Clinical Trials
Risk Management

Martin Robinson
Simon Cook

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Clinical Trials
Risk Management
Contents

About the Authors
Foreword
Acknowledgments
Abbreviations

1. Definitions and Concepts .............................................. 1
2. Assessing Drug Safety .................................................. 25
3. International Regulatory Perspectives .............................. 39
4. Types of Risk in Clinical Trials ...................................... 61
5. Risk Identification and Quantification .............................. 79
6. Threats and Opportunities ............................................ 95
7. Planning Preventative Strategies .................................... 109
8. Backup Planning .......................................................... 125
9. Project Tracking and Decision-Making ............................ 143
10. Investigational Site Risk Management ............................ 169
11. Post-Project Evaluation ............................................... 187

Conclusions ................................................................. 197
References ................................................................. 201
Index ............................................................... 205
About the Authors

MARTIN ROBINSON

Martin Robinson was educated at the University of Bath, England where he obtained a PhD in biochemistry in 1984. He has over 20 years experience in the pharmaceutical/biotechnology industry and has held a variety of posts during his career, covering drug discovery, international clinical study monitoring, and clinical trial project management. He has worked in drug development Phases I to IV and has been involved in protocol writing, CRF design, writing patient information leaflets, data management, preparing clinical trial reports, and writing SOPs. Martin’s therapeutic area experience includes oncology, infectious diseases, depression, hypertension, and HIV.

Over the past 10 years Martin has worked as a trainer and he designs and delivers educational programs for staff involved in clinical drug development. Subjects include clinical study monitoring, personal development courses for CRAs, problem solving and process improvement facilitation, project management training, and consultancy.
SIMON COOK

Simon Cook studied pharmacology at the University of Strathclyde, Scotland, and moved into the UK pharmaceuticals industry in 1984. Working initially as a formulation scientist, he quickly learned to “cut his cloth” between the needs of his marketing, production, medical, and regulatory colleagues, “turning straw into gold, but without the straw.”

As good clinical practice became formalized in Europe, Simon returned to drug research, initially as a CRA, and then as an international project manager. During this period he spent extended periods living and working in both the U.S. and Belgium, gaining valuable experience in protocol development, GCP training, monitoring and management of Phase II–III studies, clinical trial report writing, and the preparation of regulatory submissions. He was also responsible for CRO selection and management.

With his fingerprints on more than 50 clinical trials, Simon has research experience across all the major therapeutic areas, but cites his subjects of expertise as osteoporosis, dermatology, infectious disease, and oncology. With over 17 years in the industry, he is now an independent consultant based in Berkshire, UK.

Keen on outdoor activities, the author is also a qualified canoe instructor and leader in a children’s charity camping organization. Drawing on these experiences during his working day, he believes strongly that the key to business success is in building highly motivated teams, and specializes in doing this on an international scale.
Foreword

Gareth Owens began his career in the pharmaceutical industry as a technical support specialist at Roche, U.K., providing IT support to the clinical research division. He went on to lead a number of international clinical research IT projects, working closely with clinical research scientists, physicians, medical writers, and regulatory affairs professionals. In 1995 he joined SmithKline Beecham, where he led development of the company’s electronic submissions strategy and successfully influenced regulatory authorities around the world to accept electronic submissions, often shaving months off approval times in the process. In 1996 his responsibilities increased to include leading the implementation of SmithKline Beecham’s worldwide regulatory document management system. After moving from R&D IT to the commercial side of the industry, Gareth was appointed Head of IT Services for SmithKline Beecham UK. He successfully led the integration of UK IT systems for Day 1 of the merged company GlaxoSmithKline. Once the merger was complete, he left to found the Gareth Owens Communication Consultancy Ltd., an independent consultancy which focuses on bridging the gaps when business and technology meet and delivering successful business IT projects.

Drug development is a risky business. Commercially, the stakes are high. An investment of $800 million over 8–12 years may or may not result in a commercially successful product. During my career in the pharmaceutical industry over the last two decades, I witnessed the failure of many promising compounds, some just a few months away from regulatory submission. Pioneering research often yields unpredictable results. Cutting-edge pharmaceutical development frequently relies on new technologies and techniques, which, because they are unproven, increase the risks. Everyone in the industry is aware that, at the end of the day, patients’ lives are at stake.

It is against this backdrop of huge financial, scientific, technical, and medical risks that a clinical trials project manager is expected to function, effectively
identifying and managing all project risks to deliver a successful outcome. Few have received formal training in how to do so. Simon Cook and Martin Robinson have correctly identified a major industry problem: the absence of systematic risk management applied to clinical trials.

To their credit, the authors have produced this unique reference work on the subject of clinical trials risk management. I believe there is a real need for this book. The principles expounded by Cook and Robinson are sound. Their years of experience in pharmaceutical R&D shine through the narrative. Risk management has the potential to be a dry and boring topic — the pharmaceutical industry equivalent of accountancy! The authors avoid this pitfall through clever use of anecdote, example, end-of-chapter summaries, and humor. The medical physicist in me particularly appreciated an explanation of how the second law of thermodynamics applies to clinical trials. It remains to be seen whether mere life scientists will get the joke!

This book contains a wealth of background facts and data to support the authors’ arguments. There is plenty of wise advice that can be put into practice straight away to immediately improve current or planned clinical trials. Throughout the book, the style is light, lively, and interesting. I share with the authors a passion for the use of plain English to describe complex topics. They are to be commended for their efforts in this regard. In recognition that clinical research is a field Frequently Described by Acronyms (FDA), the book also includes a handy list of common abbreviations that will serve as a useful reference for newcomers to the industry.

This book deserves to be successful. I commend it to anyone involved in clinical research and to the international pharmaceutical industry. Herein is much wisdom that, if properly applied, will enable life-saving new medicines to be put more quickly, confidently, and cost-effectively into the hands of those who need them.

Gareth Owens
North Yorkshire, UK
April 2005
Acknowledgments

Andrew Catton, Miller Insurance Services, for his insight into the specialist world of clinical trials indemnification and insurance underwriting.

Kohei Wada and Tomoo Shiozawa, Daiichi Pharmaceuticals, for their helpful explanation of the Japanese regulatory agencies and pharmacovigilance system.

Mike Rees, Palisade, for his input to the simulation graphics programming.

Tom Warne, for his distinctive illustrations, more often seen in cosmetics advertising.
Dedication

For all those who unknowingly took a stroll to the beach on Boxing Day morning 2004.
Abbreviations

ABPI  Association of the British Pharmaceuticals Industry
ADME  Absorption, Distribution, Metabolism and Excretion
ACE   Angiotensin Converting Enzyme
ACWP  Actual Cost of Work Performed
ADI   Acceptable Daily Intake
ADR   Adverse Drug Reaction
AE    Adverse Event
AIDS  Acquired Immune Deficiency Syndrome
AUC   Area Under Curve
BCWP  Budget Cost of Work Performed
BCWS  Budget Cost of Work Scheduled
CA    Competent Authority
CBER  Center for Biologics Evaluation and Research
CDER  Center for Drug Evaluation and Research
CFR   Code of Federal Regulation
CHO   Chinese Hamster Ovary
CIOMS Council of International Organizations for Medical Sciences
CMS   Concerned Member State
CRA   Clinical Research Associate
CRF   Case Report/Record Form
CRO   Contract Research Organization
CTA   Clinical Trial Authorisation
CTD   Common Technical Document
CTN   Clinical Trial Notification
CTX   Clinical Trial Exemption
CV    Curriculum Vitae/Resume
DNA   Deoxyribonucleic Acid
DQRS  Drug Quality Reporting System
DSMB  Drug Safety Monitoring Board
ECG   Electrocardiogram
ED    Effective Dose
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
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<tr>
<td>EORTC-QLQ-C30</td>
<td>European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30</td>
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<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>EUDRACT</td>
<td>European Clinical Trials Database</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FPI</td>
<td>First-Patient-In</td>
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<tr>
<td>FTE</td>
<td>Full-time Equivalent</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GMC</td>
<td>General Medical Council</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<td>GOSE</td>
<td>Extended Glasgow Outcome Scale</td>
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<td>GPMSP</td>
<td>Good Post-Marketing Surveillance Practice</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<tr>
<td>ICSR</td>
<td>Individual Case Safety Report</td>
</tr>
<tr>
<td>IMPD</td>
<td>Investigational Medical Product Dossier</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>INDIA</td>
<td>Investigational New Drug Application</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>ITT</td>
<td>Intention-To-Treat</td>
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<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
</tr>
<tr>
<td>KRI</td>
<td>Key Result Indicator</td>
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<tr>
<td>LCO₂</td>
<td>Liquid Carbon Dioxide</td>
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<tr>
<td>LD</td>
<td>Lethal Dose</td>
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<tr>
<td>LPO</td>
<td>Last-Patient-Out</td>
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<tr>
<td>MAA</td>
<td>Marketing Authorization Application</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorization Holder</td>
</tr>
<tr>
<td>MHLF</td>
<td>Minnesota Living With Heart Failure Questionnaire</td>
</tr>
<tr>
<td>MHLW</td>
<td>Ministry of Health, Labor and Welfare</td>
</tr>
<tr>
<td>MHW</td>
<td>Ministry of Health and Welfare</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MRP</td>
<td>Mutual Recognition Procedure</td>
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<tr>
<td>NAS</td>
<td>New Active Substance</td>
</tr>
<tr>
<td>NDA</td>
<td>New Drug Application</td>
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<tr>
<td>NOAEL</td>
<td>No Observable Adverse Effect Limit</td>
</tr>
<tr>
<td>NUIS</td>
<td>Non-Urgent Information System</td>
</tr>
<tr>
<td>PDF</td>
<td>Probability Distribution Function</td>
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<tr>
<td>PFSB</td>
<td>Pharmaceutical and Food Safety Bureau</td>
</tr>
<tr>
<td>PhRMA</td>
<td>Pharmaceutical Research and Manufacturers of America</td>
</tr>
</tbody>
</table>
Abbreviations

PICF  Patient Information and Consent Form
PMBOK  Project Management Body of Knowledge
PMDA  Pharmaceuticals and Medical Devices Agency
PMI  Project Management Institute
PMS  Post-Marketing Surveillance
PMSB  Pharmaceutical and Medical Safety Bureau
PSUR  Periodic Safety Update Report
QA  Quality Assurance
QC  Quality Control
R&D  Research and Development
RAS  Rapid Alert System
RMS  Reference Member State
ROI  Return On Investment
SAE  Serious Adverse Event
SAER  Serious Adverse Event Report
SADR  Suspect Adverse Drug Reaction
SAP  Statistical Analysis Plan
SAR  Suspected Adverse Reaction
SF-36  Short Form 36
SOP  Standard Operating Procedure
SPC  Summary of Product Characteristics
SUSAR  Suspected Unexpected Serious Adverse Reaction
SWOT  Strengths, Weaknesses, Opportunities, Threats
TMF  Trial Master File
TNF  Tumor Necrosis Factor
Tufts CSDD  Tufts Center for the Study of Drug Development
VSD  Virtually Safe Dose
WBS  Work Breakdown Structure
WHO  World Health Organization
WHOQOL  World Health Organization Quality Of Life Assessment
WMA  World Medical Association
Chapter 1

Definitions and Concepts

WHAT IS RISK?

If you look up “risk” in a dictionary, you’ll probably come up with a definition that says something like: “the possibility of incurring misfortune or loss.” In our personal lives we routinely encounter a multitude of hazards. Nevertheless, we repeatedly avoid the dangers, and thus survive another day. The reason for this is that as we have grown from infancy, we have learned either by instruction or error to become efficient risk managers.

Nevertheless, we never stop to calculate mathematically what are the chances of suffering a disaster when we prepare a meal, get behind the wheel of a car, or take a flight. Even though the consequences of an air or road traffic accident for us would be serious, because the chances of it happening are relatively small, we often choose to ignore the risk entirely. Risks are also often overlooked if we are in a familiar situation (e.g., at home).

We find it amusing that Dustin Hoffman’s autistic character in the movie *Rain Man* should memorize public transport crash figures in order to decide how best to travel. Nevertheless this is a clear attempt to deal with the second element of risk, that is, the uncertainty of the event occurring. When describing uncertainty, statisticians use the other end of the telescope, and call it “probability.”

The formula for probability is: \[
\frac{\text{Number of actual events}}{\text{Total possible events}}
\]

For example, the probability of death from a road traffic accident is 1/15,860 journeys, compared with that of scuba diving: 1/150,000 dives. If this looks familiar it is because it is also the system used by bookmakers and gamblers to describe the “odds” or chance of winning (e.g., 1/6). These individuals are prepared to accept higher than average financial risk in order that they might profit. Thus we come to a third concept: that of a potential benefit justifying the risk associated with a particular course of action. On these occasions we nearly always weigh up in a far more scientific manner the chances of the event occurring. The serious punter who bets on a racehorse will study the form of the horse, and take into account such factors as the draw, how much weight as a
handicap the horse is carrying, whether or not the ground (or “going”) suits the horse, and so on.

Similarly, investing in the stock market requires a level of knowledge and research. How is the company doing, and how is it expected to perform? What are the market analysts’ opinions?

Occasionally we take risks such as skydiving or bungee jumping where there is little or no material reward for ourselves and we may do this purely for the excitement or having a feeling of achievement. In these situations our lives depend on the equipment being properly set up and checked before we literally take the plunge. While waiting to jump we will want to witness all our predecessors successfully and safely land on earth, or in the case of bungee
jumping, dangle harmlessly above, or slightly submerged in, a freezing river. Seeing just one person have a mishap would be enough for us to consider the risk as too great, given what is at stake.

The race-goer, the investor, and the bungee jumper all have in common that they are trying to gather as much information as they can to construct the probability calculation. Only then will they take a decision. Indeed some commentators use the terms risk analysis and decision analysis synonymously to describe this activity.

Risk management practices are indigenous to many industries and organizations. Palisade, manufacturers of risk analysis software, regard the following sectors as user groups:

- Accounting
- Advertising
- Agriculture
- Banking
- Budgeting
- Consulting
- Economics
- Engineering
- Environmental
- Finance
- Government
- Health Care
- Industrial Engineering
- Insurance/Actuarial
- Investments
- Legal
- Manufacturing
- Mining
- Oil and Gas
- Operations Research
- Pharmaceutical
- Project Management
- Real Estate
- Scheduling
- Utilities

What these organizations have in common is their potential for significant loss either financially or in terms of human lives/ quality of life. For instance, in the financial world an estimated U.S. $1,600 billion are traded daily on the world’s foreign currency markets. Even the smallest fluctuations in the often unpredictable money markets can make a big difference to a business’s bottom line despite having a good product and an otherwise sound business strategy.

Another aspect of risk management is industry’s increasing reliance on the availability of IT systems and the very real business risks presented by this dependence. The name of the game here is business continuity. Any business using an IT system is at risk of losing data which may have catastrophic consequences, particularly if the data loss is irretrievable. Risk management plays an important role in the construction industry in terms of health and safety of workers, environmental issues, and the health and safety of the end users of various construction projects.

Risk management is an important tool in the armed forces, and is integrated into military training and operations management systems. It allows commanders to conserve lives and resources, and avoid unnecessary danger, make informed
decisions about a course of action, and provide reasonable alternatives for mission or task accomplishment without compromising safety and standards.

Nowadays government departments responsible for national security adopt a risk management approach with respect to both sensitive information and the likelihood of terrorist attack.

Risk management thus plays an important role in our personal lives and the corporate world, but how does it extend specifically to project management? We need to go back and look at our definition again.

The Project Management Institute (PMI), the world’s leading project management association, defines a risk as an event which “may affect the project for better or worse.” This is clearly a more optimistic view than the dictionary, and is more akin to viewing risk as a level of probability. They are joined in this definition by their British equivalent, The Association for Project Management who describe “an uncertain event or set of circumstances, which should it occur, will have an effect on the achievement of the project objectives.” In other words, a risk may be either a positive “opportunity,” or a negative “threat.”

**Figure 1.1 Risk Outcomes.**

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**THE PRINCIPLES OF RISK MANAGEMENT**

Risk management is not a rainy day activity for bored project managers. Analysis of uncertainty is a central pillar of project life, because it provides the
basis for all major decisions. It is thus integral to directing activities, from the project’s start to finish. Since projects are dynamic entities surrounded by constantly changing parameters, it follows that risk management also needs to be a continuous process of reassessment, rather than a one-time calculation. The risk profile of a project will evolve as the venture moves through its definition, planning, implementation, and close-out phases. Typically, uncertainty will be highest before the initiation of a project, with probability estimates of the outcome becoming increasingly accurate as the end draws near. The principles which all project risk management schemes have in common are definition, planning, risk identification, risk quantification, action, measurement, outcome assessment, and a post-project review.

DEFINITION SETTING

It is not possible to analyze a risk without having a goal or standard to refer to. The first port of call is thus to compile a project definition. Here the management team agree to the objectives, quality requirements, timelines and budget, prioritizing constraints, describing the project scope, geographical distribution, lines of communication, assumptions, responsibilities, and the general skills required. In order to produce a realistic set of definitions, it is typically necessary to conduct some kind of information gathering, usually in the form of a brief feasibility survey. This will combine experience accrued from past projects with the anticipated requirements, to see if previous methodology is predictive of success. A negative answer at this stage does not necessarily mean the death of the project, but would certainly suggest that a novel, and hence less certain, approach will be required. Alternatively, it may be that one or more of the definition parameters (goalposts) need to be moved.

PROJECT PLANNING

Once the project has been defined, its skeleton needs to be fleshed-out into a project plan. This is a detailed implementation roadmap, showing how the goals are to be achieved. The project plan will include a work breakdown structure (WBS) describing the way in which the overall scheme translates into individual tasks. The WBS will be organized into a task network listing the order in which the work will be done. Estimates are made of effort and duration of each task, the effort being the amount of work required to complete the task and the duration the total elapsed time from the start of each task to its end. From this a project timeline will be constructed, and hence the critical path (see Chapter 7). As we will discuss in Chapter 9, it is also usual to build decision milestones into the project plan at time-points where risk is anticipated.
Milestones will be built into the project plan.

**RISK IDENTIFICATION**

Having designed a project plan, the next question to ask is: “What are the threats and opportunities which might throw this off course?” Naturally, there are a thousand and one risks that could occur. If we were to take account of everything that could go wrong we would probably never start any project. We need to prioritize by focusing on those risks most likely to occur and those which pose the greatest threat to the successful completion of the project.

This journey begins with the relatively straightforward collection of information. Project stakeholders, in-house specialists, and external consultants are invited to list potential risks which they either perceive or expect, based on previous experience with similar situations. In order to begin prioritizing the
risks, simple ranking of estimated impact and probability is then made. This is collated into a risk register (see Chapter 5).

**QUANTITATIVE ASSESSMENT**

The information held in the risk register is, at this stage, largely qualitative. In order to give this some kind of perspective, the next step is to measure the risks. This is done by constructing quantitative risk models. Each risk is described as a probability density function (PDF), and computer-generated random numbers used to create a profile of all possible outcomes. This gives the project manager a hard metric of the odds or probability ratio of each risk occurring, combined with its associated impact on the project (see Chapter 5). This data is then updated in the risk register.

**CONTINGENCY ALLOCATION**

Armed with a list of risks great and small, the next step is to return to the drawing board. Where possible, adjustments should be made to the project plan to eliminate completely the potential for threats to occur. Conversely, recognizing a risk as an opportunity to add value, changes could be made to increase the likelihood of this outcome.

In the real world, the best laid plans are never enough. Thus a back-up or contingency option is required, on the assumption that despite our best efforts the unwanted outcome could still occur. It is important that the contingency is activated at the appropriate point, and therefore a trigger is embedded in the project plan for its initiation. (see Chapter 8).

The process by which contingency activities are allocated to the project plan is summarized in Figure 1.2 (see page 8).

**ACTION**

Having refined the project plan and decided on a course to be followed, the necessary instructions and resourcing should be given for its implementation. At this stage a scaled-down group of unavoidable threats will remain, but their risk probabilities have been accepted, and contingency plans laid to compensate.

**MEASUREMENT**

Running a project without measuring progress is like driving a car with a blindfold on. Not only can you not tell how close you are to a risk event occurring,
but you cannot assess the impact once it has happened. Project managers thus need metrics to understand performance. Ideally these should be tracked on a daily basis. The units of measurement should be fact-based, easy to quantify and collect, and straightforward to interpret. Second, there should be direct reporting lines so that news is being received “as it happens.” Thus the project manager should be able to respond quickly to any deviations or new risks arising. This is discussed further in Chapter 9.
OUTCOME ASSESSMENT

Once a risk event has been reached and the outcome is known, the information is reported back to the trial manager and updated into the risk register. There are some important questions to be answered. Did reality behave the way our modelling had predicted? If not, why not, and what can be done to improve the model? The result itself will increase the project knowledge, and this can often allow other probability analyses to be re-run more accurately.

Second, has the outcome produced a deviation from the project plan? Does this qualify for the activation of a contingency, or will more subtle adjustments of the tiller compensate? All these questions feed back into the risk analysis at the project plan level, creating a cyclical process.

POST-PROJECT REVIEW

Once the project has been completed and closed out, this is the opportunity to reflect on how risks were managed throughout the project and whether there are any lessons to be learned that can be applied to future projects. This should be done in an objective and blame-free environment and is a key agenda item of the post-project review meeting.

Continuous risk management through the different phases of the project life cycle can be summarized by the scheme shown in Figure 1.3 (page 10).

We will be examining this philosophy of risk management throughout the project life cycle in more detail in the forthcoming chapters.

DRUG R&D: A RISKY BUSINESS

The Drug Safety Staircase

The general concepts we have discussed so far have involved risks which threaten the successful completion of projects. However, risk assessment with respect to the health and safety of patients has, quite naturally, been at the forefront of clinical research. If we look back at the history of drug research and development, we can see examples of the role that risk management has played from the patient’s viewpoint.

The godfather of drug research and development (R&D) was Paul Ehrlich, a German chemist working in the early twentieth century. He had noticed that some arsenic-based dyes were selectively absorbed by the organisms causing African sleeping sickness and syphilis. Recognizing that these were toxic compounds, he described his research as a hunt for “magic bullets” which would kill the parasite but spare the host. In doing so he eloquently applied a
fundamental risk/benefit principle to the systematic production of new medicines.

Using this approach, the first antibacterial drug sulphanilamide was introduced in 1933, followed by penicillin in 1941. Once the revelation that these “wonder drugs” could save lives had paled, it became clear that they also brought their own hazards. The first scare came in 1937, with 107 deaths in the U.S. caused by ethylene glycol used in a sulphanilamide elixir. It was also evident that the drugs themselves could cause harm: hemolytic anemia in the case of sulphanilamide, and anaphylaxis in those hypersensitive to penicillin.

Thus, as the pharmaceutical industry began to evolve, so did the concept of measuring the safety risk posed to patients. Since ethical conventions such as the 1947 Nuremberg Code and the 1964 World Medical Association Declaration of Helsinki had established human rights in this field, safety testing was
conducted in animals. Scientists would treat rats, mice, and, most famously, guinea pigs with a range of doses. From this, they would establish the therapeutic index: the ratio of the lethal dose divided by the effective dose.

It was seen that drug toxicity was not confined to the newly discovered chemicals. Digoxin, the cardiac glycoside in foxglove tea was found to have a therapeutic index of only two (i.e., twice the therapeutic dose is lethal) while social drug alcohol is only marginally better at 10. In fact, it is not unreasonable to expect that medicines are hazardous. After all, they are compounds which have been painstakingly selected for their ability to penetrate the body’s normal protective mechanisms, circulate freely, resist metabolism, and interfere with physiological functions. Many are based on naturally occurring plant or animal poisons. Drugs inevitably have a potential to produce toxicity which biologically inert chemicals do not.

Thirty years after the discovery of sulphanilamide, the safety screening and marketing of medicines was still an ad hoc affair however, largely dependent on the discretion of the manufacturer. The “big bang” for drug R&D came as a result of the thalidomide disaster. Thalidomide was a glutarimide sedative which acute animal toxicity testing had shown to be extremely safe, with no observable lethal dose. It was also found to provide effective relief to women suffering from morning sickness in early pregnancy. Unfortunately it had teratogenic effects on the fetus when taken exactly during this time. An epidemic of 10,000 phocomelia cases in the late 1950s was directly linked to the drug, and it was withdrawn from sale.

The U.S. immediately responded with the 1962 Food Drug and Cosmetic Act. The European Economic Community (consisting at the time of six member states) followed in 1965 with a Directive for member states to pass into local law, which described a national marketing authorisation approval system for new medicines. In the UK, the Medicines Act was approved in 1968 and became operative in 1971. Most other industrialized nations soon passed similar legislation.

While there were significant differences in the fine detail, there was a common philosophy. It became illegal to sell medicines without a licence from the national health authority (e.g., U.S. Food and Drug Administration). In order to obtain such a licence, the manufacturer or sponsor was obliged to submit a dossier containing the results of experiments proving statistically that the drug was both a safe and effective treatment in humans. It was also necessary to provide supporting animal pharmacology, pharmacokinetic (ADME), single dose toxicity, repeated dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity data (see Figure 1.4), demonstrate manufacturing quality (GMP), and show that ethical clinical research principles had been followed (Declaration of Helsinki). In the U.S. this is known as a New Drug Application (NDA), and in Europe a Marketing Authorisation Application (MAA). This is discussed further in Chapter 3.
Figure 1.4 Safety Studies Conducted During “Conventional” Drug Development.

In order to control the risks to humans participating in the prelicensing clinical trials of a medicine, a second tier of regulation was created. In the US this took the form of investigational new drug (IND) status. This is a permission from the Food and Drug Administration (FDA) to administer an unlicensed drug to humans for the purpose of medical research. The sponsor is obliged to submit an IND Application (INDA). This should contain data on the animal pharmacology and toxicology (except long term studies), and any human results already gathered in other countries. Second, it will present chemical, manufacturing,
stability and batch quality information. The submission will also describe the intended clinical development program, including proposed protocols, investigator details, and commitments to GCP principles. Variations on this scheme were adopted by other nations (e.g., UK CTX notification). In 2001 the European Union (EU) rolled out a standardized clinical trial authorization (CTA) system for member states to adopt (see Chapter 3).

The IND and CTA systems have in common a requirement that humans are exposed to a new active substance (NAS) in incremental fashion. A staircase of ever widening experiments is prescribed, known as clinical Phases I–III (see Chapter 4).

The U.S., EU, and Japan agreed at the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) on common standards for the design, conduct, recording and reporting of clinical trials. These were published in 1996 as the ICH Step 4 Tripartite Guideline on Good Clinical Practice (GCP).

One of the areas of responsibility GCP describes is that of the Institutional Review Board (IRB), an independent committee concerned with reviewing the ethical aspects of proposed clinical trials. Before each may start, the investigator must seek the approval of his local IRB by submission of all available animal safety and previous clinical data, the proposed experimental protocol, and the patient information sheet and consent form (PICF) that will be used.

A key concept enshrined in ICH GCP guidelines is patient safety. These guidelines set out the responsibilities of both the investigator and sponsor to routinely monitor the wellbeing of subjects participating in trials. One way this risk assessment manifests itself is in the required recording of any worsening in the patient health status from baseline. These are the adverse events well known to all clinical research professionals. Those which are defined as serious adverse events (SAEs) are immediately reported to the sponsor, who in turn rapidly notifies drug-related cases to the appropriate regulatory agencies, other investigators and their IRBs. The SAE definitions, reporting times, requirements and formats used in the ICH countries are reviewed in Chapter 3.

The adverse event monitoring system provides for the in-process collection of drug safety data. It allows the sponsor, investigators, IRBs, and regulatory agencies to build a cumulative awareness of the hazard or risk profile associated with the treatment. If this becomes unacceptable, then the trial(s) may be stopped before further harm is done.

Clinical trials adverse event reporting combined with the IRB review system represents a powerful risk management tool. Continuous feedback of safety information in “near-real time” provides a sensitive basis for protecting subject wellbeing, while external stop/go checks by the IRBs ensure that each escalation of the research programme can be justified by the last.

The R&D life of a drug thus follows a preset scheme determined by regulatory authorities (see Figure 1.5). Lab discovery and animal toxicity/pharmacology
Figure 1.5 The Drug R&D Process.
tests are followed by clinical expansion through Phases I–III. Simultaneously, long-term nonclinical safety studies and pharmaceutical/formulation activities will be ongoing. The resulting data is then compiled into an NDA/MAA, and submitted to regulatory agencies for review.

The rationale for this is that as drug R&D projects strive to advance our current capabilities in medical science, they attempt to achieve something that has not been done before. Thus the probability calculation of threat versus opportunity is unknown. By slowly inching up an information gathering staircase, we are able at each step to take increasingly more accurate safety/benefit decisions as the program progresses.

THE COMMERCIAL STAKES

The cost of developing new drugs is constantly and rapidly increasing. In 1987 the cost of bringing a NAS to market was approximately U.S. $231 million. By 2001 this had risen to U.S. $802 million (Tufts Center for the Study of Drug Development). Increasing demands from the world’s regulatory agencies in recent years means that this trend continues to accelerate.

The number of clinical studies required by the FDA for a NDA rose from 35 in 1988 to 65 in 1995. Studies are getting longer and more complex. The average number of procedures required by a protocol almost doubled from 100 to 190 in the period 1991–1995. This is reflected in a similar rise since the mid-1980s in the cost per clinical study patient.

It is estimated that for every one NAS launched on the market:

• 5–10,000 candidate molecules will be screened.
• 250 evaluated in preclinical models.
• 12 will enter Phase I clinical pharmacology.
• Six will progress into Phase II clinical studies and 2–3 into Phase III.

At each stage along this path, financial commitment to the drug increases. This is not so much of an issue during the early screening stages, but the corporate risk associated with NAS failure grows dramatically as development progresses into the clinic. The losses associated with failure in late Phase III can be devastating for a company (e.g., flosequinan, lexipafant). The worst-case scenario would of course to be for the drug to complete the entire R&D program (U.S. $802 million), but then receive “nonapproval” from the regulatory authorities. This reflects another aspect of drug development — the financial risk.

In order to manage this accumulation of exposure, a product development team will run several NASs on parallel tracks. As the project progresses, the most promising will be advanced, as the weaker either fail or are “weeded out.” This is achieved through a series of stop/go decisions at strategic points in the product development plan (Figure 1.6). At each assessment, the product
The development team will have to justify continued investment in the development of a potential medicine. This decision will be based on the following six criteria:
1. Clinical endpoints for the disease should be well defined and measurable.
2. The NAS should be as effective, and ideally better, at treating the target
disease than other candidates or marketed products.
3. The therapeutic margin of safety should be high.
4. The NAS should be chemically stable, in a clinically acceptable
formulation, with production costs which allow retention of profit margin
in a price-sensitive market.
5. The product should fulfil an unmet market need (e.g., previously
untreatable population, reduced side effect profile, oral administration).
6. The patent life remaining after the projected licencing date will be
sufficient to obtain an adequate return on investment.

WHY RISK MANAGEMENT IS IMPORTANT IN CLINICAL TRIALS

As we move into the twenty-first century, drug development faces an uncertain
future. Depressed global economic conditions and weak drug development
pipelines have forced pharmaceutical companies to manage R&D budgets more
conservatively. Inroads into the market by generic products and worldwide pricing
pressures are two of the key factors responsible for the rapid slowdown of
pharmaceutical sales. Never more is the pressure on clinical trial project managers
to do more for less and in an ever shorter timescale. The pharmaceutical industry
is reviewing the whole R&D process. It is developing new drug discovery
technologies that will alter the scope of clinical trials. Proteomics, metabonomics,
and genomics have great potential in revolutionizing traditional strategies in drug
research.

Companies are beginning to shy away from the historical blockbuster
mentality and are moving toward a more targeted approach to drug development.
New discovery technologies are predicted to need smaller and fewer clinical
trials resulting in reduced costs and cycle time. Novel “e-methods” are being
applied to clinical trials including electronic data capture (EDC) and information
technology is starting to be employed in the recruitment of patients.

Clinical research is being conducted in areas of the globe as yet relatively
uncharted by the pharmaceutical industry. Trial-naive patients and enthusiastic,
ICH GCP-compliant clinical investigators are being recruited in Central and
Eastern Europe, Latin America, Southeast Asia, and India. Regulations in these
and other areas of the world are becoming tougher and more complex. All of
these developments bring threats as well as opportunities for the clinical trial
project manager.

Such project challenges can be broadly categorized as relating to resources/
cost, quality, and time. These elements can be said to be balanced in triangular
relationship as indicated in Figure 1.7.
What can be noted from this equilateral geometry is that changing the emphasis on one parameter has a direct impact on another. As we will see below, there are certain minimum standards of quality required in clinical research. Thus the give and take is often between scope, cost, and time. If time is our overriding priority for example, we can accelerate the trial but it will require spending more on resources. Nevertheless, our business and project stakeholders may accept a high cost in order to complete the clinical phase by a particular date in the overall product development plan.

**Quality**

As already discussed, the marketing of pharmaceuticals relies on the approval of government regulatory agencies such as the FDA. Given the legal and ethical responsibilities of such organizations, they demand that the data submitted by sponsors in support of licensing applications is of the highest standard. To give an idea of this, the acceptable error rate for a Phase III database is <0.1% for safety and efficacy parameters (critical) and <0.5% for non-critical fields (PharmaNet). Indeed, the ICH GCP Guidelines amount to a total quality management plan for drug development, defining an auditable process for handling both the risk of exposing humans to an unproven NAS, and demonstrating the reliability of the data collected.

While the overall benchmarks are set externally by the regulatory authorities, clinical trials managers will be responsible for setting internal quality targets for
the project team. These may already exist as corporate SOPs, but otherwise can be trial-specific. In order to track how close actual performance is to the planned deliverable, key result indicators (KRI) will be measured. Investment will be made in training each project team member in their specialized contribution to the trial. There will also be an independent quality assurance (QA) group responsible for auditing both sponsor and investigator activities. Quality is fundamental to the conduct of drug development, since it is the criterion on which licensing authorities judge the value of a product.

Regulatory quality standards never take a backward step. Each safety mishap, disaster, unethical practice quite rightly results in the tightening of regulations in order to protect the rights and welfare of the clinical trial subjects. Recent legislation to cope with the increasing use of e-technology includes the FDA guidance on electronic records — 21 CFR part 11. The EU Data Protection Act has had a significant impact on clinical research including the flow of data around the world and the wording and agreement that the patient grants in the process of informed consent. The 2000 version of the Declaration of Helsinki sought to protect vulnerable patient populations from exploitation by prohibiting the practice of “get in quick get out quick” clinical research in financially impoverished areas of the world as well as attempting to set limits on the use of placebo controlled trials. The EU Clinical Trial Directive, implemented in 2004, is designed to harmonize, accelerate, and standardize clinical research practices while at the same time giving legal force to the implementation of GCP and has caused the industry to review its processes and SOPs. While changes such as these often arouse controversy in some sectors, the general trend is toward conformism and the raising of quality standards.

Costs and Resources

In 2000, worldwide pharmaceutical R&D spending was U.S. $53 billion, and is expected to continue at a steady growth of 10% each year to a value of U.S. $77 billion in 2005 (Credit Suisse First Boston). Industry analysts consider that approximately 40% of the cost of bringing a NAS to market goes on synthesis, formulation, and preclinical research, and the remaining 60% on clinical development and licensing.

About one half of the development budget will be consumed by sponsor manpower and operating costs, with the remainder covering direct expenses for investigator research, laboratory testing, IRB approvals, travel, courier shipping, and regulatory authority reviews (Windley). The PhRMA estimated in 1996 that 29.5% of the cost of discovering and developing a medicine was consumed by the clinical trials themselves. This is the largest price tag in the R&D program.

Clinical trials project managers are thus empowered to take $1 million decisions. It goes without saying that the quality of their management skills,
especially those associated with risk, is thus crucial to the financial health of the sponsor corporation.

Risk management guides written for project managers working in the construction, oil, manufacturing, and engineering industries spend a lot of time talking about how to control the costs of raw materials, component delivery dates, and how to decide on the most efficient equipment to invest in. The majority of this thinking does not apply to clinical trials however. This is because the product is intellectual: information, its collection, validation, and analysis.

There are, of course, some notable exceptions. There would be no trial without the manufacture, packaging and distribution of the trial medication, case report forms (CRFs), and laboratory test sampling kits. In general, the diagnostic equipment used to assess the clinical progress and well-being of subjects will already be in place at the hospital or clinic. There may however be situations where it is necessary to purchase and distribute standardized measuring or calibration devices to investigators.

Any computer hardware and software systems required for the project should be procured and validated in time use in for their intended role. These may be project management tracking, case report form (CRF) EDC, lab result transfer, interactive voice response system (IVRS) randomization, data management, or SAE reporting tools. It may be an exciting idea to introduce a new system to improve trial management, but it will be useless if not up and running when needed. In this area of course the clinical trial project manager relies heavily on the support of the IT function, but in turn has a responsibility to specify the system’s requirements and delivery dates early in the planning stage. It follows that as well as having functional IT, the necessary staff are trained to operate it. This brings us to the largest resource issue faced by the clinical trial project manager, manpower, and with it, the associated risks.

The conduct of a clinical trial involves the coordinated input of a wide range of highly specialized staff. These are drawn from the following groups:

- **Biostatistics:** statistical analysis plan, study design, randomization schedule; data tables and listings, difference testing.
- **Study production:** study drug manufacture, packaging, distribution, randomization.
- **Clinical monitoring:** investigator selection, training, site management, monitoring.
- **Investigators:** patient recruitment, consent, drug administration, data recording, IRB liaison.
- **Central laboratory:** shipment, analysis, reporting of biological specimens.
- **Pharmacovigilance:** SAE reporting and quality control (QC).
- **Data management:** CRF, database/edit check design, data entry, and QC.
- **Medical writing:** protocol, clinical study report.
Other departments which will contribute to the study on an as-needed basis are:
regulatory affairs, quality assurance, manufacturing, marketing, preclinical
development, drug discovery, medical communications, and finance.

The utilization profile of each work category will, of course, shift like desert
sand dunes as time progresses. During the planning and set-up phase, there will
be a high level of project physician, project manager, and clinical trial pharmacist
input. Then as the study progresses into clinical treatment, investigator, clinical
team leader, clinical research associate (CRA), lab analyst, and drug safety
officer involvement will grow, peaking at last-patient-out. From then on,
emphasis will turn to data management staff, statisticians, and medical writers as
the project draws to a close.

Training, organizing, and managing this ever-changing team is a major
challenge. The project manager will need to manage resource risks by ensuring
that the staff skills and head count are efficiently matched to the project demands.
Clearly staff must be in place as work becomes necessary, but conversely over-
manning represents a threat to the budget. While it can be the subject of an entire
book in itself, it should also be remembered that communicating with the team,
managing and tracking their activities in accordance with the project plan is a
major preoccupation of the clinical trial project manager.

The advance of technology will require changes in the skill sets of clinical
trial project teams. Some organizations may choose to have their staff develop
more specialized skills. For example, a CRA working on a study employing
EDC will not be spending time reviewing the CRF for internal consistency. EDC
will allow them to focus more on reviewing the quality of source data, checking
patient eligibility, ensuring that informed consent has been properly sought, and
so on. Project team members will have to adopt new mindsets and working
practices very rapidly. Project team training is a valuable tool in minimizing the
risks that arise in this environment.

Working in new areas of the world requires intensive training of local staff, the
first of whom are pioneers of these new frontiers. Worldwide field-based
networks of CRAs are needed to cover the large geographical areas in which
patients are recruited. New web-based technology allows continuous round-the-
clock data entry and management. Project managers are having to be truly global
as they manage their teams across ever widening time zones and diverse cultural
tapestries. Pioneering these new frontiers brings new risks in the form of both
threats and opportunities.

Increasing time and costs constraints are stretching resources to the limit and
project teams are having to work ever more efficiently without compromising
quality. A glance at the jobs vacancy page in any clinical research journal or
publication reveals the unceasing demand for new talent and the recruitment
agency business is thriving in attempting to quench this thirst for resource.
The expected lead-time for a NAS from discovery to market approval is 11–13 years, depending on indication (CMR International). Thus, over half of the 20-year patent term will have expired by the product launch. Once off-patent, generic manufacturers who have not borne any of the R&D costs are able to sell their own cheaper versions of the drug. To give an idea of the scale of this, in the first year off-patent, 42% of Glaxo Wellcome’s earnings from the anti-ulcer drug ranitidine were lost to generic competition.

Time-to-market before patent expiry is a major profitability issue for pharmaceuticals manufacturers. Before any return on investment can be seen, the enormous R&D costs must first be recouped. This situation is compounded by the trend among government authorities to cut healthcare budgets by imposing price controls. Thus, delays on completion of development can threaten the commercial viability of a product. In addition to loss of patented market life, competitor products will be launched ahead which diminish market share of the product and further erode its revenue capacity.

Historically, delays in the clinical phases of development are those which have had the greatest impact on the market approval date. To put this in perspective, Kermani and Findlay estimated in 2002 that a globally marketed blockbuster NAS could expect to lose U.S. $2.7 million in sales a day, every day that launch is delayed. This is very sobering, particularly when the reality is that few of the project managers responsible for clinical trials have ever had any formal education in risk management. They are typically graduates in biochemistry, nursing, or pharmacy with strong leadership qualities, who often make decisions intuitively.

Given the extent of corporate financial exposure that a candidate drug represents, the attractiveness of a risk management approach to clinical trials becomes apparent. This book sets out to identify the typical threats and opportunities encountered in clinical trials, and provide a systematic methodology for analysing these, taking preventative measures, and activating contingencies. In the knowledge that they are pursuing a course based on sound principles, the reader can then start to enjoy the feeling of saving U.S. $2.7 million every time they shave a day off the timeline to product launch.
THE MAIN POINTS AGAIN

- Project risk is the probability of an event occurring which produces a deviation from the plan.
- Risks can be either positive (opportunities) or negative (threats).
- Risk management is a continuous process which is the basis of project decision-making.
- Risk management can be divided into eight stages: definition, planning, risk identification, risk quantification, action, measurement, outcome assessment, and a post-project review.
- Drugs possess the potential to do harm as well as good to patients, a concept measured as the ratio of lethal dose/effective dose, known as the therapeutic index.
- In recognition of the dangers of drugs, national government agencies have been established to regulate the development and marketing of medicines through a licensing system. This sets out drug R&D as an experimental staircase, beginning with animals and then progressing into ever-larger clinical trials. Safety and efficacy information is gathered at each level, and evaluated to justify progressing to the next.
- Compliance with ICH GCP is required from clinical trial sponsors. These amount to a total quality management plan for drug development, defining an auditable process for handling both the risk of exposing humans to an unproven NAS, and demonstrating the reliability of the data collected.
- In addition to the possible safety hazard to patients, there is substantial commercial risk to manufacturers. Time to market before patent expiry (11–13 years) is a major profitability issue. Before any return on investment can be seen, the enormous R&D costs (U.S. $802 million) must first be recouped.
- Clinical trial managers face challenges relating to resources/cost, quality, and time. Resourcing mainly involves training and coordinating specialist staff, and the management of IT systems. Nevertheless clinical trials are the largest single cost in an R&D program. Quality standards are extremely high, and benchmarked by government health authorities. However, there is immense pressure to reduce the clinical development timeline. Delays in completion of development can threaten the commercial viability of a product (U.S. $2.7 million/day).
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