A Guide to European Medical Device Trials and BS EN ISO 14155

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Abbreviations


ABP Animal by-product

AIMDD Active Implantable Medical Devices Directive

AR Authorized Representative

BFS German Federal Office for Radiation Protection

BSE Bovine spongiform encephalopathy

CA Competent Authority

CAS Central Allocation System

CE Conformité Européenne

CEN Comité Européen de Normalisation

CENELEC Comité Européen de Normalisation Électrotechnique

CIP Clinical Investigation Plan

CRF Case Report Form

CSR Clinical Study Report

DH Department of Health

EC European Commission

EEA European Economic Area

EFTA European Free Trade Area

EN European standard

ER Essential Requirement
Abbreviations

ETSI European Telecommunications Standards Institute
EU European Union
FDA Food and Drug Administration (U.S.)
GCP Good Clinical Practice
GHTF Global Harmonization Task Force
IB Investigator’s Brochure
IC Informed consent
ICRP International Commission on Radiological Protection
IFU Instructions for use
IRAS Integrated research application system
ISO International Organization for Standardization
IVD In vitro diagnostic
IVDD In Vitro Diagnostic Directive
MDD Medical Devices Directive
MRA Mutual recognition agreement
MRS Manufacturers’ Registration Scheme
NB Notified Body
NHS National Health Service
PMCF Post-market clinical follow-up
SOP Standard operating procedure
STB Scientific and Technical Board
TSE Transmissible Spongiform Encephalopathies
VAT Value-added tax
1. Introduction

We live in a time when the words ‘impossible’ and ‘unsolvable’ are no longer part of the scientific community’s vocabulary. Each day we move closer to trials that will not just minimize the symptoms of disease and injury but eliminate them.

Christopher Reeve, Actor, 1999

The above statement is a testament to the faith and the acceptance that the general population has in the development of new technologies, and the role that clinical trials play in testing them, to cure disease. However, this is a recent phenomenon and the path to ensuring that only safe and effective medical devices reach the market has been a long and troubled one.

This book will examine and describe the major changes that have occurred in the regulation of clinical trials and act as a basic guide to how those regulations should be interpreted to create an efficient and successful study of medical devices. The book is aimed to provide a valuable guide to new researchers and a good reference point for experienced researchers, while also providing an insight into the area of clinical trials for anyone involved in producing or marketing medical devices.

1.1 The history of medical device legislation and clinical trials

The UK’s Select Committee on Patent Medicines stated in 1912 that:

For all practical purposes, British law is powerless to prevent any person from processing any drug or making any mixture, whether patent (or not). Advertising it in any decent terms as a cure for any disease or ailment; recommending it by bogus testimonials and the invented opinion and facsimile signatures of fictitious physicians; and selling it under any name he chooses, on the payment of a small stamp duty for any price he can persuade the credulous public to pay.
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It was not until 1936 in the UK that a Medical and Surgical Appliances (Advertisement) Bill was introduced. This Bill had a very limited scope. Its purpose being to alleviate some of the worst abuses of the pharmaceutical trade by prohibiting the advertisement of cures for certain afflictions and diseases such as blindness, Bright’s disease, cancer, tuberculosis, epilepsy, fits, locomotor ataxy, fits, lupus or paralysis. However, despite marginal tightening of legislation it was the initiation of national health insurance in 1911 and the subsequent establishment of the National Health Service in 1948 that had the major effects on improving the safety of therapies. This was because they reduced the recourse of the population to self-medication in order to avoid doctors’ fees and doctors were increasingly asking for evidence from clinical trials to prove the efficacy of therapies.

The first body to manage clinical trials, the Therapeutic Trials Committee, was set up in the UK in 1931 by the Medical Research Council (MRC), in co-ordination with the Association of British Chemical Manufacturers, to speed up the process of making potentially useful synthetic products into usable clinical products. They stated that:

The Therapeutic Trials Committee will be prepared to consider applications by commercial firms for the examination of new products, submitted with the available experimental evidence of their value, and appropriate clinical trials will be arranged in suitable cases.

It has been proposed that 1931 was also the year in which the first true randomized trial was conducted. This trial was conducted by Amberson to study the treatment of tuberculosis with sanocrysin on 24 patients who were divided into two groups of equal size on the basis of a coin toss to determine which group would receive sanocrysin and which one the placebo. It was also a blind trial, as none of the patients knew to which group they had been assigned. Prior to 1931, several randomized trials had been reported, but the method of randomization was either not stated or was open to selection bias. For centuries, the structure of clinical testing was shaped by methodological and medical considerations, whereas the concerns of the individuals involved in the studies was of subsidiary importance. The Nuremberg trials drew attention to the unscrupulous experiments inflicted on humans during World War II by the Nazi regime and kindled a worldwide ethical discussion about the performance of clinical trials. Finally, in 1947, the Nuremberg Code laid down ten basic tenets for the protection of subjects and patients. Among other things, these provided for a voluntary declaration of consent by trial participants; the right of trial participants to comprehensive information on the nature, purpose, and potential risks of the experiment; and the right of trial participants to withdraw from the trial.


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1.1 The history of medical device legislation and clinical trials

at any time. In addition, it stated that the performance of a trial must be warranted by the expected results, and the risks involved must not be disproportionate to the social and humanitarian significance of the problem being addressed.

The Nuremberg Code was followed in 1964 by the World Medical Association’s Declaration of Helsinki. The Declaration developed the ten principles first stated in the Nuremberg Code, and tied them to the Declaration of Geneva (1948), a statement of a physician’s ethical duties. The Declaration more specifically addressed clinical research, reflecting changes in medical practice from the term ‘Human Experimentation’ used in the Nuremberg Code. A notable change from the Nuremberg Code was a relaxation of the conditions of consent, which was ‘absolutely essential’ under the Nuremberg document. Now doctors were asked to obtain consent ‘if at all possible’ and research was allowed without consent where proxy consent, such as a legal guardian, was available. Although it is not a legally binding instrument in international law, the Declaration of Helsinki draws its authority from the degree to which it has been codified in, or has influenced national or regional legislation and regulations and it has been revised six times, the most recent occurring at the General Assembly in October 2008.

The Declaration of Helsinki stimulated the independent development, in a number of nations, of legislation to protect the wellbeing of human subjects during clinical trials but a major spur to develop further safeguards was the Thalidomide tragedy that occurred in Europe in 1962. During the 1960s, Thalidomide was used in Europe as a treatment for insomnia, mostly in pregnant women, and for morning sickness. When the company who manufactured the drug made a submission to the U.S. Food and Drug Administration (FDA) to market the drug on the American market, Frances Kelsey (an FDA employee) reviewed the application and kept it off the market. Her reason being that she felt it did not conform to the 1938 Federal Food, Drug & Cosmetic Act, which required proof of safety to be submitted to FDA before a drug could be approved for marketing. However, the drug was allowed onto the market in Europe where it was consequently associated with causing deformities in approximately 8,000 children. The result was a tightening and amending of the Food, Drug and Cosmetic Act of 1938 with a number of additions such as the Kefauver-Harris Drug Amendments of 1962, which among other things required proof of drug effectiveness as well as safety, controls over clinical trials, and better quality assurance practices in drug manufacturing. Better quality assurance practice in drug manufacturing meant the development of Good Manufacturing Practice, which was implemented in 1963.

Eventually, from the mid-1970s, the FDA found it necessary to reject clinical research from other countries, since they felt that they didn’t
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have the same ethical and safety standards as the U.S. Europe and Japan each developed their own set of Good Clinical Practice (GCP) guidelines.

1.1.1 The specifics of medical devices

Laws specific to medical devices before the 1950s were few and far between as it was felt that there were few devices that offered appreciable risk to either the patients or the operators. However, the risks from infected devices and X-ray equipment were recognized and regulations based on the recommendations of the International Commission on Radiological Protection (ICRP), to protect excessive exposure to ionizing radiation, were implemented by a number of countries. Later in the 1960s regulations to control the sale of sterilized medical devices were introduced into the pre-existing legislation for drug safety in many countries. Throughout Europe, however, regulations varied significantly between the various countries.

Using the UK as an example, the rapid growth in the availability and complexity of medical equipment in the 1960s, resulted in product specialists being recruited to advise hospitals and to develop standards and purchasing specifications. In the late 1960s, the defect and adverse incident reporting system and the Scientific and Technical Branch (STB) of the Department of Health (DH) were established to improve the quality and safety of medical equipment along with a voluntary quality assurance system covering design and production.

Health care provision outside of the National Health System (NHS) was regarded as negligible and control of medical devices used in the NHS was seen as inadequate to protect public health. The main instrument of regulation was therefore instructions from the DH to Health Authorities and, in particular, the Supplies Officers to those authorities, that they should purchase only devices that conformed to an appropriate British (or comparable) Standard. Compliance with a standard was to be part of every purchasing contract and could therefore be enforced by civil contract law. Laws of general application, such as the Trades Descriptions Act 1968 and the Consumer Protection Act 1987 applied to such purchases in addition to contract laws.

The system was strengthened by the development of the Manufacturer Registration Scheme (MRS), which was launched in April 1982, and was a voluntary registration scheme initially for manufacturers of sterile medical devices and surgical products. The Supplies Technology Division and later the Medical Devices Directorate evaluated manufacturing practices of those who chose to register and carried out audits on manufacturers’ quality systems. Manufacturers who were assessed as being satisfactory were named on the register that was issued to NHS Supplies Officers with a recommendation to buy from registered manufacturers whenever possible.
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The first of the guides to Good Manufacturing Practice were published in 1981 and this was followed by six others until by 1988 almost the entire field of medical devices was covered. As the scope of the scheme grew and the number of manufacturers on the register increased, it became difficult for non-registered manufacturers to sell to the NHS. In addition, being registered also became a useful indicator of quality when marketing to other countries. At its height, the MRS registered 580 manufacturing sites worldwide, but the scheme was disbanded in June 1998 when the Medical Devices Directive 93/42 became fully operational.

1.1.2 Harmonization

The lack of a coherent and consistent system for assessing the safety and efficacy of medical devices throughout Europe added substantial expense to the cost of selling devices in Europe and often acted as a technical barrier to trade within the various countries. It was therefore felt that a harmonized approach to creating safety standards across the member countries of the European Community was needed to remove such trade barriers and simplify the process of bringing medical devices to the markets of the member states. In 1985 it was therefore decided to gradually remove the product safety requirements of the individual countries and replace them with Essential Requirements (ERs) that would cover all of the European Economic Area (EEA).

In brief, the goal of the new regulations was to provide a vehicle whereby European legislation could be harmonized, product compliance with the ERs for safety and performance could be ensured, device safety, quality and performance could be improved, and trade barriers would be removed.

Prior to the 1990s each country had their own quality standard mark, such as the Kitemark of the BSI in the UK and the TÜV GS mark in Germany, and other countries either had the choice of accepting these marks as sufficient proof of suitability or could demand that they be tested by their own standards before allowing them to be marketed in the country. The development of the MDD and their application to the awarding of the European CE mark of quality, theoretically, removed national barriers and allowed such marked devices freely to enter any European market. In practice, however, there were initial teething problems with purchasers in some countries, such as Germany, demanding that the quality standard of their own country be displayed on a device in addition to the CE mark before they would consider buying it. When the European Union (EU) began to tighten up on such practices other tactics were used by some countries to maintain control of what they felt should enter the market. France, for example, developed legislation that would require a three-month pre-market declaration for certain high-risk medical devices that had already received a CE mark. Seven EU member
states and the EC submitted comments to France that this was a violation of the EU regulation. In addition, French purchasers were only accepting medical devices that had received their CE mark approval from a French notified body.

Although such practices do still occur, the implementation of the directives and the establishment of the CE mark has been a major step forward in creating a safe, open and harmonious market in Europe and central to the award of CE mark certification for medical devices is proof of conformance to certain ERs.

The ERs for medical devices are set out in directives and, an important element of these ERs is risk management, which must be performed on all devices to provide an assessment of the inherent risks of the device in comparison with its benefits. The most recent revision of BS EN ISO 14155 makes BS EN ISO 14971:2007 (Application of risk management to medical devices) a normative reference. This means that it is not possible to meet the requirement of a clinical investigation without conducting risk management.

Both the directives and BS EN ISO 14155 have changed radically in recent years and this has major implications for the medical device industry. In the subsequent chapters this book will therefore examine the directives applicable to medical devices, the changes that have occurred to them and to BS EN ISO 14155, and provide a guide to how clinical trials should be conducted in light of these changes.

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