women						
≤44 years	32.95%	164,764	1.01	1.66	0.01	0.19
45–54 years	8.09%	40,455	17.48	7.07	0.05	0.83
55–64 years	7.02%	35,117	49.48	17.38	0.11	2.03
65+ years	2.09%	10,449	120.34	12.57	0.08	1.47
Total	100.0%	500,000	17.89	91.50	0.60	10.70
Total expected annual treatment-eligible patients						11.3

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Note: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2012 Sub (2000–2010) <Katrina/Rita Population Adjustment>, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission. The incidence rates are calculated from the crude incidence rates and reported for the following age groups: ≤44, 45–54, 55–64, and 65+ years. This model consists of advanced-stage NSCLC, which is defined as stages IIIB–IV. The ICD-O-3 codes for non-small cell (8000–8040, 8046–8245, and 8247–9989) are derived by excluding the codes for small cell (8041–8045, 8246) from all the ICD-O-3 codes (International Agency for Research on Cancer 2007)

DCCPS Division of Cancer Control and Population Sciences, *EGFR* epidermal growth factor receptor, *ICD-O-3* International Classification of Diseases for Oncology, Third Edition, *NSCLC* non-small cell lung cancer

Inputs based on observed data will include information about the efficacy and associated side effects for all the drugs in the treatment mix and the daily doses used. In addition, current condition-related outcomes that can be translated into condition-related costs, not including the costs for drugs in the treatment mix, might also belong in this category and need to be presented to the user of the analysis.

In Box 11.5, we present examples of two input tables presenting clinical and cost inputs with data sources from a budget-impact analysis of a new drug combination for advance pancreatic cancer.

Box 11.5 Clinical Inputs and Costs for a Budget-Impact Analysis of a New Drug Combination for Advanced Pancreatic Cancer

Danese et al. (2008) estimate the budget impact of adding erlotinib to current therapy for advanced pancreatic cancer. Patients eligible for erlotinib are currently treated with gemcitabine only. As a result, budget scenarios were (1) treatment with gemcitabine alone compared with (2) 40% treated with erlotinib + gemcitabine and 60% treated with gemcitabine alone. In the table below, the authors present the adverse event rates with monotherapy and combination therapy based on information presented in the erlotinib package insert, per event costs to treat each adverse event based on assumed treatment algorithms, and the unit costs.

Clinical trial results and adverse event costs in patients with locally advanced, nonresectable, or metastatic pancreatic cancer (100-mg/d cohort) (Danese et al. 2008, Table 2)

Parameter	Erlotinib + gemcitabine (n = 259)	Gemcitabine monotherapy (n = 2S6)	Cost per adverse event, USA $ (2006)
Treatment duration, median, week	15.7	12.3	n/a
Grade 3/4 adverse events			
Fatigue	16%	15%	115
Infection	16%	11%	7242
Abdominal pain	10%	13%	4597
Vomiting	8%	5%	4597
Nausea	7%	7%	4597
Anorexia	7%	6%	842
Diarrhea	6%	2%	639
Dyspnea	6%	5%	115
Bone pain	5%	2%	839
Rash	5%	1%	185
Constipation	4%	6%	2413
Interstitial lung disease	3%	0%	6369
Cerebrovascular accident	2%	0%	6680
Myocardial infarction	2%	1%	8576
Thrombocytopenia	1%	0%	7045

In the table below, the authors present the unit costs and data sources for each of inpatient stays and outpatient visits and other drug-related costs used for the treatment of adverse events.

Unit cost of resources in patients with locally advanced, nonresectable, or metastatic pancreatic cancer (Centers for Medicare and Medicaid Services 2006; Danese et al. 2008, Table 3)

Resource	Cost, USA $ (2006)	Reference
Outpatient visit	115	CPT 99215[a]
Inpatient stay		
Myocardial infarction	8,313	DRG 121, circulatory disorders with acute myocardial infarction and major complications discharged alive[b]
Interstitial lung disease	6,107	DRG 92, interstitial lung disease with complications and comorbidities[b]
Digestive disorder	4,334	DRG 182, esophagitis, gastroenteritis, and miscellaneous digestive disorders with complications and comorbidities[b]
Infection	6,980	Blend of DRG 416, septicemia ($8,642), and DRG 89, pneumonia ($5,317)[b]
Nutritional disorders	3,747	DRG 296, nutritional and metabolic disorders with complications or comorbidities[b]
Thrombocytopenia	6,782	DRG 397, coagulation disorders ($6,691), and physician fees for CPT 36514, therapeutic plasma exchange ($91.53)[b]
Cerebrovascular accident	6,417	DRG 14, intracranial hemorrhage or cerebral infarction[b]
Malignancy	6,982	DRG 203, malignancy of hepatobiliary system or the pancreas[b]
Consult	187	CPT 99255[a]
Follow-up	76	CPT 99233[a]
Loperamide hydrochloride (2 mg)	4	30-count bottle[c]
Clindamycin gel (Cleocin T[d]) (60 g)	70	60-g tube[c]

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CPT Current Procedural Terminology, *DRG* diagnosis-related group
[a]2006 Medicare physician fee schedule
[b]2006 Medicare payment rate
[c]Wholesale acquisition cost
[d]Trademark of Pfizer, Inc., New York, New York

The final set of input values that should be presented are based on assumptions because their actual values cannot be or have not been observed. These input values are based on assumptions about the future using expert opinion or imputation from previous changes in treatment patterns for the condition of interest or related conditions. These may also include input values about costs that may be based on assumptions or treatment algorithms rather than observed data. These include the following:

- Forecasted treatment shares for the new drug over the analysis time horizon
- Redistribution of treatment shares for currently used drugs or expected new entrants to the treatment mix, including generic drugs and new chemical entities
- Costs of treating side effects and costs and health outcomes associated with new entrants to the treatment mix

In Box 11.6, we present an example of the presentation on these types of inputs where the assumptions about eligible population and treatment shares with and without the addition of a new drug for smoking cessation are presented for the budget-impact analysis time horizon.

Box 11.6 Changes in Treatment Shares over Time with and without the New Drug in the Treatment Mix

In this budget-impact analysis, Taylor et al. (2009) present the percentage of smokers attempting to quit annually based on results of a national UK survey and market (treatment) shares of pharmacological treatments with and without varenicline in the treatment mix based on Pfizer market projections. The percentage of those who attempt to quit each year who use a pharmacological treatment is assumed to be 25%, but no source is provided for this assumption.

Marketplace dynamics in each of the 5 years of the model (Taylor et al. 2009, Table 3)

	2007	2008	2009	2010	2011
Percentage of smokers attempting to quit annually					
18–24 years old	21.8%	22.6%	23.4%	24.2%	25.1%
25–44 years old	35.2%	36.6%	37.9%	39.2%	40.6%
45–64 years old	24.9%	25.8%	26.8%	27.7%	28.6%
>65 years old	13.5%	14.0%	14.5%	15.0%	15.5%
Market shares without varenicline[a]					
Bupropion	4.36%	4.54%	4.71%	4.89%	5.06%
Nicotine replacement therapy	95.64%	95.46%	95.26%	95.11%	94.94%
Market shares with varenicline[a]					
Varenicline	11.09%	16.01%	20.94%	25.86%	30.79%
Bupropion	4.00%	3.60%	3.21%	2.81%	2.42%
Nicotine replacement therapy	84.91%	80.38%	75.85%	71.33%	66.80%

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[a]Pfizer market projections

11.2.4 Reporting the Base-Case Budget Impact

Results of the analysis should be presented after the presentation of the model structure, structural assumptions, input parameters and their values, and data sources and derivations. These may be presented in different worksheets in the interactive

computer program and in the text or appendices of the report or publication. Since the users of budget-impact analyses have different perspectives and are interested in different types of outcomes, the presentation of the results should reflect these multiple perspectives. Thus, results should be reported both with and without the new drug in the treatment mix for the population costs, resource use, and health outcomes. The costs may be disaggregated by the following cost categories:

- Drug acquisition costs
- Drug diagnostic testing costs
- Drug administration costs
- Drug monitoring costs
- Drug side effects costs
- Other condition-related costs

Total drug-related costs and total drug- and condition-related costs should also be presented. The per-member per-month costs can also be presented for the aggregated and disaggregated costs for countries with a private health insurance market.

Resource use outcomes might include number of hospitalizations, number of hospital days, and number of physician visits each year of the budget-impact analysis time horizon. Health outcomes might include deaths, symptom days, or relapses each year of the budget-impact analysis time horizon.

The difference between the annual costs, resource use, and health outcomes with and without the new drug in the treatment mix should be presented. The interactive computer program should be designed so that the user can choose which costs and other outcomes to look at, for how many years, and whether to look at the results in tabular or graphical format.

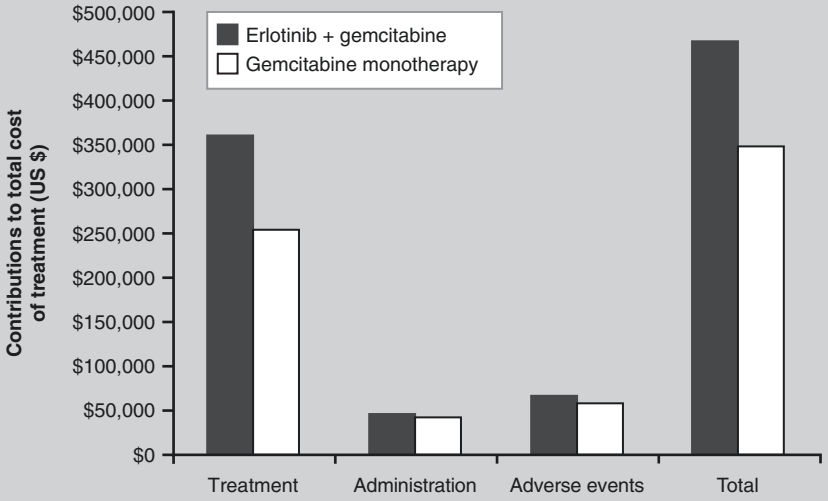
The costs and other outcomes should be presented for each year in the analysis time horizon. If desired, cumulative costs and other outcomes over the analysis time horizon can also be presented. These should be undiscounted since the budget-impact analysis is measuring cash flow rather than the time value of money for costs. If unit costs (e.g., drug, physician visit, hospitalization) for inputs are expected to change over time, changes in these expected costs should be included in the program. Changes might occur in each direction. For example, decreases in some drug costs might be expected as generic drugs enter the market, while increases in condition-related costs might be expected because of general inflation.

In Box 11.7, we present an example of the presentation of the results of a budget-impact analysis disaggregated by type of cost and in graphical and tabular formats.

Box 11.7 Disaggregated Results of a Budget-Impact Analysis in Graphical and Tabular Formats

Danese et al. (2008) estimated the budget impact of adding erlotinib to current therapy for advanced pancreatic cancer. Patients eligible for erlotinib were currently treated with gemcitabine only. As a result, budget scenarios were (1) treatment with gemcitabine alone compared with (2) 40% treated with erlotinib + gemcitabine and 60% treated with gemcitabine alone. The figure and table below present the results of the analysis in graphic and tabular formats, respectively.

Results for a new combination therapy for advanced pancreatic cancer (Danese et al. 2008, Fig. 3).



Budget impact of adding erlotinib to gemcitabine therapy for locally advanced, nonresectable, or metastatic pancreatic cancer in the base-case analysis for a health plan with 500,000 members. Results assumed erlotinib was used in 40% of gemcitabine-treated patients in the erlotinib + gemcitabine treatment strategy (Reprinted from Danese et al. 2008, Copyright 2008, with permission from Elsevier)

Budget-impact results in 24 patients with locally advanced, nonresectable, or metastatic pancreatic cancer (Danese et al. 2008, Table 4)

Budget component	Erlotinib + gemcitabine[a]	Gemcitabine monotherapy
Treatment	358,900	250,800
Administration	44,400	40,300
Side effects	63,400	55,600
Total	466,700	346,700
Difference	120,000	
Per member per month	0.020	

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Note: Values are 2006 USA dollars
[a]Results assumed erlotinib was used in 40% of gemcitabine-treated patients in the erlotinib + gemcitabine treatment strategy

11.2.5 Reporting the Scenario and Sensitivity Analyses

Finally, the results of the scenario analyses and one-way sensitivity analyses should be presented in tabular and/or graphical format. The following are examples of scenario analyses that should be presented:

- Alternative current patterns of drug use by the health plan
- Alternative projected rates of uptake for the new drug

- Alternative redistribution patterns from the current drug to the new drug
- Alternative health plan population characteristics, including age, sex, and condition incidence or prevalence rates
- Alternative restrictions on use planned by the health plan
- Alternative prices for the new drug

In Box 11.8, we present a hypothetical example of how to present the results of a scenario analysis when varying the estimated uptake rates for a new drug over the budget-impact analysis time horizon.

Box 11.8 Results of a Hypothetical Scenario Analysis Estimating the Budget Impact with Varying the Drug Uptake Rates

The budget-impact results are shown below for three different uptake scenarios for a new drug added to the treatment mix for a specific condition. In the health plan, we have assumed that 100 people are eligible for treatment, the total annual drug-related costs are $2000 (new drug), $1500 (drug A), $1000 (drug B), and $500 (drug C). We also assumed that the annual condition-related costs when taking drugs are $350 (new drug), $600 (drug A), $600 (drug B), and $1000 (drug C).

Results of scenario analyses for treatment mix with new drug

	Treatment shares before new drug (current scenario)	Scenario 1 with new drug[a]	Scenario 2 with new drug[b]	Scenario 3 with new drug[b]
Treatment share				
New drug	0%	10%	20%	10%
Drug A	20%	18%	20%	20%
Drug B	40%	36%	40%	40%
Drug C	40%	36%	20%	30%
Total drug-related costs	$90,000	$101,000	$120,000	$105,000
Total condition-related costs	$76,000	$71,900	$63,000	$69,500
Total drug- and condition-related costs	$166,000	$172,900	$183,000	$174,500
New drug scenarios vs. current scenario: drug costs only	N/A	$11,000	$30,000	$15,000
New drug scenarios vs. current scenario: condition costs only	N/A	−$4100	−$13,000	−$6500
New drug scenarios vs. current scenario: drug and condition costs	N/A	$6900	$17,000	$8500

N/A not applicable

[a]Assuming treatment shares for the new drug are taken equi-proportionately from all current drugs

[b]Assuming treatment shares for the new drugs are only taken from drug C

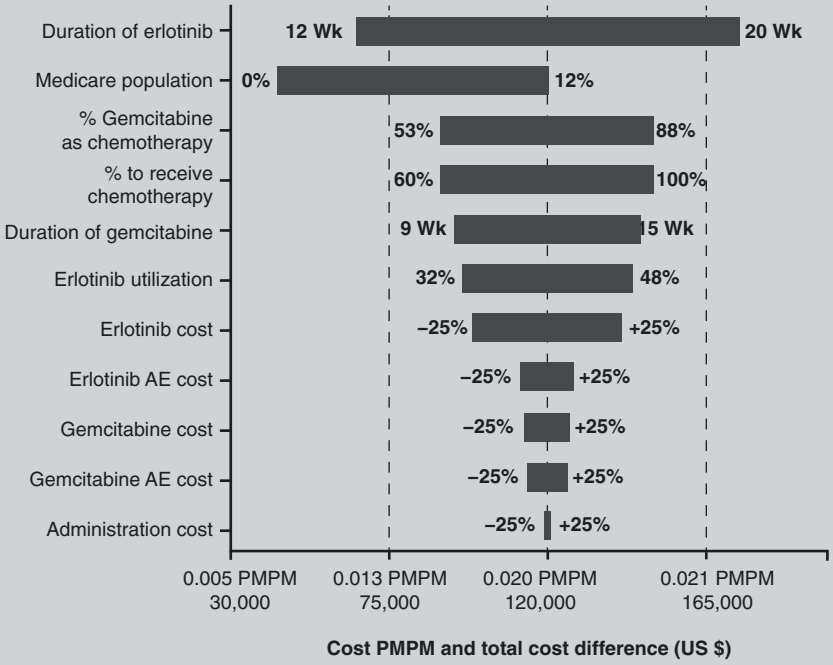
One-way sensitivity analyses can be presented in the form of tables or tornado diagrams both in interactive computer programs and in reports and publications. Tornado diagrams present the results in an easy-to-interpret format. Tornado diagrams should include the ranges tested in the analysis and indicate which bar represents which end of the range. The following are examples of input parameter values for which one-way sensitivity analyses should be presented:

- Inputs with observed variability (e.g., standard deviation or standard error of the mean) in efficacy rates for current and new drugs based on formal meta-analyses
- Inputs with observed variability in rates of side effects for current and new drugs based on formal meta-analyses
- Inputs with observed variability in rates of discontinuation for current and new drugs based on formal meta-analyses
- Inputs with observed variability in drug-related or condition-related costs

In Box 11.9, we present an example of a one-way sensitivity analysis presented in a tornado diagram.

Box 11.9 One-Way Sensitivity Analysis Results Presented as a Tornado Diagram for a New Combination Therapy for Advanced Pancreatic Cancer

Sensitivity of results expressed as either per-member per-month or total annual costs to assumed ranges of input parameter values (Danese et al. 2008, Fig. 4).



Sensitivity analyses: Total cost difference and cost per member per month (PMPM) between erlotinib + gemcitabine and gemcitabine monotherapy. *AE* adverse event. Values at the end of each bar indicate either the low and high values used or the change from the base-case. (Reprinted from Danese et al. 2008, Copyright 2008, with permission from Elsevier)

Danese et al. (2008) estimate the budget impact of adding erlotinib to current therapy for advanced pancreatic cancer. Patients eligible for erlotinib are currently treated with gemcitabine only. As a result, budget scenarios were (1) treatment with gemcitabine alone compared with (2) 40% treated with erlotinib + gemcitabine and 60% treated with gemcitabine alone. The figure above presents the one-way sensitivity analysis when changing treated population, treatment patterns, and drug-related costs. Although not presented in the standard manner, the figure shows the base case difference in pmpm and total costs on the midpoint of the x-axis of switching to a budget scenario with 40% on erlotinib + gemcitabine and 60% on gemcitabine from a budget scenario in which patients are only talking gemcitabine alone. The ranges used in the sensitivity analysis for each parameter are presented by the respective bar in terms of upper and lower bounds (e.g., duration of erlotinib) and increases and decreases in the base case parameter (e.g. erlotinib cost). The resulting difference in costs given the change in each parameter is found by observing where the end of the bar falls along the x-axis. For example, if erlotinib utilization is at 48% while all other parameters are at their base case values, the difference in total costs is about $140,000.

11.2.6 Reporting Model Validation

All validation of the model should be reported in the interactive computer program, report, and publication. In Chap. 9, we have described how to validate the budget-impact model, including establishing face validity and performing internal validation of the computer program used to estimate the budget impact and external validation of the results of the analysis. To the extent that these steps have been completed, they should be fully reported as shown in the examples in Chap. 9.

11.2.7 Reporting Other Population Outcomes

When the budget-impact analysis has included the impact of adding the new drug to the formulary on condition-related outcomes, the model developer will have estimated annual changes in population size, severity mix, and clinical outcomes. These changes will generally be associated with changes in resource use associated with changes in condition-related, clinical events attributable to the addition of the new drug as well as those that are drug-related, such as diagnostic testing, administration, monitoring, and side effects. The drug-related and condition-related outcomes will have been used to estimate their budget impact as previously described in Chaps. 5 and 6.

Estimates of changes in annual treated population size, clinical outcomes, and resource use can be very useful for healthcare budget holders. For example, estimates of a reduced number of hospital stays by the eligible population with the new

drug on the formulary could be useful to healthcare budget holders considering whether there is a need for expansion of hospital beds in their jurisdiction. In addition, estimates of the annual changes in clinical outcomes can be of value to healthcare budget holders who are trying to justify the addition of a new drug to the formulary that will increase annual budgets. Thus, where credible estimates are available and the changes in resource use or clinical outcomes occur during the analysis time horizon, the annual changes in treated population size, resource use, and health outcomes should also be presented as part of the budget-impact analysis.

In Box 11.10, we present the impact of a new salvage combination treatment regimen for highly treatment-experienced patients with HIV infection on total health care costs and on the number of people being treated, the annual number of hospital days, and the annual number of cases of cytomegalovirus infection, an opportunistic infection.

Box 11.10 Impact on Population Size, Hospital Bed Days, and Cytomegalovirus Infection Cases from a Hypothetical Budget-Impact Analysis of a More Effective Salvage Therapy for Highly Treatment-Experienced Individuals with HIV Infection (Mauskopf et al. 2016)

Mauskopf et al. (2016) present the budget impact of a new HIV treatment regimen indicated for highly treatment-experienced people with HIV infection for whom HIV treatment is failing. These estimates were generated using a Markov model of HIV disease progression assuming both incident and prevalent populations switching to the new treatment regimen. Outcomes include increased annual costs for antiretroviral therapy and decreased annual costs for condition-related costs as well as changes in the annual number of people being treated, the number of hospital days, and the number of cases of cytomegalovirus (CMV) infection, one of the opportunistic infections associated with late-stage disease. This presentation allows the budget holder to see the benefits associated with the additional healthcare expenditures.

Impact of new HIV treatment regimen on budget and on population size, hospital days, and CMV cases

	Change year 1	Change year 2	Change year 3	Change year 4	Change year 5
ART costs	$2.15 m	$3.53 m	$4.88 m	$5.68 m	$6.30 m
Other costs	−$0.71 m	−$0.46 m	$0.19 m	$0.42 m	$0.57 m
Total costs	$1.44 m	$3.07 m	$5.07 m	$6.10 m	$6.87 m
# of persons	25	50	75	90	102
Hospital days	−759	−686	−273	−146	−87
CMV cases	−10	−9	−4	−3	−2

ART antiretroviral therapy, *CMV* cytomegalovirus, *m* million

11.2.8 Reporting the Results of a Combined Cost-Effectiveness and Budget-Impact Analysis

Although the focus of this book is on budget-impact analysis, as mentioned in Chap. 7, budget-impact analyses may be developed in combination with cost-effectiveness analyses using the same computer program. There are several efficiencies with this approach:

- Many of the same model assumptions and inputs are used for both models. These include the drug- and condition-related costs and efficacy and safety of current and new drugs.
- Some outputs from the cost-effectiveness model might be needed as inputs for the budget-impact model, for example, the changes in condition-related symptoms and/or clinical events over time after beginning treatment with different drugs.
- There is convenience in having both calculations performed using a single piece of software.

A combined cost-effectiveness/budget-impact computer model will need to clearly report the model structure, structural assumptions, input values, and results for both the cost-effectiveness analysis and the budget-impact analysis. All components for both analyses need to be presented so that the reader can easily understand both analyses. This can be achieved by developing this type of model in modular format. Clearly, where the same input values are used for both types of analyses, they need only to be provided once. But all the additional input parameter values needed in a budget-impact analysis (population size and relevant descriptors, condition severity mix, and current and estimated treatment mixes with and without the new drug) should be presented in tables and denoted as specific to the budget-impact analysis. A description of how the model structure and assumptions are used for the budget-impact analysis can be presented separately or presented such that it is easy for the reader to understand how these components were adapted from the cost-effectiveness analysis to provide estimates of the budget impact. Since dossiers and journals typically allow for supplemental appendices of any length, there is no reason to abbreviate the reporting of either the cost-effectiveness or budget-impact model to meet dossier or journal page limits.

Exercises

Exercise 11.1 Obtain a presentation of a budget-impact analysis from the peer-reviewed literature. Compare the reporting of this analysis with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement checklist (Husereau et al. 2013). How well did this publication follow the checklist?

Exercise 11.2 Using the publication obtained in Exercise 11.1, critically evaluate each component within the title and abstract. What components of the checklist did the publication include and exclude?

Exercise 11.3 Using the publication obtained in Exercise 11.1, critically evaluate each component within the methods. What components of the checklist did the publication include and exclude?

Exercise 11.4 Using the publication obtained in Exercise 11.1, critically evaluate each component within the results. What components of the checklist did the publication include and exclude?

Exercise 11.5 A budget-impact analysis was created for a health plan. The parameters, their values, and sources included in the analysis and results are presented in the tables below. Write an abstract and title for this budget-impact analysis such that it follows the CHEERS guidance.

Inputs

Parameter	Value	Source
Health plan population	1 million lives	Known with certainty by health plan
Incidence of condition	1%	Published literature
Percentage of patients with condition who are treated	90%	Known with certainty by health plan
Current market share		
Drug 1	50%	Manufacturer estimate
Drug 2	50%	Manufacturer estimate
New drug	0%	Manufacturer estimate
Projected market share: year 1		
Drug 1	45%	Manufacturer estimate
Drug 2	45%	Manufacturer estimate
New drug	10%	Manufacturer estimate
Drug cost		
Drug 1	$100	Known with certainty by health plan
Drug 2	$125	Known with certainty by health plan
New drug	$150	Known with certainty by health plan
Hospitalization costs	$1000	Published literature
Hospitalizations per year		
Drug 1	2.00	Published literature
Drug 2	1.75	Published literature
New drug	1.50	Published literature

Results

Costs/outcomes	Budget scenario without new drug	Budget scenario with new drug
Drug costs	$1,012,500	$1,046,250
Other medical costs	$16,875,000	$16,537,500
Total costs	$17,887,500	$17,583,750
Hospitalizations	16,875.00	16,537.50

Exercise 11.6 Given the budget-impact analysis presented in Exercise 11.5, write a Methods section for a report such that it follows the CHEERS guidance.

Exercise 11.7 Given the budget-impact analysis presented in Exercise 11.5 and an alternative set of values for various parameters as outlined below, write a Results section for a report such that it follows the CHEERS guidance.

Parameter	Current value	New value
Health plan population	1 million lives	2 million lives
Incidence of condition	1%	0.5%
Percentage of patients with condition who are treated	90%	85%
Current market share		
Drug 1	50%	45%
Drug 2	50%	55%
New drug	0%	0%
Projected market share: year 1		
Drug 1	45%	40%
Drug 2	45%	40%
New drug	10%	20%
Drug cost		
Drug 1	$100	$125
Drug 2	$125	$150
New drug	$150	$150

Exercise 11.8 Assume that the budget-impact analysis as outlined in Exercise 11.5 was constructed for a population within the United States. This analysis now needs to be adapted for use in the United Kingdom. Discuss how the inputs and results would change and how reporting of this updated analysis would be presented with respect to the title/abstract, methods, and results.

Exercise 11.9 Discuss the importance of reporting budget-impact analyses and why following a guidance document is useful. What may be some disadvantages of following guidances?

Exercise 11.10 Results of a budget-impact analysis are presented in Box 11.10. How else might the results of this budget-impact analysis be presented? What other types of results could be presented? Write a report presenting these results along with tabular and graphical presentations of the results.

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Chapter 12
Additional Pragmatic Topics

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Abstract A variety of pragmatic issues can come up when developing budget-impact analyses. Some of these issues can have a substantial impact on drug budgets and can reverse the expected results. Therefore, payers and budget holders may require the consideration of some of these issues in the main analyses. In this chapter, we review three common pragmatic issues: (1) off-label drug use, (2) the impact of adherence and/or persistence, and (3) the importance of understanding the cost perspective. All of these issues should be carefully considered when developing budget-impact analyses for new drugs.

Keywords Budget-impact analysis • Off-label use • Adherence • Persistence • Costs • Accounting • Revenue

Chapter Goal
To provide an overview of three additional topics that might need to be considered when performing a budget-impact analysis: (1) whether and how to include off-label usage with current treatments and the new drug, (2) how to account for adherence and persistence to the new and current drugs, and (3) consideration of the type of costs to use within a budget-impact analysis.

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In this chapter, we consider three additional topics that might need to be considered when designing a budget-impact analysis.[1] These are the inclusion of off-label drugs, the effect of adherence and persistence to treatment on the budget-impact estimates, and selection of appropriate costs to include such as fixed or variable costs, charges, or reimbursement rates.

12.1 Off-Label Drug Use

Drugs are given labeled indications by regulatory agencies such as the United States Food and Drug Administration and the European Medicines Agency. These indications are the use of the drug for which the regulatory agencies have deemed it appropriate based on adequate demonstration of its safety and efficacy. Most prescription drugs will be used according to these labeled indications. However, there are cases in which prescription drugs are prescribed or used outside of the approved indication. This is often referred to as nonapproved or off-label use.

Off-label use may occur for two primary reasons. First, the drug may have been on the market and used for treating certain conditions for such a long time that regulatory agencies have not retrospectively reviewed the safety and efficacy of the drug within the condition due to limited availability of clinical trials according to today's standards. In these instances, the drug is considered beneficial by both physicians and patients perhaps based on belief, published results from real-world data, or small randomized controlled trials. A second reason that a drug may be used off label may be when a patient has exhausted all options with approved drugs without achieving effective relief. A physician may then prescribe a drug off-label for which clinical trials or published case series data are available for the indication, but the regulatory agencies have not approved such use due to need for additional trials, which the manufacture did not pursue because of perceived limited return on investment, limited beneficial effect, or other reasons.

When developing a budget-impact analysis, off-label drug use may be relevant. Perhaps the most common instance in which off-label drug use should be considered is when some of the drugs used in the current treatment mix for the condition of interest are being used off label. If there is reason to believe that the treatment shares of these drugs will change when the new drug is added to the treatment mix, then they should be included in the estimates of the current and new treatment mix (Sullivan et al. 2014). The data providing their treatment shares, dosing levels, and number of pills per day should be obtained using the same data sources as used for the on-label drugs if possible.

In Box 12.1, we present an example where only off-label drugs are currently used to treat a rare condition, neuromyelitis optica, and in Box 12.2, we present several other examples of off-label use of current drugs.

[1] In this chapter we make the simplifying assumption that the budget-impact analysis is based on the introduction of a new drug to the current mix of drugs for treatment of a condition. Changes in our recommended approaches to estimate the budget impacts of other types of healthcare interventions (i.e., vaccines, diagnostics, surgery, and devices) are discussed in Chap. 13.

Box 12.1 Prevention of Relapses in Neuromyelitis Optica: Use of Off-Label Drugs

Neuromyelitis optica (NMO) is a rare condition that results from inflammation and demyelination of both the optic nerve and the spinal cord. It is often misdiagnosed as multiple sclerosis, but the same drug treatments that are used for multiple sclerosis are not effective for NMO. Most patients have a relapsing remitting form of the disease, with each relapse associated with increasing permanent disability. For example, in those with relapsing disease, up to 50% may have blindness or paralysis in one or both legs within 5 years (Wingerchuk 2006).

There are currently no drugs indicated for the treatment of NMO. However, many immunosuppressive drugs indicated for other conditions have been tested in case series or small trials and have been shown to be effective at reducing the frequency of relapses and slowing the increase in disability over time. In addition, intermittent plasma exchange is an alternative treatment that has been shown to be effective. If a new drug were to be indicated for the treatment of NMO, the following treatments that might be displaced by this drug would all be off label (Sellner et al. 2010):

- Azathioprine
- Prednisolone
- Rituximab
- Cyclophosphamide
- Mitoxantrone
- Mycophenolate mofetil
- Intravenous immunoglobulin
- Methotrexate
- Intermittent plasma exchange

Treatment with combinations of these drugs may also be used. Treatment shares for current drug regimens could be obtained from observational database studies or expert opinion. Treatment shares for a new drug approved for NMO and changes in the treatment shares for the currently used drugs could be estimated based on expert opinion.

Box 12.2 Other Examples of Off-Label Use of Drugs (Walton et al. 2008)

Drug (brand name)	Approved indication in the United States	Common off-label use
Quetiapine (Seroquel)	Schizophrenia, acute treatment of manic episodes associated with bipolar I disorder (Seroquel extended release prescribing information 2013)	Bipolar disorder, maintenance
Warfarin (Coumadin)	Prophylaxis and treatment of venous thrombosis, pulmonary embolism, complications with atrial fibrillation, and cardiac valve replacement (Coumadin prescribing information 2011)	Hypertensive heart disease

Escitalopram (Lexapro)	Acute and maintenance treatment of major depressive disorder and acute treatment of generalized anxiety disorder (Lexapro prescribing information 2014)	Bipolar disorder
Montelukast (Singulair)	Prophylaxis and chronic treatment of asthma, prevention of exercise-induced bronchoconstriction, seasonal allergic rhinitis (Singulair prescribing information 1998–2012)	Chronic obstructive pulmonary disease
Celecoxib (Celebrex)	Osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain, primary dysmenorrhea (Celebrex prescribing information 2013)	Fibromatosis

However, a problem may arise with estimating the administration, monitoring, and/or condition-related costs associated with the off-label drug. Specifically, there may be limited data on efficacy or safety for the off-label drugs that are included in the current treatment mix as their impact may not have been examined in clinical studies. In addition, published information about the product, although available for other indications, may not give sufficient information to assess its administration or monitoring costs for people with the condition of interest. Thus, expert opinion might be needed to supplement the published and label data likely available for other indications for these off-label drugs.

Another way in which off-label use might need to be considered for the budget-impact analysis is when physicians may consider a new drug for uses other than those in the approved indication (i.e., expanded use of a new drug). In jurisdictions where such use is allowed, budget holders might be interested in obtaining estimates of this possible use, as was expressed by the authors of commentaries on the most recent International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force report on budget-impact analysis (Watkins and Danielson 2014; Goettsch and Enzing 2014) (see Chap. 2).

There are several problems with including off-label use for a new drug in the budget-impact analysis. First, if the analysis is being prepared by the product manufacturer, this might be viewed as off-label promotion and banned by the regulators. Second, just as we saw for the inclusion of other drugs that may be used off label, there be may be limited or no data available for the new drug in the off-label indications. The safety data from the approved indication might be transferrable to the off-label indications. However, if the drug has not been studied within the off-label indication, there will be no data on its safety, efficacy, or the relevant dosing for the off-label indications. Third, to include estimates of the budget impact of off-label use in a different condition would require consideration of this off-label indication in addition to the indicated condition. Thus, input data that are required for the approved indication, including treated population size, current treatment mix, costs, and efficacy and safety, are required in addition to input data for the other indication, which could be substantially different from the approved indication. For all these reasons, off-label use of the new drug is rarely included in budget-impact analyses.

12.2 Adherence and Persistence

When evaluating the economics of a specific drug, we typically gather evidence from well-controlled studies. These studies are controlled so that the proper evaluation of a drug's safety and efficacy can be measured.

We use these data to support the potential economic impact, whether it be to examine the drug's cost-effectiveness or budget impact. However, when taking the drug into the real world, adherence and persistence rates similar to those observed in a controlled trial setting may not be valid assumptions. Adherence and persistence to all drugs used for treatment are likely to be lower in a real-world setting, especially for chronic conditions where long-term treatment might be needed. Thus, the efficacy observed during the clinical trial may not translate into effectiveness in general practice. As a result, when estimating the impact that a new drug will have on a payer's budget, adherence and persistence may greatly affect both drug-related costs and condition-related costs.

12.2.1 Definitions

Before we examine the issues around incorporating adherence and persistence into budget-impact analysis, we need to define exactly what these terms refer to. Adherence is taking the medication as prescribed, while persistence is continuing on therapy. As an example, a patient is prescribed 10 mg of an antibiotic daily for 10 days. The patient takes only 5 mg per day for the 10 days. The patient in this case is only 50% adherent to the prescribed regimen. If the patient takes 10 mg per day, but then stops after 5 days, the patient is not persistent with the medication.

12.2.2 Impact of Adherence or Persistence on Costs

In order to more accurately assess the impact that a drug will have on a payer's budget, adherence and persistence might be considered. In actual clinical practice, poor adherence leads to suboptimal treatment. It not only decreases the impact on the pharmacy budget as less drug is being purchased by the patient, but it also may lead to a reduction in the expected benefits of treatment. Specifically, clinical efficacy may be affected by decreased intake of the drug, which leads to a lower concentration of the drug in the body and probably less efficacy. If the efficacy of a drug in a controlled setting (i.e., adherence is close to 100%) reduced the use of other medical resources such as hospitalizations, then reduced adherence may result in a lower impact on the use of these other medical resources compared with those observed in the clinical trials.

When applying adherence to estimating the drug-related or side effect-related costs, a direct relationship might be appropriate to include in the model calculations. Specifically, drug and/or side effect costs are only incurred when patients are fully adherent and are reduced in a linear fashion with lower adherence or persistence. However, issues such as wastage costs may need to be considered. For example, all patients may purchase the prescribed drug, which incurs a cost to the budget

holder. However, patients may not take all the drug as prescribed. In this case, the budget holder would be responsible for the full cost of the drug regardless of how adherent the patients are. The extent to which pills are wasted rather than prescriptions not refilled as frequently might vary from jurisdiction to jurisdiction.

Estimating the impact of adherence or persistence on other condition-related costs and outcomes may be more difficult. The best sources for these estimates are studies that have estimated the impact of adherence on health outcomes or condition-related costs. However, such studies are rare or are not performed in a manner in which the impact of adherence or persistence on health outcomes or condition-related costs are available and/or directly known. Depending upon the evidence that exists for applying the impact of nonadherence or nonpersistence, several approaches could be or have been used. For example, when considering discontinuation or lack of persistence, it is common to assume in the absence of data that those who stop treatment experience the same risks as untreated patients. This would be a worst-case scenario. Patients could incur untreated risks immediately upon discontinuing the medication. Alternatively, as has been shown in osteoporosis, where bone mineral density levels are improved with the use of osteoporosis drugs, there may be some therapeutic effect for some time after discontinuation until untreated risks are restored. For nonadherence during treatment, a functional relationship could be assumed between the degree of nonadherence and the magnitude of clinical benefit. This relationship could be linear or exponential or a mix of these at different levels of adherence.

In Box 12.3, we present an example where the relationship between adherence and hospitalization rates was measured directly using an observational database, and we present an example of the budget-impact calculation using that relationship.

Box 12.3 Estimating the Potential Relationship Between Adherence and Clinical Outcomes for a Budget-Impact Analysis

A new, once-daily drug has been approved for the maintenance treatment of chronic obstructive pulmonary disease (COPD). In the line of treatment in which this drug will be placed, all other maintenance treatments are twice daily. As a result, an adherence benefit may result due to patients only needing to take the new drug once a day. How might an adherence benefit be included in a budget-impact analysis accounting for an improvement in clinical outcomes with improved adherence?

Toy et al. (2011) performed an analysis of administrative health care claims that included both pharmacy and medical claims for patients with COPD. The authors categorized current COPD drugs as being administered once daily, twice daily, thrice daily, and four times a day. Overall, patients on once-daily drugs were more adherent, having an average proportion of days covered (PDC) of 43.3%, whereas patients on twice-daily drugs were less adherent, having an average PDC of 37.0%. In the analysis, they estimated that "a 5% point increase in adherence would lead to a 2.6% decrease in hospital visit costs and a 0.2% decrease in the outpatient visit costs." Assuming that severe exacerbations are associated with a hospitalization and nonsevere exacerbations are associated

with a physician's visit, we might be able to apply these changes in adherence rates to the severe and nonsevere exacerbation costs.

Example of the Budget-Impact Calculation Using the Relationship Above

In the example below, we show how to calculate the annual budget impact if a jurisdiction reimburses for the new once-daily drug versus the twice-daily drugs. The new once-daily drug will cost $7000 per year, and the twice-daily drugs cost $5000 per year if patients are 100% adherent. If annual hospital costs are $10,000 when not on a maintenance drug and annual outpatient costs are $1000 when not on a maintenance drug, the calculation below shows the total annual costs for being on a once-daily drug versus a twice-daily drug.

In this example, we see that the drug cost (assuming no wastage costs) for

***I**nput parameters*

Parameters	PDC	Annual costs
Once daily drug	0.433	$7,000
Twice daily drug	0.370	$5,000
Hospital cost adjustment	0.026	
Outpatient cost adjustment	0.002	
Hospital cost (0% adherent)		$10,000
Outpatient cost (0% adherent)		$1,000

PDC proportion of days covered

Estimating the budgets while considering adherence for treating with a once-daily versus a twice-daily drug

Estimation of Annual Budget	Once Daily	Twice Daily
Estimated drug costs		
Drug cost (100% adherent)	$7,000	$5,000
Adherence	0.433	0.370
Annual drug cost	$3,031	$1,850
Estimated nondrug costs		
Hospital cost	$7,748.40	$8,076.00
Outpatient cost	$982.68	$985.20
Annual estimated nondrug costs	$8,731.08	$9,061.20
Estimated total cost (drug and nondrug)	**$11,762.08**	**$10,911.20**

each budget scenario is as follows:

Annual drug cost
= drug cost if 100% × adherence rate

For estimating the other medical costs of hospital and outpatient costs, we take the annual cost when not adherent and multiply it by the adjustment. The equations for calculating annual hospital and outpatient costs are as follows:

Annual hospital cost
= hospital cost if not adherent × (1–([PDC/0.05] × hospital adjustment))

Annual outpatient cost
= outpatient cost if not adherent × (1–([PDC/0.05] × outpatient adjustment))

12.2.3 Adherence and Persistence Estimates: Sources and Use in Budget Impact Analyses

Adherence and its potential impact on health outcomes or costs may be examined a number of ways:

- Prospective studies set up to examine drug assays or markers in patients
- Prospective studies set up to collect automated or self-reporting of medication use
- Prospective studies set up to perform pill counts
- Reviews of retrospective pharmacy records or administrative data to measure prescription refills

Although there have been comparisons made among these different methods of collecting data to assess adherence, there really is no gold standard method to measuring adherence. Thus, when considering an adherence impact that has been extracted from a particular study, it is important to understand the setting and what exactly is being measured.

Once we know what is being measured, we must ensure that double counting is not occurring. For example, a budget-impact analysis may obtain its efficacy data from an observational trial such that it is actually measuring effectiveness (that accounts for suboptimal adherence) and not efficacy (as measured in a controlled clinical trial where adherence is likely to be high). If this is the case, applying another measure of nonadherence to the analysis on condition-related costs would be double counting.

It is important to understand the setting to which adherence is being applied in the budget-impact analysis. For example, a budget-impact analysis of a hospital-administered medication may use the efficacy of the medication or its impact on condition-related costs from a controlled-setting study. Two examples of such medications are tissue plasminogen activator for acute ischemic stroke and antifungal treatments for nosocomial invasive fungal infections. Being hospitalized is a controlled setting itself. As such, adherence is likely to be very high and similar to that observed in a clinical trial. For a budget-impact analysis in an outpatient setting, the actual adherence is likely to be lower than that observed in a clinical trial.

It is also important to understand the patient's condition in which adherence is being considered. For example, adherence may be high for conditions in which symptoms occur when medications are not taken as prescribed (e.g., pain). Conversely, adherence may be low for conditions in which symptoms may not be evident if the patient stops treatment (e.g., osteoporosis).

In Box 12.4, we present examples of issues that can arise when attempting to include published or observed estimates of adherence in the budget-impact analysis.

Box 12.4 Is Adherence and Persistence Included in a Budget-Impact Analysis Correctly?

When considering adherence and persistence, care must be taken in understanding what is actually being applied to the analyses, as applying an adherence calculation may be very different from applying a persistence calculation, for example. So it is important that model developers clearly define what is being measured. In addition, it is important to ensure that this adherence and persistence definition is being applied correctly. The following are examples of issues that could arise when considering adherence and persistence that make incorporating them in budget-impact analyses more difficult.

Example 1: Adherence was examined in a retrospective healthcare claims analysis. The researchers reported that 63% of patients were considered adherent. The modified medication possession ratio (MPR) was calculated, and patients were classified as being adherent if MPR > 0.80. Retrospective claims studies frequently report adherence in this manner. However, this is not a value that can be incorporated into a budget-impact analysis, as only the proportion of patients who use their drug over 80% of the time is known. It is unknown how adherent patients are when taking the drug or whether they discontinue taking the drug at some time during the analysis period.

Example 2: Model developers may note that adherence is considered in the budget-impact analysis. However, their incorporation of nonadherence in the model only reduces drug costs but has no effect on health outcomes. Caution should be taken in understanding how these measures are applied.

Example 3: In HIV, it is known that effectiveness can be increased if patients are 95% adherent to their drug regimen. A drug regimen in HIV frequently includes three drugs, often not offered as a fixed dose combination all in one pill. A lot of research has been performed to examine the adherence to the backbone, which is often a fixed-dose combination of two of the three drugs. Research also shows that adherence to the backbone improves adherence to the third component drug. However, adherence to the backbone cannot be used as a proxy measure for adherence to the full drug regimen, which is required in order to get the full effectiveness from the multi-pill regimens being taken.

Example 4: The impact of suboptimal adherence or persistence on condition outcomes may be different. For example, it may be that reducing the intake of aspirin from every day to every other day may not affect efficacy much. In this case, in a year, patients take aspirin only 50% of the time (i.e., every other day rather than daily). However, if persistence is 50% in 1 year, it would mean that patients take aspirin daily for the first half of the year and then do not take it for the last half of the year. Patients again take aspirin only 50% of the time. In the case of persistence, the impact on efficacy/outcomes would be very different in that one would expect full efficacy in the first half of the year and then no efficacy in the second half of the year.

12.3 Cost Type

Budget holders have different perspectives depending on whether they are the providers or payers for the service. As described in Chap. 2, cost data may represent production costs (the monetary amount needed for a medical practice to provide goods and services), charges (the amount that the medical practice will invoice for the goods and services), or reimbursed amounts (the amount that a payer will pay the medical practice for its goods and services). A payer (e.g., a public or private health insurer) may be more interested in the reimbursed amount because this is what the insurer will actually pay the medical practice for the goods and services. Budget holders acting on behalf of a healthcare provider (e.g., NICE for the UK National Health Service) may be most interested in production costs because this is the amount the provider will incur in providing the service. A medical practice or hospital may be interested in understanding the impact on their production costs in providing the services as well as the reimbursement amount, which represents their income from the services provided.

Budget-impact analyses are usually constructed from the payer's perspective. This perspective is that of the organization responsible for paying the provider of care for their services. In this case, the reimbursed amount is the cost of primary interest for the analysis. This is how much the payer will actually pay the medical practice for their goods and services.

Reimbursed amounts may be publicly available in the case of a public/governmental payer. However, in the case of the private payer, these reimbursed amounts are more difficult to access. These reimbursed amounts are often negotiated values between the payer and the medical provider that are often not available to the general public as it is part of the cost of doing business between two entities. Discounts and rebates may be offered for some medical goods and services but may not be available for others. This is particularly evident in the USA jurisdiction, where the payer system is dominated by many private payers.

In these cases, how does the model developer estimate the "costs" to be used in a budget-impact analysis? The ideal situation is to be able to obtain these negotiated values for populating the budget-impact analyses. However, when these values are not available, it is not uncommon to populate the analysis with publicly available reimbursement values. The analysis is then built so that these values can be easily replaced with a payer's own values upon receipt of the model.

Budget-impact analyses can also be constructed from both the revenue and cost perspectives. For example, consider a budget-impact analysis that might be used by a hospital. The hospital may be interested in the impact on its budgets from the cost perspective. This is the cost for the hospital to provide a particular service. In addition, the hospital may be interested in the impact the new drug will have on its revenue. This is how much money the hospital will collect as a result of the goods and services being provided by the hospital. The revenue may be their charge or the reimbursed amount. It is very important to understand the differences in these cost types as they can greatly affect the results of the analysis. Finally, the hospital may also be interested in the impact of the new drug on its net revenue (revenue minus costs).

In Box 12.5, we demonstrate the effect of these different perspectives.

Box 12.5 Budget-Impact Analysis Using Reimbursed Versus Revenue Values

A new drug is approved for preventing stroke in patients with atrial fibrillation. The cost (not including the cost of drugs for prevention of stroke) of a hospital stay for a patient with atrial fibrillation who incurs a stroke is $10,000, but a typical payer will only pay $8000. The standard treatment for these patients prior to the approval of the new drug is warfarin, which is very cheap for the hospital at $100 per patient during the hospital stay. The cost of the new drug to the hospital is $1500 per patient during the hospital stay. The reimbursed amounts for warfarin and the new drug are $200 and $1600, respectively. By using the new drug, rehospitalizations will be reduced by 20%. Typically, a hospital will treat 100 readmissions in a year for stroke in patients with atrial fibrillation when treated with warfarin.

Cost Perspective

What is the cost impact to the hospital if all patients are switched from warfarin to the new drug?

In this analysis, we are interested in the cost values. The following annual costs will result if the hospital treats with warfarin versus the new drug.

Budget parameter	Current year with warfarin only	Projected year with new drug
Number of rehospitalizations in year	100	80
Cost of a rehospitalization	× $10,000	× $10,000
Total rehospitalization costs in a year	*$1,000,000*	*$800,000*
Number of rehospitalizations in year	100	80
Cost of drug during hospital stay	× $100	× $1500
Total drug costs in a year	*$10,000*	*$120,000*
Total rehospitalization and drug costs in a year	**$1,010,000**	**$920,000**

Revenue Perspective

What is the revenue impact to the hospital if all patients are switched from warfarin to the new drug?

In this analysis, we are interested in the reimbursed values. The following annual costs will result if the hospital treats with warfarin versus the new drug.

Budget parameter	Current year with warfarin only	Projected year with new drug
Number of rehospitalizations in year	100	80
Revenue from a rehospitalization	× $8000	× $8000
Total rehospitalization revenue in a year	*$800,000*	*$640,000*
Number of rehospitalizations in year	100	80
Revenue from drug in a year	× $200	× $1600
Total drug revenue	*$20,000*	*$128,000*
Total revenue in a year	**$820,000**	**$768,000**

Summary

From the above, we see that the results are very different. From the cost perspective, we would say that using the new drug is less costly to the hospital. However, from the reimbursement perspective, the hospital observes that they receive less money (lower reimbursed amount) if they switch to treating patients with the new drug. At first glance, it may be perceived that the hospital would be better off in keeping patients on warfarin. However, since hospitals tend to lose money on stroke hospitalization in atrial fibrillation patients, the hospital actually loses less money if it switches patients from warfarin to the new drug. Specifically, the hospital saves $38,000 per year by switching patients to the new drug.

Budget elements	Current year with warfarin only	Projected year with new drug
Total revenue in a year	$820,000	$768,000
Total costs in a year	−$1,010,000	−$920,000
Net loss in a year	−$190,000	−$152,000

Exercises

Exercise 12.1 Provide examples of off-label use in specific conditions. How would this off-label use affect budget-impact analysis?

Exercise 12.2 Disease X is a rare disease that affects all parts of the body. One in 1,000,000 patients is diagnosed with disease X each year. There currently is no cure, and no drugs have been indicated to treat the disease. However, physicians have been treating this disease with corticosteroids for years. How might a budget-impact analysis for a new drug specifically indicated to treat disease X be affected?

Exercise 12.3 A budget-impact analysis is being developed for a new drug to treat blood clots. When examining the payer's reimbursed population, it was found that 50% of patients are being treated with drugs that do not have a formal indication for treating blood clots. Given this information, what should the developer of the analysis do? What would the payer's view be?

Exercise 12.4 Drug X is a common drug being used to treat chronic low back pain. However, drug X is not indicated for use in chronic low back pain, rather it is approved for acute pain after surgery. How might drug X be included into a budget-impact analysis for a new drug to treat chronic low back pain? Explain how treatment shares, dosing, treatment effect on condition-related costs, etc. would be obtained and incorporated into the analysis.

Exercise 12.5 Describe a situation in which persistence would be considered over adherence in a budget-impact analysis. Describe a situation in which adherence would be considered over persistence in a budget-impact analysis.

Exercise 12.6 Given a lack of evidence on the impact of adherence on health outcomes, how might adherence be assumed to affect condition-related costs in a budget-impact analysis? Give examples.

Exercise 12.7 Describe a setting in which adherence may not be appropriate to consider in a budget-impact analysis.

Exercise 12.8 Describe how adherence might affect the expanded use of a new drug. How would the population, treatment mix, drug cost, and condition-related costs be affected?

Exercise 12.9 A new drug is under review for approval for treating chronic low back pain. A budget-impact analysis is being developed, and it has been noted that adherence may be an issue because drug X, which is being used off-label (see Exercise 12.4), is easier to administer. List some issues that the budget holder may need to consider for incorporating adherence. How might these issues be resolved?

Exercise 12.10 List and describe other issues outside off-label use and adherence that might be important to consider in a budget-impact analysis.

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Chapter 13
Alternative Interventions

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Abstract The focus of this book has been on estimating the budget impact when adding new drugs to the current mix of drug treatments. The components that need to be completed when estimating the budget impact of other types of health care interventions are the same, but the approach needed for each component may be different. In this chapter, we provide an overview of differences in approach needed for estimating the budget impact of new vaccines, diagnostic tests, surgical procedures, and devices. We also present examples of budget-impact analyses that have been performed for these types of health care interventions.

Keywords Budget-impact analysis • Vaccines • Diagnostics • Surgery • Medical devices

Chapter Goal
To discuss specific issues that may require different approaches for budget-impact analyses of nondrug interventions, including vaccines, diagnostic tests, surgery, and medical devices.

In addition to new drugs for treating diseases/conditions, budget-impact analyses can also be performed for other health care technologies such as vaccines, diagnostic tests, surgeries, and medical devices. Understanding how these health care interventions affect a health plan's budget is just as important. For example, consider screening women for breast cancer. How often screening should occur and what screening interventions should be used has been examined for standard guidelines from a

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cost-effectiveness perspective (USA Preventive Services Task Force 2009; Nelson et al. 2009). However, implementing screening will significantly affect health plan budgets, particularly since it adds payment for incurring the use of a health care technology that would not be incurred otherwise. Additionally, if cancer is identified, then the health plan incurs the cost to treat immediately, which it may not have incurred even though the treatment costs may be greater if the cancer is identified later.

Developing budget-impact analyses for these types of health care interventions is no different than developing budget-impact analyses for new drugs. The same six-step process still applies in which we need to consider the eligible population, time horizon, current and projected treatment share, treatment costs, condition-related costs, and reporting the budget and health outcome impact. However, with vaccines, diagnostic tests, surgeries, and medical devices, there may be some nuances that need additional consideration. In the sections below, we discuss some of these nuances and present examples.

13.1 Vaccines

Budget-impact analyses for vaccines can estimate just the costs of the vaccination, or they can include the offsetting costs from the reduced number of cases of the vaccine-preventable disease if these are expected within the analysis time horizon. Estimates of the cost of the vaccine will include similar cost categories to those included in estimates of the costs of a new drug. For a vaccine, these cost categories will be direct medical care costs including acquisition cost of the vaccine, administration costs, and costs of treating any vaccine side effects. Indirect costs, such as productivity loss associated with getting/not getting the vaccine, might be of interest for an employer-sponsored, self-insured plan. Operational costs associated with developing an employer-sponsored vaccination program and delivering the vaccine might also be considered as these would also affect the costs of an employer-sponsored, self-insured plan.

The annual costs for the vaccination will be calculated by multiplying the per-person costs by the number of people getting vaccinated each year. As with a budget-impact analysis for a new drug, the number of people getting vaccinated each year will be determined by the number of people eligible for vaccination and the uptake rate in the eligible population. The number of people eligible will generally be determined by the indicated population as well as any reimbursement or other restrictions on the size of the eligible population imposed by different jurisdictions. For example, influenza vaccine might only be reimbursed for those who are considered at high risk of complications in some jurisdictions, whereas it might be reimbursed for all health plan members in other jurisdictions.

Another factor that needs to be taken into account in the budget-impact analysis for a new vaccine is whether there will be a "catch-up" population eligible for vaccination in the first few years after it becomes available on the market. For example, if a new meningitis vaccine is introduced for adolescents to be given at age 12 to protect them against meningitis through their early 20s, will those who are age 13 to age 20 at the time it is first introduced be eligible to receive the vaccine in the first few years after its

introduction? If so, this will increase the budget impact for the first few years of availability. This is similar to the catch-up effect for a new drug for a chronic condition.

To generate estimates of changes in the annual condition-related costs with a vaccine for prevention of a disease, initial estimates are needed of the annual number of cases of the disease in the population by age group (if applicable) expected over the analysis time horizon. Cost offsets are then estimated based on the number of cases of disease expected to occur given the vaccine and not given the vaccine. Specifically, cost offsets are determined by the avoidance of disease and their associated costs.

Vaccines differ from other pharmaceuticals in that even persons not taking the vaccine may benefit from its efficacy. This is often referred to as "herd immunity" or "indirect effects." This reduction in exposure to infection in the unvaccinated population that might occur when a new vaccine is introduced (i.e., reducing the incidence of disease) can affect condition-related costs, and thus it should be taken into account. Budget-impact analyses will tend to either not account for the herd immunity effects or account for them through some range of different approaches. One approach is to apply a factor between zero and one to the vaccinated person's efficacy to approximate the disease risk reduction in those not vaccinated. This approach has been used for estimating the impact of meningitis vaccination in the USA using a factor derived from the herd immunity rates observed in the UK when the meningitis vaccination was implemented (Ortega-Sanchez et al. 2008). An alternative approach is to use estimates of the total number of cases of the disease avoided derived using an epidemic model (e.g., a dynamic transmission model or agent-based model) that captures the vaccine-related efficacy and herd immunity effects for the total population (Pitman et al. 2012).

Vaccines are associated with other epidemiological issues that might also need to be considered because they may affect the budget impact. These may include serotype replacement or breakthrough cases of disease. Breakthrough disease is the occurrence of disease in spite of being vaccinated, whereas serotype replacement is the occurrence of disease due to serotypes not covered by the vaccine. Specifically, vaccines target their efficacy on certain serotypes of the disease in order to prevent the occurrence of the disease through those serotypes. However, other serotypes may exist that cause the disease but against which the vaccine has not proven effective. As vaccines prevent disease from covered serotypes, the incidence of disease from noncovered serotypes might increase. These effects can be excluded from the budget-impact analysis but this might reduce the credibility of the budget impact analysis. If included, they may be captured using fixed factors or using the outputs from an epidemic model that accounts for these effects.

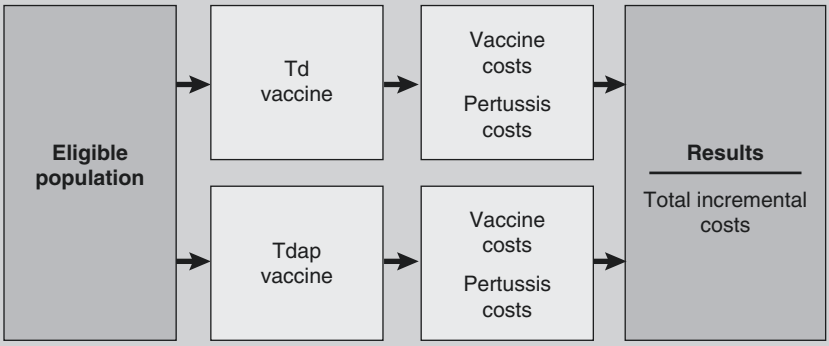
Overall, these indirect effects will change the annual budget impact of the new vaccine. Both the direct and indirect effects of a new vaccine are estimated with uncertainty and frequently change over the first few years of the availability when using an epidemic model, making annual estimates of the budget impact unreliable.

In Box 13.1, we present an example of a budget-impact analysis for a combined tetanus and pertussis vaccine for those presenting with open wounds in which a static model that did not account for herd immunity was used to estimate the changes in condition-related costs. In Box 13.2, we present an example of a budget-impact analysis for a varicella vaccine that used estimates from a dynamic transmission model.

Box 13.1 Budget-Impact Analysis of Tetanus, Diphtheria, and Acellular Pertussis Vaccine for Those with Open Wounds (Talbird et al. 2015)

For many years, standard of care for those presenting to a health care provider with an open wound was to offer tetanus/diphtheria (Td) vaccine if the patient had not had a tetanus vaccination within the last 5 or 10 years. In 2006, because of an increase in pertussis cases despite infant vaccination against pertussis, the Centers for Disease Control and Prevention recommended that the combined tetanus/diphtheria/acellular pertussis (Tdap) vaccine be offered to those presenting with open wounds if they had not had a tetanus vaccination within the last 5 or 10 years and who had not previously received vaccination for pertussis. In this budget-impact analysis, Talbird et al. (2015) compared a scenario of giving Tdap to all eligible patients with a scenario of giving only Td. In the figure, we present a model structure that represents the model flow. In this analysis, the eligible population is identified. Given this eligible population, 2 budget scenarios are calculated: a budget scenario in which patients receive Td and a budget scenario in which patients receive Tdap. Vaccine acquisition costs and the cost of treating pertussis if it occurs are estimated. The budget impact is then calculated as total costs when treated with Tdap minus total costs when treated with Td.

Model flow diagram: budget impact of Tdap versus Td vaccine



Results showed that using Tdap instead of Td increased annual costs by $47,438,595 in years 1, 2, and 3. Pertussis costs were reduced by $3,923,963 in year 1, by $7,340,942 in year 2, and by $10,317,444 in year 3 due to a reduction of 7,630 pertussis cases in year 1, of 14,311 cases in year 2, and of 20,162 cases in year 3 (Talbird et al. 2015).

Box 13.2 Annual Budget Impact of Varicella Vaccination in the United Kingdom at Steady State Using a Hypothetical Dynamic Transmission Model (Thompson et al. 2012)

A simplified, age-structured susceptible, infectious, recovered (SIR) dynamic transmission model was developed. The model structure is presented in the figure below. Epidemiologic and economic input parameters were obtained from previously published UK data.

The dynamic transmission model used a one-day time step and was run for a 100-year period or until the epidemic reached a steady state both with and without a varicella vaccination program. The coverage rate for vaccination was assumed to be 90% and efficacy of 96% with no waning. Thus, very few varicella cases occur at steady state. Given the number of births each year and the vaccine coverage and efficacy, the number of children vaccinated, number of varicella cases, number of office visits, and number of hospitalizations (undiscounted) in the steady state can be obtained from the dynamic transmission model. To estimate the budget impact, these parameters can be multiplied by the relevant costs.

Let us assume a constant number of 697,085 births per year. In the steady-state year with vaccination, the dynamic transmission model estimates 627,377 children vaccinated, 690,361 varicella cases avoided, 414,216 office visits avoided, and 2071 hospitalizations avoided. The budget impact of the vaccination program compared with no vaccination program can be estimated as seen in the table below when the vaccine cost is £39.44, the cost per office visit is £30, and the cost per hospital visit is £900.

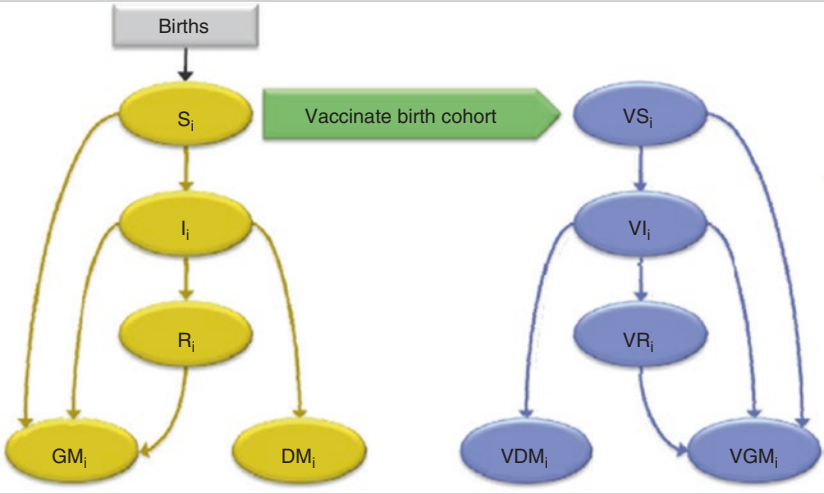
The budget impact, including increased vaccine costs and decreased direct medical care costs for treatment of varicella, is shown for the whole population for 1 year at steady state. Shorter time horizons (results not shown) result in a higher annual population budget impact for the first 50 years, before a steady state of near-negligible varicella cases is reached, because the number of avoided cases is lower in the early years of the vaccine program.

The budget impact will generally be less favorable (higher) for higher vaccine prices, lower estimates of vaccine efficacy, for lower levels of vaccine coverage if they do not induce herd immunity, or when vaccine waning or negative indirect effects of vaccination (e.g., increased incidence of herpes zoster) are included. The budget impact will generally be more favorable if lost productivity costs for a parent to stay home with a sick child are included; however, these costs are typically not included in budget-impact analyses, which are from the payer perspective.

In this example, we presented the budget impact and the estimated number of vaccinees, varicella cases, office visits, and hospitalizations that would occur in a steady state year. However, the values of these population estimates

from the dynamic transmission model for each year of the vaccination program starting from its initiation may be more useful for budget holders than the values at steady state (Mauskopf et al. 2012) because it more accurately represents the budget impact expected in the first three to 5 years of the vaccination program.

Dynamic transmission model: varicella vaccination



DM disease-related mortality, *GM* general mortality, *I* infected, *R* recovered, *S* susceptible, *V* vaccinated, *i* denotes age group i

Budget and health impact in a steady state year (after more than 50 years) after initiation of vaccine program assuming 90% coverage and 96% efficacy and no waning for the UK population

Outcomes	No varicella vaccination	Varicella vaccination	Vaccine – no vaccine
Births	697,085	697,085	0
Number vaccinated	0	627,377	627,377
Number of varicella cases	690,361	0	–690,361
Number of office visits	414,216	0	–414,216
Number of hospitalizations	2071	0	–2071
Vaccine costs	£0	£24,743,729	£24,743,729
Outpatient costs	£12,426,480	£0	–£12,426,480
Inpatient costs	£1,863,900	£0	–£1,863,900
Total costs, at steady state	£14,290,380	£24,743,729	£10,453,349

13.2 Screening and Diagnostic Tests

Diagnostic tests are important in medicine for diagnosing the existence of disease, but they may also be used to identify biomarkers in patients to predict how a patient may respond to a particular treatment or if a patient is susceptible to a particular adverse event if treated with a certain drug. Diagnostic tests can also be used as an add-on or replacement technology in the treatment pathway, which may be dictated by the diagnostic test's characteristics, such as noninvasiveness, improved sensitivity or specificity, etc. Overall, these characteristics may affect the way in which a budget-impact analysis is constructed.

Given these characteristics, budget-impact analyses for diagnostic tests may be designed to examine the costs incurred during the period of diagnosis only, or they may be designed to incorporate costs for the full treatment pathway, which considers the differences in the costs associated with subsequent treatments and condition management that might result because of the introduction of the diagnostic test. The latter is typically seen because the new diagnostic test may have improved sensitivity and/or specificity or may affect downstream treatment in some way. If only the costs incurred during the period of diagnosis are considered, the analysis may be similar to a simple, budget-impact analysis in which only drug costs are considered. Specifically, the calculation captures estimating the number of patients eligible for the diagnostic test, and then the weighted average of the treatment share among the diagnostic tests and cost of the diagnostic tests are estimated for budget scenarios in which the new diagnostic is or is not introduced.

In some cases, the new diagnostic test may be added to a series of diagnostic tests (i.e., not replacing an existing test used in the same way). In these cases, it is important to understand the implication of the addition of another test. Not only are we interested in whether the diagnostic test will prevent further testing or better identify patients for treatment, but we are interested in the downstream effect of who will be eligible to receive the new diagnostic test. In Box 13.3, we summarize a budget-impact analysis for a new epigenetic assay that may be used in conjunction with biopsies for the diagnosis of prostate cancer. In this case, the costs of subsequent biopsy procedures are determined by the proportion of patients with a positive test result for the new diagnostic. Therefore, data for the proportion of patients with positive and negative results would need to be incorporated into the analysis.

If the new diagnostic test differs from alternative diagnostic tests in its sensitivity and/or specificity, it may be appropriate for the budget-impact analysis to incorporate differences in the costs associated with subsequent treatments and condition management. Specifically, the improved identification of true-positive, false-positive, true-negative, and/or false-negative results can affect treatment and eventual offsetting costs and outcomes. In Box 13.4, we summarize a budget-impact analysis for a novel gene expression assay for the diagnosis of malignant melanoma that is used in ambiguous, difficult-to-diagnose biopsy samples. This kind of analysis requires data for test sensitivity and specificity and costs for each patient category as well as population size, diagnostic test mix, and diagnostic tests costs.

Box 13.3 Budget-Impact Analysis of Adding a Diagnostic Test to a Current Series of Diagnostic Tests (Aubry et al. 2013)

Aubry et al. (2013) performed an analysis to estimate the budget impact of a new epigenetic assay that may be used in conjunction with biopsies for the diagnosis of prostate cancer. The epigenetic test is used after the first biopsy. Patients with a negative assay result are spared a repeat of the biopsy, thereby reducing the number of unnecessary biopsy procedures. Specifically, this analysis examined the budget impact of moving from a status quo of current clinical care in which the epigenetic test is not used to a hypothetical budget scenario in which "men at risk for repeated biopsy are evaluated with epigenetic assay" (Aubry et al. 2013). In the analysis, only the costs associated with alternative tests incurred during the period of diagnosis were considered.

For each budget scenario, the model estimated the cost of the epigenetic test, the number of patients predicted to have subsequent biopsies, the cost of the repeated biopsies, and the cost of complications associated with repeated biopsies.

Box 13.4 Budget-Impact Analysis of a New Diagnostic to Identify Melanoma Versus Non-Melanoma (Cassarino et al. 2014)

Cassarino et al. (2014) presented an analysis for a new diagnostic test with improved sensitivity and specificity for diagnosing melanoma versus non-melanoma in difficult-to-diagnose cases. Since this diagnostic test has demonstrated improved sensitivity and specificity over current practice, there is potentially an important downstream effect on costs and outcomes to consider. As such, this analysis estimated differences in the costs associated with subsequent treatments and condition management arising from differences in the number of false-positive and false-negative diagnoses.

The analysis evaluated the novel gene expression assay for the diagnosis of malignant melanoma that is used "in ambiguous, difficult-to-diagnose, suspicious pigmented lesion biopsy samples" (Cassarino et al. 2014). The clinical care given to these patients was modeled over 10 years, including natural progression to more advanced stages of melanoma. Based on a budget scenario in which all patients received current clinical practice (without the assay) compared with a budget scenario in which all patients received the new diagnostic test (with the assay) during initial diagnosis, 10-year costs were estimated for correct diagnoses of melanoma (true positives), misdiagnoses of melanoma (false positives), correct diagnoses of benign or dysplastic nevus (true negatives), and misdiagnoses of benign or dysplastic nevus (false negatives). The sensitivity and specificity of the new assay and the current clinical practice were used to calculate the number of true positives, false positives, true negatives, and false negatives in the population.

13.3 Surgery

Surgeries and procedures (referred to as surgeries for the rest of this section) are unique in that they can compete with other surgeries as well as other nonsurgical health care technologies, but they also may be considered within a regimen of treatments (i.e., surgery is not performed without additional drugs or diagnostic tests being administered). For budget-impact purposes, a surgery is usually not just the cost of the procedure, but may also include multiple components that would need to be costed, such as preparation for operation and postsurgery hospital stay. Since surgeries are very costly, major scrutiny occurs regardless of whether surgery is designated as a replacement technology or is an add-on to other treatments. As a result, understanding the budget impact of a specific type of surgery or including surgery within a budget-impact analysis as a treatment alternative is important.

Budget-impact analyses for new surgical techniques might compare a mix of surgical treatments with and without the new surgical techniques or might compare a mix of treatments including both surgical, drug, or other treatment modalities with and without the new surgical technique. In either case, the methods used for analyses including these treatment modalities are similar to those for budget-impact analyses when comparing treatment mixes of drugs alone. When comparing two or more surgical modalities, differences between these modalities need to be estimated.

The primary difference is that estimates of the costs of the new and current surgical techniques include a different set of costs. These may include presurgical preparation costs; surgeon, nurse, anesthesiologist, and facility fees for performing the surgery; postsurgical care and monitoring for complications; and treatment of postsurgical complications. These costs can be estimated using published studies, medical record reviews, or observational database analyses. Estimation methods for population size and relevant descriptors and treatment shares and changes in condition-related costs are similar to those for drug budget-impact analyses.

In Box 13.5, we present an example of a budget-impact analysis for a new chemical ablation technique compared with only interventional therapies for the treatment of chronic venous disease.

In Box 13.6, we summarize a budget-impact analysis for a noninvasive procedure in which multiple technologies are used. Specifically, magnetic resonance imaging (MRI) is combined with high-intensity ultrasound for thermal ablation of uterine fibroids. In this analysis, the authors detailed the annual maintenance and operating costs of technologies that were needed to perform the surgery.

Box 13.5 Budget-Impact Analysis for a New Chemical Ablation Technique Compared with Interventional Therapies for the Treatment of Chronic Venous Disease (Carlton et al. 2015)

Interventional treatments for chronic venous disease include surgical and vein ablation techniques. In this budget-impact analysis, the budget impact of a new intervention (injectable polidocanol foam) was estimated assuming a 5% treatment share. The analysis estimated a one-year budget impact assuming treatment duration of 8 weeks for a hypothetical USA health plan with one million members.

In many cases, multiple interventions are needed when the first intervention fails to provide relief. This analysis considered laser ablation, radiofrequency ablation, surgery, sclerotherapy, and polidocanol injectable foam as single modalities and as various multimodality combinations. The frequency of the different types of treatments was obtained from an analysis of retrospective health care claims and is presented in the table below.

Budget-impact analysis: assumed current and new treatment utilization (Carlton et al. 2015; Mallick et al. 2014)

Treatment	Current treatment utilization	New treatment utilization
Laser ablation	31.8%	30.2%
Radiofrequency ablation	20.7%	19.7%
Surgery	11.0%	10.5%
Multimodality treatment	25.6%	24.3%
Sclerotherapy	10.9%	10.4%
Polidocanol injectable foam	0.0%	5.0%

The costs for polidocanol injectable foam included acquisition, administration, and professional and facility procedure costs. The costs for ablation and surgery included both professional fees and facility fees and were estimated using Current Procedural Terminology codes and Centers for Medicare and Medicaid Services (2015) unit costs. The costs for budget scenarios with and without polidocanol injectable foam were then computed as the weighted average of the costs for each intervention and the intervention frequency.

For the hypothetical USA health plan, the incremental total budget impact of the use of polidocanol injectable foam, assuming a 5% treatment share, would be $87,074, and the per-member–per-month impact would be $0.01.

Box 13.6 Budget-Impact Analysis of Introducing Magnetic Resonance-Guided High-Intensity Focused Ultrasound as a Treatment for Symptomatic Uterine Fibroids (Babashov et al. 2015)

The budget impact was estimated for the introduction of magnetic resonance-guided, high-intensity focused ultrasound (MRgHIFU) for the treatment of symptomatic uterine fibroids in women in Ontario, Canada. The goal was to determine the one-year cost burden of implementing MRgHIFU to replace currently used uterine fibroid treatments. The current annual utilization and costs of nonpharmacological management of uterine fibroids (i.e., hysterectomy, uterine artery embolization [UAE], and myomectomy) were estimated for all women in the target population in Ontario using administrative data. Pre-, peri-, and post-procedure costs were estimated for each of the interventions as follows:

- Preprocedure costs included diagnostic tests, consultation with experts, and additional MRI for MRgHIFU and UAE procedures.
- Periprocedure costs included applicable professional fees and direct and indirect costs. Procedure costs for MRgHIFU were estimated by dividing annual maintenance and operating costs by an annual caseload (estimated by clinical experts) and adding the physician fee, supplies, and disposables. Annual maintenance and operating costs included maintenance of the magnet and focused ultrasound system, MRI technician salary plus benefits, physician salary plus benefits, and nurse salary plus benefits.
- Postprocedure costs included follow-up with experts and ultrasound imaging.

13.4 Medical Devices

Medical devices may be considered similar to surgery in that many medical devices require surgery in order to use the device. Examples of such medical devices may include pacemakers, stents, and knee, hip, and shoulder prostheses. Budget-impact analyses for these medical devices would follow the same approach to budget-impact analyses for surgeries, but may include additional considerations such as monitoring of the device, use of additional drugs because the device is invasive material in the body, and periodic check-up throughout the use of the device. For implants, it is important to consider differences in the cost of the surgical procedure (e.g., resulting from differences in surgery time) or in care costs during the recovery period, compared with current interventions (if relevant to the budget holder). These are all additional issues that may affect the costs. However, with this additional cost, the benefits in terms of improved outcomes may occur. As with budget-impact analyses for drugs, the consideration of these improved outcomes in the budget-impact analysis for devices may depend upon when these outcomes occur. Can they be considered immediately or do they occur beyond the budget-impact time horizon?

Not all medical devices require surgery, however. Examples of such medical devices may include orthotic inserts, continuous positive airway pressure devices, and bone growth stimulators. For these types of devices, a surgery may not accompany the use of the device, but other costs such as purchasing or renting the device or the cost of tailoring the device for the individual may be appropriate to include.

Overall, budget-impact analyses for a single-use medical device (i.e., where one device is used for each procedure) can be constructed using the general six-step process. In Box 13.7, we summarize an analysis for insertion of a drug-eluting stent for the treatment of peripheral arterial disease. The analysis estimated the population eligible for treatment, costs of standard care (a bare metal stent), and costs of the new intervention and included cost offsets resulting from decreased revascularization procedures within the analysis time horizon.

Box 13.7 Budget-Impact of the Use of Drug-Eluting Stent in Patients with Peripheral Arterial Disease Above the Knee (Health Quality Ontario 2015)

The budget impact was estimated for the introduction of a paclitaxel-eluting stent for the treatment of de novo or restenotic lesions in peripheral arterial disease in Ontario, Canada. The standard of care was assumed to be a bare metal stent. The number of individuals in Ontario with peripheral arterial disease in 2015 who would require stenting and nonstenting interventions for the superficial femoral artery was estimated from administrative data using a specified set of procedure codes. Costs included in the analysis were device acquisition costs, implantation procedure costs, physician fees, and the cost of subsequent revascularizations within the 5-year analysis time horizon.

Exercises

Exercise 13.1 Identify characteristics of vaccines that are different from basic pharmaceuticals that a budget holder may deem important to consider in a budget-impact analysis. Discuss how these characteristics might affect the budget holder's budget.

Exercise 13.2 Identify a new vaccine that is expected to come to market. Considering the six-step process to developing budget-impact analyses, how would you design a budget-impact analysis for this vaccine? Discuss issues around the population, comparators, time horizon, current and projected treatment mix, treatment and condition-related costs, and outcomes of the analysis and how they may be the same as or different from those in a budget-impact analysis developed for a drug.

Exercise 13.3 In developing a budget-impact analysis for supporting a new diagnostic test, identify some issues that may be important to consider that would not occur in a budget-impact analysis for a basic drug. How might these issues affect the budget holder's budget?

Exercise 13.4 Identify a new diagnostic test that is expected to come to market. Considering the six-step process to developing budget-impact analyses, how would you design a budget-impact analysis for this diagnostic test? How would you identify the eligible population? What are the comparators? Will there be condition-related cost offsets (if so, what are they)?

Exercise 13.5 A new diagnostic test has been found to diagnose disease X early. However, the health plan budget holder is refusing to reimburse for this diagnostic before performing any analyses, saying that encouraging patients to receive this diagnostic test will just increase their plan's budgets. Discuss why this perception may or may not be true. How might you be able to convince the budget holder otherwise?

Exercise 13.6 A delicate surgical approach is expected to be improved through the use of robots (i.e., robot-assisted surgery). However, the use of robots is expected to increase the cost of the surgery dramatically. In developing a budget-impact analysis for this new surgical approach, what issues would be important to capture to accurately examine the impact to a budget holder's budget? Discuss issues that might affect costs and outcomes.

Exercise 13.7 Identify a new or recent surgical approach that is expected to or has come to market. Considering the six-step process to developing budget-impact analyses, how would you design a budget-impact analysis for this surgical approach? Discuss issues around the population, comparators, time horizon, current and projected treatment mix, treatment and condition-related costs, and outcomes of the analysis. How they may be the same as or different from those in a budget-impact analysis developed for a drug?

Exercise 13.8 Medical devices may be invasive or noninvasive. In building a budget-impact analysis for these devices, what are some of the issues around current and projected treatment mix and costs and outcomes that should be considered that may differ from a budget-impact analysis for a drug? How might a budget-impact analysis for an invasive medical device differ from one for a noninvasive medical device?

Exercise 13.9 Identify a new medical device that is expected to come to market. How would you design a budget-impact analysis for this medical device? Discuss issues with respect to the population, comparators, time horizon, current and projected treatment mix, treatment and condition-related costs, and outcomes of the analysis. How they may be the same as or different from those in a budget-impact analysis developed for a drug?

Exercise 13.10 A new drug is expected to come to market to treat condition A. In order to use the new drug, a companion diagnostic test must be administered to screen out patients who are likely to have devastating side effects. How might a budget-impact analysis be constructed for this drug? How are the eligible population, comparators, treatment and condition-related costs, and outcomes affected?

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Chapter 14
Creating Your Own Budget-Impact Analyses Today and Tomorrow

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Abstract This chapter summarizes the importance of budget-impact analysis as a tool to assess the impact on population health and payer budgets of new health care interventions. We discuss the complementary nature of budget-impact analysis and cost-effectiveness analysis and provide a reminder about differences in purpose, structure, assumptions, and inputs between these two types of analysis. We also provide a brief overview of this book's recommendations for budget-impact analysis, both in terms of essential components and calculations as well as strategies to design analyses that are credible and useful to budget holders. Example budget-impact analyses are presented to demonstrate how components have been added to these analyses to make them more credible and useful for the budget holder. Finally, areas are suggested where future development in budget-impact analysis methods is needed.

Keywords Budget-impact analysis • Key components • Methods development

Chapter Goal
To summarize the key components of a budget-impact analysis, provide examples of how to ensure that the budget-impact analysis is useful for budget holders, and describe areas where further methods development is needed.

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14.1 Overview

We believe that budget-impact analysis should be part of a comprehensive economic evaluation of a new health care intervention. This is not only because of the budget constraints that affect all health care systems but also because the opportunity costs of a new intervention are directly related to its budget impact as well as the cost-effectiveness (Cohen et al. 2008). An intervention can be very cost-effective based on a standard threshold value, but it also can have a budget impact that would require massive redistribution of resources from other health care interventions and/or from public or private programs such as highway safety, education, or defense. Estimates of both cost-effectiveness and budget impact for a new health care intervention are needed to allow the budget holder to have a full understanding of both the value of the new intervention and its likely impact on population health or other public or private program outcomes.

Methodological reviews of published budget-impact analyses have demonstrated that there is great variability in the design of these analyses, and they frequently do not follow generally accepted methodology (Mauskopf and Earnshaw 2016; Faleiros et al. 2016; van de Vooren et al. 2014; Orlewska and Gulácsi 2009; Mauskopf et al. 2005, 2014). We believe that part of the reason for this variability and the frequently observed substandard methodology in the published budget-impact analyses is because there are limited sources providing step-by-step instructions for the design and development of budget-impact analyses that follow generally accepted methodology. Therefore, in Chap. 2 through Chap. 13 of this book, we have provided such step-by-step instructions illustrated by multiple examples. These instructions are designed to help the reader create a budget-impact analysis that follows published guidelines (Sullivan et al. 2014; Mauskopf et al. 2007; Marshall et al. 2008; Patented Medicine Prices Review Board 2007; Neyt et al. 2015; Pharmaceutical Benefits Advisory Committee [PBAC] 2015; Agency for Health Technology Assessment [AHTA] 2009; WellPoint 2008; National Institute for Health and Care Excellence [NICE] 2013) as well as recommendations in other publications that present methods that should be used in budget-impact analyses (Mauskopf 1998, 2000; Trueman et al. 2001; Nuijten et al. 2011; Mauskopf et al. 2013). We have also provided a set of exercises for each chapter so that the reader can gain facility completing each component of the analysis.

In this book, we recommend designing and building transparent budget-impact analyses that provide budget holders with credible estimates of the impact of new drugs on population health and payer budgets. To accomplish this goal, the design of the analysis must carefully consider all the components that affect population health and payer budgets while simultaneously balancing comprehensiveness with simplicity and transparency. Any budget-impact analysis must include appropriate estimates of the current and future size of the eligible population and relevant descriptors, the expected mix of treatments in the two budget scenarios to be compared (e.g., a budget scenario with the new drug available on the market and a budget scenario without the new drug available), and drug-related and

condition-related costs associated with each included treatment. Over the time horizon of the analysis, which is typically between 3 and 5 years, these components work in tandem. The calculations of the budget-impact analysis combine the population size and relevant descriptors with per-person costs and treatment mix data to yield budget and health outcome estimates for each budget scenario. The projected impact of the new drug is simply the difference between the two budget scenarios.

In addition to providing recommendations about the essential components of any budget-impact analysis, this book also recommends a number of strategies to help readers design and build budget-impact analyses that are as credible and useful as possible to budget holders. These recommendations center on transparency, credibility, and ease of use. The model structure should be kept as simple as possible, using a static approach in simple spreadsheet software whenever possible. Results should be presented annually for each year of the time horizon, using an appropriate level of disaggregation so that budget holders can see a helpful breakdown of the budget outcomes. Presenting population health outcomes alongside budget-impact results can help budget holders understand the potential benefits associated with any budget increases. Sensitivity and scenario analyses add credibility and can help budget holders understand the impact on the results of uncertainty and various plausible scenarios. The user interface for the analysis should be transparent and should clearly present the model structure, inputs, calculations, and results. The user should be able to easily progress through the model, customize input values for his or her own circumstances, and view the corresponding results. Finally, steps should be taken to confirm the face validity, internal validity, and external validity of the model. By following these recommendations, readers should be able to design and build budget-impact analyses that provide budget holders with relevant and credible estimates of population health and budget impact for emerging treatments.

14.2 Budget Impact Versus Cost-Effectiveness

Budget-impact analyses examine the impact of introducing a new health care intervention on a payer's budget in the presence of the use of alternative health care interventions.

There are two primary differences between a budget-impact analysis and a cost-effectiveness analysis:

- A budget-impact analysis focuses on the difference in annual costs expected to be incurred with respect to a payer's financial budgets for the total population being treated each year; a cost-effectiveness analysis focuses on the difference in total costs per difference in total outcomes expected to be accrued for a single cohort for as long as the treatment effect is experienced.

- A budget-impact analysis examines budget scenarios with the treatment mix without the new drug compared with the treatment mix with the new drug; a cost-effectiveness analysis generally examines treatment with the new drug compared with treatment with the standard of care.

Estimating the size and relevant descriptors of the treated population each year of the analysis time horizon with and without the new drug and estimating who will get these treatments are critical components of a budget-impact analysis.

In a budget-impact analysis, costs assigned to the drug- and condition-related costs are the costs borne by the budget holder. In a cost-effectiveness analysis, these costs reflect the opportunity costs for the resources used, although these opportunity costs are frequently assumed to equal the costs borne by the budget holder. Differentiating between fixed and variable costs in the short run is likely to be more important for budget-impact analyses.

Although uncertainty analyses are important for both budget-impact and cost-effectiveness analyses, the types of analyses are different because of differences in perspective. For a cost-effectiveness analysis, a societal perspective or a typical payer perspective is used. One-way, multiway, and probabilistic sensitivity analyses are performed. These generally estimate the impact only of the uncertainty in parameter values where quantitative measures of uncertainty are available from clinical trial or observational data. For a budget-impact analysis, a specific health plan perspective is used. One-way and multiway sensitivity analyses are performed for input parameter values where quantitative measures of uncertainty are available from clinical trials or observational data as well. But in a budget-impact analysis, many input parameters are predictions of the future for which there are no data sources to estimate this uncertainty. In addition, the budget-impact analysis includes many variables that are known with certainty to the health plan but vary among health plans. Since uncertainty in the future values and variability in the health plan-specific variables are likely to change the estimated budget impact of a new drug (possibly more than the uncertainty in the input parameter values taken from clinical trial or observational data), probabilistic sensitivity analyses are generally not recommended for budget-impact analyses. One-way, multiway, or scenario analyses are the recommended approaches.

Finally, as with any analysis, validation of the budget-impact analysis will increase the credibility and usefulness of the analysis. Validity has three main steps:

- Face validity testing to ensure that the analysis structure, assumptions, and input parameters are credible to the budget holder and capture all the resources for which they are responsible
- Internal validation to ensure that the input data have been correctly extracted and derived from the data sources and that all the calculations are performed correctly
- External validation to ensure that the results from the analysis mirror those that have been observed or will be observed in specific health plans

External validation is rarely done, but matching the estimates for the current treatment mix in the current year when using health plan-specific inputs in the analysis to those observed in the health plan will provide limited external validation.

14.3 Balancing Methods with Credibility

Even with the various methodological guidelines for developing budget-impact analyses (Sullivan et al. 2014; Mauskopf et al. 2007), we still need to consider the budget holder and the setting. As stated throughout the book, we believe that since budget-impact analyses are designed to help the health plan budget holders manage their resources, simple models that are populated with credible input data are more transparent than complex models and will be more credible and useful for budget holders. But we also want to caution that this might not always be the right thing to do.

For example, one of the authors of this book had developed a relatively simple budget-impact analysis estimating the impact of atypical schizophrenia drugs compared with typical drugs (Mauskopf et al. 2002). The impacts on costs in the analysis were initially only estimated for drugs and other direct health care service use. However, when the model was shown to some community mental health care budget holders to test its face validity, they asked why the model did not include changes in the resources used and costs for assertive community treatment and other behavioral interventions that were increased with use of atypical rather than typical drugs. The reply given was that changes in these costs were not included because they were not measured in the clinical trials. As a result, there were no data to estimate the changes. But the budget holders replied that this omission reduced the value of the analysis for them because they had to pay for those resources as well. In order to have an analysis that would be useful for them, estimates of the impact of atypical drugs on these costs were added to the model based on estimates of changes in use of these interventions. Since these data were not available in the published literature, these estimates were derived only from conversations with providers. The lesson learned was that a budget-impact analysis needs to include all the costs viewed as important to the budget holders whether or not there are good data to support all the input resource use and cost estimates.

Another consideration is the value of including estimates of the annual changes in the health care resource use and health outcomes in addition to the annual financial impact. These outcomes can be useful for helping the budget holders justify the increased budget and also for planning health target, personnel, or facility needs. They also are useful in settings where costs are negotiated. As such, any cost estimated by the budget-impact analysis may not accurately reflect the payer or budget holder's costs.

An example of the importance of reporting outcomes for planning budgets is the first budget-impact analysis that one of the authors completed. It was for the AIDS Drug Assistance Program (ADAP) of the State of North Carolina. The budget holders in the ADAP wanted to request increased state funding for the ADAP in the 1990s so that they could add coverage for their enrollees of drugs for prophylaxis of opportunistic infections. The budget-impact analysis provided the ADAP budget holders with estimates of the annual increase in funding they would need to request from the state to cover the costs of providing these drugs. But the analysis also provided the ADAP budget holders with estimates of the number of opportunistic

infections and hospitalizations for those infections that they would avoid each year with the increased funding. The funding request was approved by the State Budget Appropriations Committee. Providing the health and resource benefits alongside the increased costs gave the committee tangible information about the benefits from the increased budget that made approval more likely.

An example of the importance of considering health outcomes because of the variability expected between budget holders due to variations in costs is in a budget-impact analysis that another one of the authors created for a manufacturer to take to a hospital. In this analysis, a new drug was coming to market to treat atrial fibrillation. In the hospital model, pharmacy and other direct health care costs were considered. From an outcomes perspective, hospitalizations avoided were estimated. Several hospital administrators reviewed the analysis. All hospital administrators agreed that the cost impact would be variable for different hospital settings, but the administrators all found the impact on hospitalization as feasible and credible. Consensus from all administrators was that showing that this new drug would reduce the number of hospitalizations that occurred within a year was the most important result that could be presented to them.

14.4 Closing

Although we have tried to provide detailed instructions in this book for developing a budget-impact analysis for any new drug intervention, we must point out that every condition and drug is different, and our instructions might not always be appropriate for every situation. In Chap. 13, we have indicated how the instructions might change for other types of health care interventions. For all budget-impact analyses, one always needs to (1) estimate the treated population size and relevant descriptors and associated future treatment shares, (2) estimate drug-related and condition-related costs for the current drugs and the new drug, and (3) perform uncertainty analyses. But exactly how this is done will depend on the condition and on how the new drug or other health care interventions affect the current treatment mix and the condition outcomes.

Nevertheless, modeling methods evolve over time. This is true for budget-impact analysis. One area where better methods are needed for budget-impact analyses is incorporating drug switching or titration or discontinuation into the treatment mix estimates and accounting for these changes in the estimates of changes in condition-related costs. For example, for a chronic condition where there are many treatment alternatives that can be used sequentially to achieve the desired outcome (HbA1c to goal, blood pressure or lipids below target levels, or viral suppression in those with HIV infection), it might be reasonable to assume that anyone taking one of the treatments has achieved the desired outcome. This is based on the assumption that if they do not achieve the desired outcome with one treatment, they will switch to a second treatment. When a new, more effective drug is added to the treatment mix in this situation, this might change the treatment mix but not change the clinical outcomes (other than maybe shortening the time to the desired treatment outcome).

Alternatively, if patients for whom treatment failed are no longer actively treated, the addition of a more effective drug might increase the size of the drug-treated population. Methods for accounting for the condition-related costs in these circumstances are not very well developed.

Another area where methods are not well developed is in estimating the changes in treatment mix over time both with and without the new drug in the treatment mix. Current approaches typically start with an estimate of the current treatment mix without the new drug based on analyses of a health plan's current setting. However, projections of change in treatment mix once the new drug is introduced or without the new drug in the treatment mix tend to be based on assumptions or best-guess estimates. Often, the default uptake of the new drug in a budget-impact analysis is overestimated, which results in an overestimate of the budget impact. Manufacturers and payers tend to perform forecasting for the new drugs but are often hesitant to share this information with other budget holders. Guidance for methods to estimate uptake of the new drug and changes in market share among other comparator treatments could be useful.

We anticipate future editions of this book to expand on these methods and others as budget-impact analyses evolve. Further research will enable us to present more advanced topics, and we will be able to provide instructions and examples for using them.

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