Chapter 8
Risk–Benefit Evaluation in Clinical Research Practice

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ABSTRACT
A core element in protecting human participants in clinical research is the assurance of a favorable risk-benefit balance, in accordance with the ethical principle of beneficence. However, the assessment of risks and benefits may sometimes be challenging. In this chapter, the authors review the concepts, ethical principles, and applicability of those terms. The assessment approaches used by regulators and research reviewers who are working in clinical practice are then discussed, together with a highlight of the new trends in risk-benefit analysis and their impact on drug development and approval. Analysis of some research situations which pose particular challenges are presented at the end of the chapter.

INTRODUCTION
Assuring a favorable risk-benefit balance is crucial to human subjects’ protection in clinical research and thus complies to the principle of beneficence in the Belmont report, written and published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979. It is a critical requirement for all research regulations that guide each step in research. It is also the main criteria for determining the approvability of categories of participants and reviewing those categories, the degree of protection required for each category of participants, according to the type and frequency of monitoring study.

The objective of this chapter is to highlight the:

1. Concepts, principles, and types of risks and benefits;
2. Methodology of risk-benefit analysis;
3. Applications and impact of data science technology in clinical research practice;
4. Challenges to risk-benefit analysis and suggested resolutions.

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BACKGROUND

Evaluation of the risk-benefit balance in research is a complex process, which is sometimes straightforward, but in other cases it is more challenging.

Balancing risks to patients against the total benefits to science or to future patients is one of the most difficult issues, especially in research involving vulnerable populations.

The aim of this chapter is to lead the readers through the decision-making process of risk-benefit evaluation of clinical research.

The scope: Throughout the three main sections of this paper, we discuss the main principles, approaches and challenges of risk and benefit assessment in clinical research.

SECTION I: PRINCIPLES OF RISK-BENEFIT ASSESSMENT IN CLINICAL RESEARCH

Risk-benefit assessment is an universal requirement for protecting human participants in clinical trials. The concept and perception of risks and benefits, their types, degree, and relative weight are complex attributes which can vary depending on the context in which the study is being conducted.

Defining Risk and Benefit

In research, risk is defined as: “a potential harm, discomfort, or inconvenience that a reasonable person in the subject’s position would likely consider significant in deciding whether or not to participate in the study”. A comprehensive definition is given in the Belmont report (NCPHSBBR, 1979) as: “a possibility that harm may occur both in chance (probability) and severity (magnitude) of envision. The term ‘benefit’ refers to something of positive value related to health or welfare”. Accordingly, risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and benefits.

The Spectrum of Risks and Benefits

1. **Types of Risks:** Participants can be harmed in various ways, including physically, psychologically, socially, economically, and legally. The first two types are the most common in biomedical research, while the latter are more frequent in social and behavioral research.

A Physical risk can be any type of bodily injury, pain or discomfort. These can be related to the type of research intervention or to the withdrawal of a certain standard treatment (washout) (CHOP, 2018).

A psychological risk can occur in stressful situations (e.g., the disclosure of sensitive information, such as an untreatable serious disease or the results of a survey regarding sensitive personal medical data). The “Milgram Obedience to Authority” experiment is a classic example of induced anxiety in psychological research (McLeod, 2007).

A social risk is mainly related to the invasion of privacy and/or breach of confidentiality. The first risk concerns the access to a person’s body or behavior without his/her consent (e.g., research involving