1

The discipline of Statistics: Introduction and terminology

1.1 Introduction

It is common to start a textbook with a definition of the book's topic. However, in the case of the discipline of Statistics (indicated in this book with a capital "S"), it is difficult to find a universally accepted definition. Different textbooks are written for different target audiences, and their goals can therefore be quite different. So, before going any further, it is appropriate to identify our target audiences, and to provide you with a definition of Statistics that is informative and meaningful in the context of this book.

The discipline of Statistics is discussed in the context of pharmaceutical clinical trials because two of the primary target audiences for this book are students of pharmacy and students of clinical research. A clinical trial can be defined as an experiment testing a medical treatment on humans (Piantadosi, 2005). In this definition, the words "human" and "clinical" are closely linked. However, this definition also makes it clear that clinical trials can be performed to test a variety of medical treatments. In addition to pharmaceutical trials, the focus of this book, clinical trials are conducted to test medical devices (see Becker and Whyte, 2006) and some surgical practices.

In addition to being suitable for students of both pharmacy and clinical research this book is also suitable for other students who are interested in the development of new pharmaceutical drugs, including students of medicine, nursing, and other health-related professions where pharmacotherapy is of relevance. Statistics courses are typically part of such degree programs, and we have designed this book so that these students will also benefit from the material presented and taught. Our goal in this book is to introduce you to basic statistical methodology and analysis in a meaningful and very relevant context, the conduct of pharmaceutical clinical trials. We use the phrase "clinical trials" from now on with the understanding that all discussions are about the development of pharmaceutical drugs.

By teaching Statistics in a context that is very relevant to you, the statistical analyses that you will learn about will not simply be abstract ideas: They will be techniques that meaningfully collect and analyze numerical information of importance in your profession. The development of new drugs, whether brand-new chemical entities (NCEs), biologics, or new forms of existing drugs, requires three steps:

1. collection of numerical representations of information
2. analysis and interpretation of this numerical information
3. decision-making based on this analysis and interpretation.

By the end of this book you will have a solid conceptual knowledge and understanding of the experimental methods and statistical analyses used in new drug development. In addition, you will have gained computational knowledge: You will have learned how to conduct the most commonly used statistical analyses and how to interpret the results of these analyses. This combination of conceptual and computational knowledge and understanding is a powerful one that will serve you well in the rest of your studies.

A couple of conceptual points are useful here. First, there is much more to the discipline of Statistics than "obligatory calculations" at the end of a study. Rather, the discipline of Statistics is an integral component throughout the entire

new drug process. Second, conducting the statistical analyses most commonly employed in new drug development is really not that hard. The hard parts of new drug development are asking the correct research questions, making sure that the correct study design is used in each clinical trial, and making sure that the correct experimental methodologies are used to acquire optimum quality data during the clinical trial (we talk more about these issues in Chapters 3 and 4). If good research questions are asked, and the correct study designs and experimental methodologies used to collect optimum quality data, performing the statistical analyses is not really that difficult. As Piantadosi (2005) commented, "good trials are usually simple to analyze correctly."

1.2 The discipline of Statistics

The discipline of Statistics is a well-developed and powerful discipline that involves much more than simply number crunching. Crunching numbers is certainly part of it, but, unless those numbers have been carefully and meaningfully collected, crunching them is not going to provide any useful information.

Statistics is a scientific discipline because it adopts the scientific method: A method of thinking and conducting business in a certain way. You are very likely familiar with the sciences of biology, chemistry, and physics, but these are not the only sciences. Individual fields of investigation can be called a science, or a scientific discipline, if they adopt the scientific method of inquiry. In this method, theories lead to hypotheses, and these hypotheses are then tested in the scientific manner. A key characteristic of scientific hypotheses is that they need to be able to be disproved. If repeated evaluations of a theory via appropriate hypothesis testing do not disprove the theory, compelling evidence starts to accumulate that the theory may have merit. It is then deemed reasonable to proceed on the basis that the theory does indeed have merit, but with the knowledge and acceptance that future investigations may provide evidence that the theory does not have merit (see Turner, 2007).

In this book we have adopted the broad operational definition of Statistics provided by Turner (2007). In this definition, Statistics is regarded as a multi-faceted scientific discipline that comprises the following activities:

- Identifying a research question that needs to be answered.
- Deciding upon the design of the study, the methodology that will be employed, and the numerical information (data) that will be collected.
- Presenting the design, methodology, and data to be collected in a study protocol. This study protocol specifies the manner of data collection and addresses all methodological considerations necessary to ensure the collection of optimum quality data for subsequent statistical analysis.
- Identifying the statistical techniques that will be used to describe and analyze the data in an associated statistical analysis plan that is written in conjunction with the study protocol.
- Describing and analyzing the data. This includes analyzing the variation in the data to see if there is compelling evidence that the drug is safe and effective. This process includes evaluation of the statistical significance of the results obtained and, of critical importance, their clinical significance.
- Presenting the results of a clinical study to a regulatory agency in a clinical study report, and presenting the results to the clinical community in journal publications.

This functional definition makes clear that the discipline of Statistics is indeed multi-faceted and essential throughout clinical trials. It is critical at the start of the clinical trial process so that a study can be designed appropriately to facilitate the collection of optimum quality data, which then need to be organized and managed correctly. These data are then described and analyzed, and the numerical results of these analyses are interpreted in the context of the particular study. Finally, the numerical results of the analyses and the authors' interpretation of these results are presented to regulatory agencies to request permission to market the drug, and published in clinical communications to provide information to physicians.

This functional definition of Statistics may well contain some concepts and terms with which you are not familiar at this point, and that is fine. This book's goal is to make you familiar with these terms and concepts so that you will understand the statistical processes and procedures that are used in clinical trials. Individual chapters address different parts of this definition. However, it is important for us to emphasize here that the individual aspects presented in the chapters are really seamless components of one overall experimental approach to gaining knowledge, the discipline of Statistics. These components act together to ensure that high-quality data acquisition, correct analysis, and appropriate interpretations provide optimal answers to good research questions.

1.3 The term "statistic" and the plural form "statistics"

Having operationally defined the discipline of Statistics, we will now operationally define the terms "statistic" and "statistics," each written with a lower case "s." A statistic typically involves one piece of numerical information. For example, the number of states in the United States of America is 50, and the number of countries comprising the United Kingdom is 4. In some circumstances, however, a statistic can usefully involve more than one piece of numerical information. Consider how you might describe a sports team's performance in a season. A simple numerical representation of this success might be the number of games they won, perhaps 17. However, it is probably more useful to provide information about wins and losses (assume no draws), and therefore to provide the total number of games as well. In this context, a "17-3" summary of the season's performance (a winning season) is quite different from a "17-23" summary of performance (a losing season), even though the number of wins is the same. So, if you want to regard 17-3 as a single statistic, even though it contains two numbers, this seems perfectly reasonable to us. Indeed, one medical example of a single statistic involving two pieces of numerical information, a person's blood pressure, is particularly relevant for the discussions in this book concerning the development of a new investigational drug that is intended to reduce high blood pressure. This point is discussed further in Section 1.10.

The word "statistics" with a lower case "s" is used throughout the book as simply the plural of the term statistic. A listing of the sports team's wins and losses for the last 10 seasons, perhaps along with similar details for every other team in the same division or conference, would very adequately be described as statistics.

1.4 The term "statistical analysis"

The term "statistical analysis" has two meanings. Statistical analysis, used in a general sense, can be regarded as a global description or plan of how data collected will be analyzed. The term "a statistical analysis" refers to an individual analytical technique that is used to describe and analyze numerical information. This book teaches you how to conduct a collection of statistical analyses that are appropriate for use in analyzing the results of clinical trials.

1.5 Association versus causation

If we were to measure a number of characteristics (for example, age, height, and bone mineral density) in a large group of individuals we would undoubtedly find that they were related in some sense. For example, as we age from infants to young adults, our height increases from 18 inches (or 45 cm) or so to 50 inches (1.27 m) or more. If we were to examine the age and height of children aged less than 17 years, we would not find many (if any) 17-year-old children who were 18 inches (45 cm) tall, and we would not find many (if any) 2-year-old children who were 60 inches (1.52 m) tall. Biological and medical traits with such a relationship are said to be associated.

When someone suffers an acute injury such as a cut from a kitchen knife the immediate bodily response *may* include bleeding and sharp stinging pain. Various biological responses to the trauma can lead to a number of measurable effects. Had the trauma not occurred at this time the finger would not have bled and nor would the sharp stinging pain have occurred. Some cuts are so minor that they do not result in either bleeding or pain so the occurrence of the trauma does not perfectly predict the effects bleeding and pain. The philosophical description of causative effects is controversial. Without delving into this controversy we can think of cause-and-effect relationships as being established on the basis of:

- biological plausibility
- temporal relationship between the antecedent (cause) and the result (effect)
- some quantitative demonstration that occurrence of the "cause" increases the likelihood of observing the effect.

The two concepts association and causation occur throughout this text and they should not be confused. Association of two characteristics is a requirement to establish causation, but the converse is not true. It is truer to say that aging "causes" human growth than to say that growth causes aging. There are a number of research methods, especially in the field of epidemiology, that may be used to study the relationship among various health risks (including the use of medical treatments) and health outcomes. However, the randomized clinical trial is considered the gold standard when it comes to establishing cause-and-effect relationships. In this book we discuss the likely causative effects of new drugs on health outcomes of interest.

1.6 Variation and systematic variation

The study of the biological sciences has major differences from the physical and mathematical sciences. In the physical sciences, the same operation done under the same conditions always produces the same result. For example, a ball dropped off the same building always accelerates towards the earth at the same rate, a rate governed by the gravitational pull between the earth and the ball. In the biological sciences, including the clinical sciences, this is simply not the case. The same dose of medicine (even dose adjusted for weight) will not have an identical effect on two different people. In a large group of people there will typically be considerable variation in response. Similarly, the optimum clinical care of one patient will likely involve a different combination of therapeutic interventions than the optimum care of another. In clinical research we have to deal with variation, and examining data for systematic variation falls squarely within the province of Statistics. The topic of variation is discussed further in Chapter 5.

1.7 Compelling evidence

Compelling evidence in Statistics might be thought of as the inverse of 'reasonable doubt' in the legal system, but with the advantage that it can be quantified according to the precise rules of Statistics. The discipline of Statistics has been developed as a widely accepted method of conducting scientific investigation in many fields, including drug development. Data are collected, analyzed, interpreted, and presented in a certain way such that the scientific and clinical communities at large recognize the validity of the study.

In the practice of law, each attorney presents his or her evidence in a certain manner to a jury under the scrutiny of a judge, who makes sure that each component of the evidence is legitimate in that it meets an acknowledged level of acceptance. It is often true in legal cases that absolute proof is not possible (unless there is incredibly strong evidence such as a video of the crime, and even then the defense lawyer will probably argue the existence of extenuating circumstances), so the prosecutor's arguments have to be demonstrated to be likely true beyond a reasonable doubt. In the context of clinical trials the discipline of Statistics incorporates accepted methods of data collection and data analysis that can provide compelling evidence that an investigational drug does indeed do what

it is intended to do. A clinical trial may provide compelling evidence that an investigational drug does indeed lower blood pressure. The term "compelling evidence" is not the same as the term "proof" because a single clinical trial cannot prove that a drug is effective. However, it can certainly provide compelling evidence.

1.8 The terms "datum" and "data"

The word data is a plural word indicating more than one piece of numerical information. The singular form of the term is datum. As the statistical analyses described in this book always analyze more than one data point the term "data" is used throughout. Accordingly, accompanying plural words are used in conjunction with the word data. Examples are "the data are, the data were, these data, the data show."

If you have any uncertainty as to how to construct a phrase including the word data, replace the word data in your mind with the word results. While the words data and results are not synonymous, the word results is a plural construct, as is the word data. This strategy will likely help you express a phrase including the word data correctly.

The word datum does not occur again in this book.

1.9 Results from statistical analyses as the basis for decision-making

Many decisions have to be made throughout the drug development process. A lot of these decisions concern whether it is prudent to continue to the next phase of development, as outlined in Chapter 2. To allow rational decisions to be made we need reliable, quantitative information upon which to base our decisions. In a very real sense the main contribution of the discipline of Statistics in research endeavors is providing numerical representations of information that facilitate good decision-making.

Data are numerical representations of individual pieces of information. Once data have been collected in a clinical trial that employed the appropriate study design and experimental methodology, statistical analysis utilizes these individual pieces of numerical information to obtain a numerical representation of the "big picture." The results of a statistical analysis and, very importantly, the interpretation of these results in the context of the specific research question being asked provide the empirical information upon which decisions can be made. We talk a lot about decision-making in this book.

1.10 Blood pressure and blood pressure medication

We have deliberately chosen to focus on one particular therapeutic area for the worked examples throughout this book: This strategy provides a unified approach in all of the discussions about clinical trials and statistical analyses. Our discussion and worked examples focus on the development of a new investigational drug for the treatment of high blood pressure. The term hypertension is used for this condition, and drugs intended for the treatment of hypertension are called antihypertensive drugs, or simply antihypertensives.

1.10.1 Blood pressure and its measurements

The measurement of blood pressure usually involves the joint measurement of two aspects of arterial blood pressure, systolic blood pressure (SBP) and diastolic blood pressure (DBP). The SBP provides a representation of the pressure of blood as it is ejected from the heart into the body's arteries at each heart beat. The DBP provides a representation of the blood pressure in the arteries in between each heart beat. A healthy blood pressure for a young adult is often represented as "120/80." This is pronounced "one twenty over eighty." In this case, the "/" symbol does not represent the division of 120 by 80 to get a value of 1.5: It is simply used to separate the two blood pressure readings. The units of blood pressure are millimeters of mercury (mmHg), so

the actual blood pressure values in this case are an SBP of 120 mmHg and a DBP of 80 mmHg.

Suppose now that we measured someone's blood pressure five times, once every 5 minutes. The average blood pressure could be represented by calculating the average SBP (say 124 mmHg) and the average DBP (say 82 mmHg) and then writing this average blood pressure as 124/82.

1.10.2 Medical management of blood pressure

The Seventh Report of the Joint National Committee on Prevention, Detection, Evalution, and Treatment of High Blood Pressure (JNC 7: National Institutes of Health, 2004) is a definitive publication concerning the treatment of hypertension. It provides the following blood pressure classifications for adult blood pressures:

- Normal: SBP $<$ 120 mmHg and DBP $<$ 80 mmHg.
- Pre-hypertension: SBP 120–139 mmHg or DBP 80–89 mmHg.
- Stage 1 hypertension: SBP 140–159 mmHg or DBP 90–99 mmHg.
- Stage 2 hypertension: SBP $\geq$ 160 mmHg or DBP $\geq$ 100 mmHg.

These classifications are related to management strategies for hypertension. This report is the first of the JNC's series of reports to use the term "pre-hypertension," a term introduced to signal the need for increased awareness and education among healthcare professionals and the general public of the benefits of reducing blood pressure before it reaches the levels in the hypertensive categories. The relationship between blood pressure and risk of cardiovascular events is "continuous, consistent, and independent of other risk factors. The higher the BP, the greater is the chance of heart attack, heart failure, stroke, and kidney disease" (National Institutes of Health, 2004, p 2). These classifications are provided as a very useful means of directing the management of blood pressure by clinicians, who have to make a decision whether or not to treat a patient. If they decide that pharmacological treatment is warranted they need to decide what regimen should be prescribed. There are several classes of antihypertensive drugs on the market, and clinicians typically follow the recommendations in this report.

1.11 Organization of the book

As noted in Section 1.1, reading this book provides you with a solid conceptual knowledge and understanding of the experimental methods and statistical analyses used in new drug development, teaches you how to conduct statistical analyses commonly used in clinical trials, and shows you how to interpret the results of these analyses to facilitate rational, information-based decision-making. This information is taught in the context of a particular category of clinical trials that are conducted during the development of a new drug. As you will see in Chapter 2, clinical drug development programs typically consist of a progressive series of clinical trials. These range from the first trials in which the investigational drug is administered to humans to much larger trials that are conducted as the last item before requesting marketing approval for the drug from a regulatory agency. This book focuses on these larger trials, frequently called Phase III trials and also known as therapeutic confirmatory trials.

This book, therefore, is a self-contained introduction to the discipline of Statistics and its use in therapeutic confirmatory clinical trials. The first part of the book provides introductory comments about the discipline of Statistics and lays the foundations for our later discussions in the context of pharmaceutical trials. Chapter 2 presents an overview of the process of new drug development and the role of clinical trials in this process. The categories of different types of clinical trials are identified and discussed so that you will understand the types of data collected in them.

Chapters 3 and 4 discuss how research questions are asked and answered in statistical language during clinical trials, and introduce the study designs and experimental methodologies that are used to acquire optimum quality data with which to answer our research questions. Chapter 5 discusses statistical ways of describing and summarizing these data. Chapter 6

introduces hypothesis testing and estimation, two important ways of analyzing data from clinical trials.

The concepts and techniques discussed in these chapters are then developed and extended in later chapters, in which we teach you how to conduct statistical analyses commonly employed in preapproval clinical trials, that is, clinical trials that are conducted before applying for marketing approval from a regulatory agency. Chapter 7 discusses clinical trials that are conducted at the beginning of a clinical development program. While these trials are not the major focus of this book, it is appropriate to consider them briefly. The statistical challenges in early phase trials are different from those in Phase III trials, and it is appropriate to highlight these differences.

Chapters 8–11 discuss clinical trials that are conducted later during the clinical development program. These chapters address both safety data and efficacy data. Throughout these chapters, each new statistical analysis taught is addressed in the following way:

- identification of the research question (what is the decision to be made?)
- identification of data that will provide an answer to the research question
- identification of the appropriate study design (how to conduct a trial that will provide data capable of answering the research question as accurately as possible)
- identification of the best methodologies to collect optimum quality data during the study with which to answer the research question as accurately as possible
- identification of the appropriate statistical analysis to be employed
- computational steps necessary to conduct the statistical analysis chosen
- inference and decision-making: Interpreting the results in the light of the specific research question asked.

Chapters 12 and 13 then conclude the book by providing an overarching discussion of the topics covered in previous chapters, and discussing further the philosophical rationales for the employment of Statistics in new drug development.

1.12 Some context before reading Chapters 2–11

The purpose of this section is to provide you with a conceptual framework within which to assimilate the statistical material presented in Chapters 2–11. While this book teaches you the computational skills to conduct some statistical analyses, as an introductory statistics textbook should, we also want to provide you with a conceptual knowledge and understanding of why these analyses are undertaken. Rephrasing this last point, we want to provide you with a conceptual knowledge and understanding of how the information gained from a clinical trial is used in various forms of decision-making.

1.12.1 Decision-making during a clinical development program

The process of developing a new drug is an extremely expensive one. While we do not know the precise exchange rate on the day that you are reading this, estimates of US$1bn and £600m are certainly very meaningful at the time of writing. A related and highly relevant observation is that most drugs fail to reach marketing approval. For every 10 000 potential drug compounds only 10 make it to initial clinical trials in which the investigational drug is administered to humans for the first time. Of these ten, only one, or maybe two, will successfully make it through all phases of clinical trials and be approved by a regulatory agency for marketing. Given that the other eight or nine investigational drugs will not receive marketing approval, that is, they will "fail," it makes sense from many perspectives that they fail as early as possible.

This statement may initially (and very reasonably) seem counterintuitive to you: Isn't the goal to approve a new drug? It certainly is, but, to get a drug approved, we need to provide a regulatory agency with compelling evidence that the drug is both safe and efficacious. If a drug is not safe and efficacious, the sooner we find out the better, for various reasons. First, money spent on a drug that fails cannot be spent on developing another drug that might receive marketing

approval – that is, from a business perspective, it is not optimal. Second, and more importantly, individuals volunteer to be in clinical trials.

In later phase clinical trials, individuals with the disease or condition of interest, that is, the desired indication for the investigational drug under development, volunteer for these trials. One crucial ethical aspect of preclinical trials is that we must be uncertain about whether the investigational drug works. If we know that the drug works we should not be giving a placebo to half of our participants. If we know (or arguably even strongly suspect) that the drug does not work we should not administer it to clinical trial participants. In addition, in the case of relatively less common diseases, there are only so many individuals who can participate in clinical trials, and we would prefer that they participate in a trial employing an investigational drug with a relatively higher chance of being approved than in one employing a drug with a relatively lower chance. Therefore, we should be constantly looking for evidence that our investigational drug does *not* work, and we should stop the clinical development program at that point. The discipline of Statistics provides the information that forms the rational basis for making the decision to stop the clinical development program, that is, to kill the drug.

1.12.2 Decision-making during evidence-based clinical practice

Evidence-based clinical practice has two components:

1. Providing the evidence: This is the domain of clinical research and, in the case of drug development, the province of clinical trialists. The discipline of Statistics is a central and critical component of the planning, conduct, analysis, and interpretation of clinical trials.
2. Using the evidence to decide on the best treatment for individual patients on a case-by-case basis. This is the domain of clinical practice.

Both components are vital to evidence-based clinical practice. Katz (2001, p xvii) has written persuasively and eloquently on this issue:

> All of the art and all of the science of medicine depend on how artfully and scientifically we as practitioners reach our decisions. The art of clinical decision making is judgment, an even more difficult concept to grapple with than evidence.

1.12.3 Summary

This book introduces you to the statistical methodology employed in drug development at both a conceptual and a computational level. Statistical methodology provides numerical representations of information that facilitate rational, information-based decision-making during regulatory considerations and clinical practice.

1.13 Review

1. When studying the effect of an investigational antihypertensive drug, what sources of background variation might we be concerned with in measurements of blood pressure?
2. Describe three cases where two biological or health traits are associated.
3. Describe three cases where two biological or health traits represent a cause and effect.

1.14 References

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2

The role of clinical trials in new drug development

2.1 Introduction

This chapter provides an overview of the process of new drug development. It introduces you to this process in a relatively succinct way, but still provides enough details for you to understand the relevance and importance of the statistical methodologies discussed in the following chapters.

As well as evaluating how well a new drug does its job (for example, how well an investigational antihypertensive drug lowers blood pressure), it is vital to evaluate the safety of the drug. Both safety and efficacy are investigated very thoroughly in preapproval clinical trials, and the discipline of Statistics provides the tools to conduct these investigations. As you will see in due course the types of statistical analyses used in the assessment of safety and of efficacy are quite different. Moreover, the evaluation of data collected during postmarketing surveillance once the drug has been approved for marketing employs additional types of statistical analyses. Hence, there is a wide variety of statistical analyses, and it is critical to use the appropriate methodologies and statistical analyses in each case.

New drug development is a very long, complex, and expensive undertaking. The process starts with the identification of a drug molecule, a chemical compound that may become an approved drug many years later. Extensive formulation and chemistry research must be undertaken to put the drug molecule in a form that may be used in nonclinical (animal) and clinical studies. The characteristics of a new drug that make it useful include the following (Norgrady and Weaver, 2005):

- It is safe.
- It is efficacious.
- It can successfully navigate all necessary regulatory oversight, including those that govern nonclinical trials and preapproval clinical trials, and be approved by regulatory agencies for marketing.
- It can be manufactured in sufficiently large quantities by processes that can comply with all necessary regulatory oversight and that are financially viable for the sponsor.

This list of attributes provides a good map for our discussions in this chapter.

2.2 Drug discovery

Drug discovery is the first part of the process of drug development. It can be conceptualized as the research done from the time of the recognition of a therapeutic need to the time that a drug candidate is selected for initial nonclinical testing. A drug candidate may be a small molecule or a biological macromolecule such as a protein or nucleic acid. Drug discovery activities vary between small molecules and biological macromolecules but the way in which preapproval clinical trials are structured is very similar in both cases. The descriptions here address small molecule drug discovery.

The ultimate goals of drug discovery are to identify a lead compound, a drug molecule that is the first choice candidate for the next stage of the drug development process, and then to optimize the molecule. This latter activity is called lead optimization. It refers to searching for a closely related molecule or chemically engineering

modifications in the lead drug molecule to produce the molecule that is best suited to progress to nonclinical testing. Contemporary disciplines such as genomics and proteomics, bioinformatics, structural–activity relationships, and *in silico* computer modeling (see Turner, 2007) are used to maximize the chance of an identified molecule producing the desired biological result (having beneficial pharmacodynamic activity) while simultaneously minimizing its chance of producing unwanted side-effects (having pharmacotoxic activity). Once a drug molecule that appears to have a 'good' chance of being suitable for human pharmacotherapy is identified (someone has to make this decision) the candidate drug is tested extensively in nonclinical research.

2.3 Regulatory guidance and governance

Once a certain point in a nonclinical development program is reached, compliance with regulatory governance becomes necessary. From that point on all aspects of the drug development process – manufacturing, the remaining nonclinical studies, and clinical trials – are conducted following regulatory guidance and governance. This section provides an overview of regulatory agencies and their work and responsibilities.

There are many regulatory agencies around the world, each charged to be responsible for public health within their respective countries. While there are some differences among these agencies, there are also many similarities: The activities of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, a long name that is usefully represented by the acronym ICH, have led to greater homogeneity. The ICH is an amalgamation of expertise from regulatory agencies and trade associations in Europe, Japan, and the USA. This chapter includes overviews of two regulatory agencies, the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA), and of the regulatory dossiers submitted to them during the development of a new drug.

2.3.1 The Food and Drug Administration

The US FDA is part of the Executive branch of the US government, and it is the country's regulatory agency responsible for the governance of new drug development. The FDA is housed within the Public Health Service, part of the Department of Health and Human Services. When a sponsor has generated sufficient discovery, formulation, and nonclinical data to justify (in their opinion) initiation of studies in humans, they prepare an investigational new drug application (IND). Generally, an IND includes data and information in four broad areas:

1. Animal pharmacology, pharmacokinetic, and toxicology studies.
2. Manufacturing information: These data address the composition, manufacture, stability, and controls used for manufacturing the drug.
3. Clinical study protocol: When originally submitted the general investigational plan should outline the overall plan, but it need articulate only the studies to be conducted during the first year of clinical development. The clinical study protocol submitted includes precise accounts of the design, methodology, and analysis considerations necessary to conduct the proposed study and analyze their results (see Section 4.8). A clinical investigator brochure is also typically included.
4. Investigator information: Information on the qualifications of clinical investigators is provided to allow assessment of whether they are qualified to fulfill their duties at the investigational sites used during the clinical trials.

As the IND progresses further clinical study protocols and the results of completed studies (manufacturing, nonclinical, and clinical) are submitted, and the IND grows accordingly.

When the clinical development program is complete and all nonclinical studies being conducted contemporaneously are complete, the sponsor submits a new drug application (NDA) (in the case of a biologic product, a biologics license application [BLA] is submitted). Typically,

sponsors meet with the FDA to discuss the content and format of an NDA before its preparation, because this "pre-NDA meeting" can be crucial for the sponsor to understand the content and format that will best facilitate the FDA's review (see Regulatory Affairs Professionals Society or RAPS, 2007, for more details). Marketing approval by the FDA means that a drug can be marketed in all 50 states within the USA.

While the ICH publishes an extensive list of guidances, the FDA also publishes guidances for industry that can be very helpful and can be located via the FDA's website (www.fda.gov).

2.3.2 The European Medicines Agency

The European Medicines Agency (EMEA: the second E is correct here) has its headquarters in London and is responsible for the evaluation and supervision of medicines for human (and veterinary) use in Europe. The EMEA coordinates the evaluation and supervision of medicinal products throughout the European Union, bringing together the scientific resources of the 27 (at the time of writing) European Union member states. It cooperates closely with international partners in ICH activities.

At the point where an IND would be submitted to the FDA, a clinical trial application (CTA) is submitted by the sponsor. We noted earlier that an IND grows in size as additional clinical study protocols in a clinical development program are submitted to the FDA, each being incorporated into the overall IND. In contrast, CTAs are protocol specific and one CTA must be filed for each clinical study protocol. Hence, in this case, the number of individual CTAs increases during a clinical development program. CTAs are based on summary information only; no full study reports are submitted.

At the completion of the sponsor's clinical development program a marketing authorization application (MAA) is submitted. An MAA is used for both small molecule drugs and biologics. There are two submission routes for the sponsor to choose from:

1. the centralized procedure
2. the decentralized procedure.

The centralized procedure has been in place since 1995. The review of the MAA is coordinated by nominees from the Committee for Medicinal Products for Human Use (CHMP) called the rapporteur and co-rapporteur. This procedure leads to a single EU scientific opinion, which is then translated into a pan-EU decision by the European Commission. The centralized procedure is mandatory in some cases (for example, for biotech drugs, and drugs intended for oncology, HIV, diabetes, and neurodegenerative disease indications) and it is also gaining popularity for all new NCEs.

The decentralized procedure has been in place since 2006. The review of the MAA is conducted by a single agency, called the Reference Member State (RMS). However, other EU countries in which the sponsor wishes to market the drug receive a copy of the MAA and are involved in confirming the assessment made by the RMS. These additional agencies are called concerned member states (CMSs). The decentralized procedure has its roots in the earlier "mutual recognition" procedure that was put in place in 1995. The mutual recognition procedure operated in a similar way except that the CMSs did not receive the whole MAA until after the RMS had approved the product. In both the decentralized and the mutual recognition procedure, the EMEA and CHMP do not get involved unless the RMSs and CMSs cannot reach a consensus decision.

Choice between centralized and decentralized procedures in the case of many NCEs (those for which the centralized procedure is not mandatory) involves many factors, and the decision is a strategic milestone involving medical practice, manufacturing plans, the nature of product, market forces, and the size, resources, and strengths of the sponsor in the EU (see Harman, 2004, for more details).

Similarly to the FDA, CHMP and its Expert Working Parties provide scientific and regulatory guidelines that apply across the EU to complement ICH guidance. (Regulatory agencies in other countries and regions may develop guidelines as needed.) Thus, while considerable progress towards harmonization has been made, it is still important for those seeking global regulatory approvals to consider regional and national regulatory guidance. (For further

information see www.emea.europa.eu/htms/human/humanguidelines/efficacy.htm and www.emea.europa.eu/htms/general/contacts/CHMP/CHMP_WPs.html).

2.3.3 GMP, GLP, and GCP

These three acronyms refer to good manufacturing practice (GMP), good laboratory practice (GLP), and good clinical practice (GCP). The various stages of new drug development should be conducted according to the appropriate regulations and guidance. The initial "c" can precede each of these acronyms, in each case standing for the word current. The implication here is that, in the years between rewrites of regulations and guidance, certain modifications in the generally accepted best way of performing a certain activity (best practices) may occur. Therefore, while the guidance as written in the most recent version reflects the "official" stance, it is considered wise to conform to modified ideologies as appropriate.

2.3.4 Statistical aspects in the preparation of regulatory documentation

The discipline of Statistics plays a major role in the preparation of all regulatory submissions, including the INDs, NDAs, CTAs, and MAAs that we have already mentioned. It also includes other important documents such as study protocols, statistical analysis plans, clinical investigator brochures, and the prescribing information and promotional materials that will be used by the sponsor to inform clinicians (and, in countries such as the USA where direct-to-consumer marketing is permitted, patients) about the drug. Prespecification of the statistical analysis plan is necessary to establish the credibility of study results. The accurate (and concise) presentation of the design of studies and their results is vital to ensuring a favorable marketing decision and approval of related documents.

2.3.5 Statistical aspects in the preparation of clinical communications

Sponsors typically publish the results of important clinical trials in clinical communications in medical journals, and present the results at scientific conferences. As for the preparation of regulatory documentation, scientific communications depend heavily on the discipline of Statistics. Piantadosi (2005) made the following comment about publishing clinical communications:

> Reporting the results of a clinical trial is one of the most important aspects of clinical research. Investigators have an obligation to each other, the study participants, and the scientific community to disseminate results in a competent and timely manner (p. 479).

While the format of clinical communications is different from the format of clinical study reports that are submitted to regulatory agencies, the discipline of Statistics provides the basis for the approach taken. A typical format for a clinical communication is:

- Abstract: A concise overview of the entire article
- Introduction: The rationale for the study
- Methods: The study design, study sample, methodology used, statistical analyses employed
- Results: The findings from the study
- Conclusions: The main findings and their interpretation
- Discussion: How the conclusions fit in with previous literature, and what the implications are for future research. Any limitations of the study are also a legitimate (and useful) aspect of this section.

The purpose of clinical research is to provide information that guides clinical practice. Clinical communications are read by physicians who use the information provided when deciding whether a particular treatment might be appropriate for an individual patient. These articles are

therefore extremely important, and the information must be presented accurately, meaningfully, and ethically. The term "ethically" emphasizes that authors must tell "the truth, the whole truth, and nothing but the truth" about their study in these communications (see Turner, 2007, for further discussion).

Guidelines for reporting clinical trials in clinical communications are provided by the Consolidated Standards of Reporting Trials (CONSORT) group. We recommend that you read the CONSORT statements (see www.consort-statement.org). We also refer you to Bowers et al. (2006) and Stuart (2007) for extensive coverage of this topic.

2.4 Pharmaceutical manufacturing

Once it has been decided to progress an identified drug molecule to nonclinical testing, the molecule will be tested in various ways, both *in vitro* and *in vivo*. Initial testing may require extremely small amounts of the candidate drug molecule. However, as testing progresses, larger amounts are needed. In addition, when the molecule is ready to be given to animals, it needs to be administered in a certain manner – that is, a drug molecule delivery system needs to be manufactured. Once a certain stage of nonclinical research has been reached, the drug delivery system must be manufactured according to cGMP standards as detailed by regulatory agencies. GMP regulations also apply to drug delivery systems used in clinical trials.

When an investigational drug is tested in early preapproval clinical trials relatively small amounts of drug product supplies are needed. However, if and when later stage preapproval clinical trials are conducted, considerably larger drug product supplies are needed. If the investigational drug is then approved for marketing the amount of drug that needs to be manufactured increases again. The manufacturing facilities that are needed to make the drug on a postapproval marketing scale are likely to be very different in their operation (not just bigger) from the various manufacturing facilities used during the drug development process (see Turner, 2007).

Manufacturing is a critical topic that frequently does not get the recognition and attention that it deserves. Imagine discovering a new drug molecule that could do wonders, but you cannot find a way to manufacture a drug delivery system that will get the drug safely into a patient who needs it. The drug delivery system needs to be able to be manufactured and then be readily transported from the manufacturing plant to the pharmacy in a form that demonstrates stability, and therefore has a suitably long shelf life. If you cannot do all this, the wonder drug would, for all intents and purposes, be useless (recall that the definition of a useful drug in Section 2.1 included manufacturing considerations).

There are various methods of introducing a drug molecule into the body: Tablets and injections are just two examples. In this chapter we focus on the manufacture of drugs that are given orally in tablets, because the largest percentage of drugs are administered in this manner. A tablet is a complex, manufactured, drug delivery system that gets the drug molecule, the active pharmaceutical ingredient (API) that exerts the drug's pharmacodynamic effect, into the systemic (whole body) blood supply, which carries it round the body to its target receptors.

The API is likely to be a small component of the tablet. Various other nonpharmacologically active ingredients, called excipients, are also constituents of the tablet. Each of these excipients has a specific characteristic that enables it to perform a useful function in getting the API to its target receptor. Some of the excipients protect the API from various chemical attacks in the mouth and on its way to the gastrointestinal tract. Others help it to travel through the gastrointestinal tract. Eventually the API is released from its formulation so that it can be absorbed in the small intestine and be transported around the body in the blood supply.

2.4.1 Manufacturing drug products for clinical trials

An additional consideration when manufacturing the drug products that are used in preapproval clinical trials is that they need to be "disguised." As we see later in the book, the safety and efficacy of an investigational drug are compared with those of another compound, called a control compound. In the types of trials on which we focus this control compound is typically (but not always) a placebo. The experimental methodology employed in these trials (discussed in Chapter 4) requires that neither the participants in the trials nor the investigators who are conducting them know whether the participants are being given the investigational drug or the placebo. Therefore, both clinical drug products need to look, smell, and taste the same – that is, they need to be blinded. Trials in which neither the investigator nor the participant can identify the investigational drug are called double-blind trials.

The blinding of clinical drug products adds another degree of complexity to the manufacturing needed for these trials. It involves two steps: Making the investigational drug and the placebo the same in appearance, as noted, and then packaging them in such a way that they cannot be distinguished by the package in which they are supplied to investigators. This practice is, necessarily, contrary to the manner in which marketed drugs are supplied.

2.5 Nonclinical research

Nonclinical research (often called preclinical research, but we prefer the term "nonclinical") involves the *in vitro* and *in vivo* animal research that is conducted and reported to regulatory agencies before starting preapproval clinical trials. Once the drug molecule candidate identified in drug discovery has been optimized, it moves into the nonclinical development program. While human pharmacological therapy is the ultimate goal, an understanding of nonclinical drug safety and efficacy is critical to subsequent, rationally designed, ethical, human trials. The term "efficacy" is used in drug development to refer to the desired therapeutic (biological) effect of the candidate drug. Nonclinical research gathers critical information about the best likely drug dose, frequency, and route of administration if and when research progresses to human trials. It also investigates pharmacokinetics, pharmacodynamics, and toxicology in animals.

Pharmacokinetics is the study of the effect that the body has on the drug. The pharmacokinetic phase can be regarded as the time from the drug's absorption into the body until it reaches its target receptor site. Dhillon and Gill (2006) noted that pharmacokinetics "provides a mathematical basis to assess the time course of drugs and their effects in the body." Pharmacokinetic processes that determine the concentration of a drug that has been administered include absorption, distribution, metabolism, and elimination (ADME). Pharmacodynamics is the study of the desired effect that a drug has on the body. For example, the pharmacodynamic effect of an antihypertensive drug is to lower blood pressure. The pharmacodynamic phase begins once the drug molecule reaches its target receptor. Toxicodynamics is the analogous study of the undesired effect(s) that a drug has on the body. The toxicodynamic phase begins once the drug molecule reaches a nontarget receptor(s).

Nonclinical safety pharmacology studies submitted to regulatory agencies are outlined in ICH Guidance S7A (2001), and the basic package includes evaluation of a drug candidate's effects on the central nervous system, respiration, and the cardiovascular system. Cardiovascular system evaluation includes assessment of cardiac function and cardiac electrophysiological activity.

Nonclinical toxicological testing is necessary because some compounds can be so toxic that they cause cell death, leading to loss of important organ function. Other toxicological effects are the result of interactions with various biochemical and physiological processes that do not affect the survival of the cells. ICH Guidance M3 (R1) (2000) addresses several topics related to toxicity, including single and repeat dose toxicity studies, genotoxicity, carcinogenicity, and reproductive toxicity. Relatively less evidence of

toxicity is considered as relatively greater evidence of the safety of the drug. The route of administration of the drug compound in nonclinical research is typically the intended route in clinical settings and therefore the route that will be used in clinical trials.

Exploratory toxicology studies are conducted to provide an idea of the main organs and physiological systems involved, and to estimate the drug's toxicity when administered across a relatively short period of time. These studies do not need to be conducted according to cGLP guidelines and they are not typically conducted with a drug compound that has been manufactured to cGMP standards.

Regulatory toxicology studies are submitted to regulatory agencies and are conducted according to cGLP standards. Some regulatory toxicology studies need to be done before the first clinical trials are started. Other regulatory toxicology studies are typically conducted in parallel with clinical trials. These include toxicological studies in two or more animal species lasting up to 1 year, carcinogenicity tests and reproductive toxicology studies lasting up to 2 years, and interaction studies that examine possible drug–drug interactions with other drugs that may be prescribed concurrently in humans. These studies are expensive to conduct, and so they are typically not started unless and until the drug progresses into clinical studies.

Mutagenicity is the chemical alteration of DNA that is sufficient to cause abnormal gene expression. Mutagenicity, also known as genotoxicity, includes a comprehensive set of events, of which carcinogenicity and teratogenicity are important subsets. Carcinogenicity describes activity that leads to cancer, and teratogenicity describes activity that leads to the impairment of fetal development.

Nonclinical information can be useful in another arena once a drug has been approved. Prescribing information can include the results of nonclinical toxicology studies (carcinogenesis, mutagenesis, and impairment of fertility). In instances where no human (clinical) data are available, it is possible for a clinician to incorporate nonclinical evidence into his or her decision-making process when deciding whether the benefit:risk ratio of prescribing the drug to a patient is favorable. The process of using clinical data to form such decisions can be challenging at times, and the process of using nonclinical data even more so. Nevertheless, in some instances nonclinical data may prove of assistance in this regard.

While a nonclinical development program is informative and important, no amount of nonclinical research can predict precisely what will happen once the candidate drug is given to humans. Therefore, a clinical development program is also necessary. The clinical development program builds in many meaningful ways on the results from the nonclinical development program.

2.6 Clinical trials

Clinical development programs consist of a variety of preapproval clinical trials, all designed for a specific purpose of revealing particular information concerning the investigational drug's safety and efficacy.

2.6.1 Categorization of clinical trials by phase

A common system of categorization for preapproval clinical trials includes Phase I, Phase II, and Phase III clinical trials (Phase IV clinical trials are conducted postapproval to collect additional information about a marketed drug). Phase I, II, and III clinical trials can be summarized as follows:

- Phase I: Pharmacologically oriented trials that typically look for the best range of doses to employ. These trials employ healthy adults, usually men. Comparison of the investigational drug's efficacy with other treatments (such as a placebo or a drug that is already marketed) is not a specific aim of these trials, because by definition healthy individuals do not have the disease or condition of interest. However, incorporation of an inactive control can be useful because some of the procedures employed in these trials may themselves

give rise to physiological changes that could otherwise be perceived as adverse events (see Section 7.5 for additional discussion).

- Phase II: These trials are designed to look for evidence of activity and preliminary evidence of efficacy and safety at a number of doses. Relatively small numbers of individuals with the condition or disease of interest are used. To gain an understanding of efficacy a control treatment is typically used at this stage.
- Phase III: These trials employ larger numbers of individuals with the condition or disease of interest, and they are comparative in nature – comparison with another treatment (often a placebo, but possibly an active control) is a fundamental component of the design. These trials are undertaken if Phase I and II studies have provided preliminary evidence that the new treatment is safe and effective.

While this system of categorizing preapproval clinical trials is widespread, unfortunately it is not used consistently. As Turner (2007) noted, two studies with the same aims may be classified into different phases, and two studies classified into the same phase may have different aims. An alternative system has been suggested by the ICH.

2.6.2 ICH categorization of clinical trials

The ICH has published a series of Guidances on many aspects of conducting clinical trials (see www.ich.org). One of these, ICH Guidance E8 (1997), provides an alternative approach to categorizing clinical trials, classifying them according to their objective. This system is shown in Table 2.1.

Table 2.1 ICH classification of clinical trials

Objectives of study	Study examples
Human pharmacology	
Assess tolerance	Dose–tolerance studies
Describe or define pharmacokinetics (PK) and pharmacodynamics (PD)	Single and multiple dose PK and/or PD studies
Explore drug metabolism and drug interactions	Drug interaction studies
Estimate (biological) activity	
Therapeutic exploratory	
Explore use for the targeted indication	Earliest trials of relatively short duration in well-defined narrow patient populations, using surrogates of pharmacological endpoints or clinical measures
Estimate dosage for subsequent studies	Dose–response exploration studies
Provide basis for confirmatory study design, endpoints, methodologies	
Therapeutic confirmatory	
Demonstrate/confirm efficacy	Adequate and well-controlled studies to establish efficacy
Establish safety profile	Randomized parallel dose–response studies
Provide an adequate basis for assessing benefit:risk relationship to support licensing	Clinical safety studies
Establish dose–response relationship	Studies of mortality/morbidity outcomes
	Large simple trials
	Comparative studies
Therapeutic use	
Refine understanding of benefit:risk relationship in general or special populations and/or environments	Comparative effectiveness studies
Identify less common adverse reactions	Studies of mortality/morbidity outcomes
Refine dosing recommendation	Studies of additional endpoints
	Large simple trials
	Pharmacoeconomic studies

From ICH Guidance E8 (1997).

Trials that might otherwise be categorized as Phase I, II, III, and IV trials are referred to as human pharmacology, therapeutic exploratory, therapeutic confirmatory, and therapeutic use trials, respectively.

2.6.2.1 Human pharmacology trials

Human pharmacology or first-time-in-human (FTIH) clinical trials are undertaken in an extremely careful manner in tightly controlled settings, often in residential or inpatient medical centers. Typically, between 20 and 80 healthy adults participate in these relatively short studies, and are often recruited from university medical school settings where trials are being conducted. The main objectives are to assess the safety of the investigational drug, understand the drug's pharmacokinetic profile and any potential interactions with other drugs, and estimate pharmacodynamic activity. A range of doses and/or dosing intervals is typically investigated in a sequential manner.

Participants are given extensive physical examinations before they receive their first dose of the drug, at various intervals throughout the treatment, and once they have finished the drug regimen. The trials are designed to collect data that can be compared with similar types of data collected in nonclinical studies. As noted earlier, no animal model data can ensure that a drug will be safe when given to humans. However, it can be informative to see how similar the overall pictures of animal responses and human responses are. Single-dose trials in which the dose chosen is based on the nonclinical work are conducted first. Later, dose-finding studies are conducted to determine the maximum tolerated dose (MTD) of the drug, and to answer questions concerning the side-effects that are seen, their characteristics, and whether they are consistent across participants to any notable degree.

Although the data collected during human pharmacology trials are not in themselves enough to obtain marketing approval, they can certainly have the opposite effect: Unfavorable data can lead to a sponsor's decision not to pursue further development of the drug. While achieving marketing approval of an investigational drug is the sponsor's goal, if the drug is unlikely to succeed it is financially attractive to discover this as early as possible in the drug development program. As we noted earlier, the sentiment here is "If you are going to fail, fail fast!" A well-conducted human pharmacology study can reduce the possibility of later failed trials by revealing unfavorable characteristics of the drug at this stage. This is preferable to the sponsor and, more importantly, in the best interests of individuals who may have been participants in later trials that failed.

From a statistical viewpoint the design of human pharmacology studies has certain implications. These trials include a relatively small number of participants, but a lot of measurements are collected for each participant. This strategy has both advantages and limitations. The extensive array of measurements made allows the drug's effects to be characterized reasonably thoroughly. However, few participants in these studies makes generalization of results to the general population relatively harder than for studies with larger sample sizes.

2.6.2.2 Therapeutic exploratory trials

Therapeutic exploratory trials are conducted if the results of the human pharmacology trials are considered positive (someone has to decide that the results are positive). These trials involve the comprehensive assessment of the investigational drug's safety in perhaps 200–300 individuals with the disease or condition of interest. They are typically conducted by clinical pharmacologists, and participants in these trials are often hospitalized and can therefore be closely monitored. Extensive data are collected, including self-report assessments by the participants and biochemical assessments.

Sometimes efficacy will be investigated in these trials. Participants are again typically hospitalized and can therefore be closely monitored. Assessments of efficacy are typically conducted by individuals specifically trained in clinical trial methodology.

2.6.2.3 Therapeutic confirmatory trials

If the therapeutic exploratory trials are successful (someone has to decide if this is the case), the

drug development program will proceed to therapeutic confirmatory trials. By now, the earlier human pharmacology and therapeutic exploratory trials have defined the most likely safe and effective dosage regimen(s) for use in these therapeutic confirmatory trials. These trials may employ around 3000–5000 participants, each of whom has the disease or condition of interest, and they are typically conducted as randomized, double-blind, concurrently controlled trials (see Chapter 4).

Tight experimental control is an extremely important goal in all experimental trials. Consequently, we talk a lot about how to maximize such control in these trials. However, it is simply a realistic consequence of the way that therapeutic confirmatory trials have to be conducted that the experimental control cannot be quite as tight in these trials as it is in human pharmacology trials and therapeutic exploratory trials.

As we note many times in this book there are advantages and disadvantages associated with many occurrences in clinical trials, and with the last statement of the previous paragraph. The very high level of experimental control that is possible in therapeutic exploratory trials means that these trials are better at assessing the 'pure' biological effect of the drug, that is, the efficacy of the drug under near-ideal circumstances. However, if and when a drug is approved for marketing and is being used by many patients, the drug will not be taken in the same very highly controlled manner in which it was given to participants in therapeutic exploratory trials. The data from therapeutic confirmatory trials are therefore likely to be more indicative of how the drug will actually work in the general population if it receives marketing approval.

2.6.2.4 Therapeutic use trials

Therapeutic use trials are conducted once a drug has been approved to gain additional information about the safety and efficacy, or effectiveness, of the drug: The term "effectiveness" is used to describe how well the drug works in patients once the drug has been approved. One example of this type of trial is the simplified clinical trial (SCT). The intent of the word simplified in the term "SCT" should be clarified here. It refers to the fact that the demands on participants and investigators are less than in preapproval trials. It is not meant to indicate that the implementation of these large trials is simple: On the contrary, their design and logistics are complex.

As in preapproval therapeutic confirmatory trials, participants in SCTs are randomly assigned to a treatment group. However, SCTs have several characteristics that distinguish them from therapeutic confirmatory trials. Probably the most immediately noticeable difference is the number of participants who participate in them. SCTs are designed to detect rare events by including sample sizes that are much larger than those employed in preapproval trials, and thus they are very important in safety monitoring. However, in order to facilitate the conduct of an SCT involving such a large number of participants, the amount of information collected per participant is much smaller than in therapeutic exploratory studies. The demands on both the participants and the investigators conducting the trial have to be reduced to make these studies viable. So, for example, instead of visiting the investigative site every week during a 12-week treatment period and having a large number of assessments made, participants may visit only twice (at the start and end of the treatment period) and have relatively few assessments made on those occasions. These assessments are those of most interest.

Participants in SCTs receive treatments in a more naturalistic setting than those in therapeutic confirmatory trials. Therefore, as well as more participants, the treatment settings are much more representative of how patients in general will be treated when the drug is approved. Advantages and disadvantages accompany many choices and occurrences in designing and conducting clinical trials.

2.7 Postmarketing surveillance

Postmarketing surveillance is conducted once the approved drug is in widespread use to examine safety in a more comprehensive

manner. Postmarketing surveillance monitors all reports of adverse reactions and thus can be used to compile extended safety data. This pharmacosurveillance is a critical component of the overall process of ensuring that all members of a target disease population receive the greatest protection from adverse reactions. As this book focuses on preapproval trials and their statistical methodology, postmarketing surveillance is not discussed. Readers are referred to Mann and Andrews (2007).

2.8 Ethical conduct during clinical trials

The ethical conduct of all clinical researchers is of supreme importance. Participants in all clinical trials are volunteers: while the word "volunteers" is typically exclusively used to describe participants in human pharmacology studies, all participants in all clinical trials are, by definition, volunteers (see Turner, 2007). Individuals participate in clinical trials for the greater good, not specifically to benefit themselves. Everyone involved in clinical research has an obligation to conduct all aspects of this research to the highest ethical standards.

2.8.1 Ethical principles

Several fundamental ethical principles guide drug development research in clinical trials (see Turner, 2007):

- Clinical equipoise: This requires that a comparative clinical trial must be started in the good faith that the investigational drug and the control treatment are of equal merit. The aim is to discover whether or not the investigational drug is of greater merit. Once there is compelling evidence that the investigational drug is of greater merit, it becomes unethical to give the control drug to participants.
- Respect for individuals: Investigators must give potential trial participants all pertinent information about the study, and answer all of their questions. If a potential participant then agrees to participate voluntarily (that is, he or she is not coerced in any real or implied manner), informed consent is obtained.
- Beneficence: The study design employed in the trial must be scientifically sound, and any known risks of the research must be acceptable in relation to the likely beneficial knowledge that will be obtained.
- Justice: The burdens and the benefits of participation in clinical trials must be distributed evenly and fairly. Vulnerable populations (for example, prisoners, residents in nursing homes) should not be deliberately chosen for participation in clinical trials when nonvulnerable populations are also appropriate participants. The benefits of participation, such as access to potentially life-saving new therapies, should be available to all, including those not historically well represented such as women, children, and members of ethnic minorities.

The topic of ethics in clinical trials is addressed again in Section 3.16.1, where we talk about ethical considerations in choosing the nature of the control treatment used in trials involving investigational antihypertensive drugs.

2.8.2 Ethical considerations in statistical methodology

It is appropriate here to highlight the additional ethical responsibilities that are shouldered by those involved in statistical aspects of clinical trials, as outlined in the operational definition of Statistics presented in Chapter 1. Derenzo and Moss (2006) addressed the importance of ethical considerations in scientific and statistical aspects of clinical studies:

> Each study component has an ethical aspect. The ethical aspects of a clinical trial cannot be separated from the scientific objectives. Segregation of ethical issues from the full range of study design components demonstrates a flaw in understanding the fundamental nature of research involving humans. Compartmentalization of ethical issues is inconsistent with a well-run trial. Ethical and scientific considerations are intertwined.
>
> Derenzo and Moss (2006, p 4)

Ethical awareness and ethical responsibility are key aspects of statistical methodology in clinical trials. Areas where ethical and scientific considerations are inextricably linked include:

- Study design and experimental methodology: It is unethical to include people in a study where poor design and/or poor methodology will lead to less-than-optimum quality data and therefore less-than-optimum quality answers to the study's research question.
- Sample-size estimation: A trial requires sufficient participants to answer the research question without exposing them unnecessarily to the risks of the experimental therapy.
- Early termination of trials: Data monitoring committees (DMCs), independent groups charged with reviewing interim data from clinical trials, face difficult ethical challenges when deciding whether a clinical trial should be terminated early. In a recent guidance document the FDA described the roles and responsibilities of DMCs and when such committees may be useful or required (US Department of Health and Human Services, FDA, 2006).
- Communicating trial results: Researchers have an ethical responsibility to report information accurately and fully in clinical communications, as these directly impact patient care.

Correct study design is absolutely essential from both scientific and ethical perspectives when conducting clinical trials. If a study's design cannot lead to the collection of data that can be analyzed meaningfully, no meaningful information about the investigational drug can be gained. Participants in clinical trials have the legitimate expectation that their participation in the trial will help advance our knowledge of the investigational drug, and if the study's design cannot possibly provide additional knowledge about the drug their expectation is not fulfilled (Turner, 2007).

2.9 Review

1. What are the characteristics of a useful new drug?
2. Describe the ethical considerations in preparing clinical communications.
3. What is the role of pharmaceutical manufacturing in new drug development?
4. What is the role of nonclinical research in new drug development?
5. Consider the ICH classification of clinical trials: Human pharmacology, therapeutic exploratory, therapeutic confirmatory, and therapeutic use:
   (a) What is the role of each type of trial in the development of a new drug from a molecule to a new therapy?
   (b) How do results from these types of trials pertain to the use of the new drug in medical practice?

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