Guide to European Medical Device Trials

and BS EN ISO 14155

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Abbreviations

14155:2009 Amalgamated version of BS EN ISO 14155-1:2009 and BS EN ISO 14155-2:2009

14155:2011 BS EN ISO 14155:2011

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

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.

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[1] 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

[1] Amberson JB, McMahon BT, Pinner M (1931). A clinical trial of sanocrysin in pulmonary tuberculosis. *American Review of Tuberculosis* 24:401–35.

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

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.

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.

2 European Medical Devices Directive and Standards

2.1 What is Europe?

The term Europe has a number of definitions and, from a legislative position, these definitions are very important as European law does not apply to all countries of the European continent, but only to those countries that are members of the European Economic Area (EEA) and those countries that have opted to adopt the laws of the European Commission (EC).

The EEA has its roots in the EEA Agreement, which entered into force on 1 January 1994 to reduce trade barriers between its member states and incorporates the EU and three members of the European Free Trade Area (EFTA).

In 2011 the EU consisted of 27 member countries: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, The Netherlands and the United Kingdom.

The members of EFTA are Norway, Iceland, Liechtenstein and Switzerland. These countries, with the exception of Switzerland, expressed the wish to participate in the Single Market, while not assuming the full responsibilities of membership of the EU. The Agreement gives them the right to be consulted by the EC during the formulation of Community legislation, but not the right to a say in the decision-making, which is kept exclusively for member states. All new EC legislation in areas covered by the EEA is integrated into the Agreement through a Joint Committee Decision and subsequently made part of the national legislation of the EEA.

Switzerland and Turkey, although not members of either the EU or the EEA, do unilaterally recognize the CE mark. This has been achieved through mutual recognition agreements (MRAs), whereby the European States recognize the certificates issued by the Swiss and Turkish conformity assessment bodies, and Switzerland and Turkey recognize the conformity assessments carried out by the Notified Bodies (NBs) in the European States. This simplifies the mandatory reporting requirements

for placing devices on the market, and permits direct distribution from Switzerland and Turkey to all EU and EFTA member states, without needing to have an authorized representative with registered offices in those states.

2.2 Regulations, directives and standards and guidelines

European Regulations (ERs) are self-executing and directly implement EU policy in member states without the need for member states to enact their own legislation, becoming immediately enforceable as law in all member states simultaneously.

The provision for this structure is established in Article 288 of the Treaty on the Functioning of the European Union, which states:

> To exercise the Union's competences, the institutions shall adopt regulations, directives, decisions, recommendations and opinions.
>
> A regulation shall have general application. It shall be binding in its entirety and directly applicable in all member states.
>
> A directive shall be binding, as to the result to be achieved, upon each member state to which it is addressed, but shall leave to the national authorities the choice of form and methods.
>
> A decision shall be binding in its entirety upon those to whom it is addressed.
>
> Recommendations and opinions shall have no binding force.

A directive requires member states to achieve a particular result without dictating the means of achieving that result. Therefore a directive can be distinguished from EU regulations, which are self-executing and do not require any implementing measures. Directives normally leave member states with a certain amount of leeway as to the exact rules to be adopted and they also give member states a timetable for the implementation of the intended outcome. The process of a member state changing its national laws to comply with a directive is known as 'transposition' and the time from adoption of the directive to its transposition is known as the 'transition period'. If a member state fails to pass the required national legislation, or if the national legislation does not adequately comply with the requirements of the directive, the EC may initiate legal action against the member state in the European Court of Justice. This may also happen when a member state has transposed a directive in theory but has failed to abide by its provisions in practice.

2.2.1 Regulations

The European Council, EC and European parliament will choose to use either a directive or a regulation depending upon their objectives. Regulations have a direct effect upon national states without the state having to pass national legislation. In contrast, however, directives require member states to alter their laws in harmony with the standard directive. The EC and Parliament may choose to use a directive in order to give more autonomy in the legislative programme to member states. When directives are used, there is usually a time period set by which the required measures should be implemented at the national level; this time period is often three years. This gives the member states control over the roll-out of the legislation.

ERs are frequently implemented in response to an issue that is deemed an immediate threat and, consequently, requires prompt action in order to prevent harm to the populations of the member states. Therefore, there are few ERs relating directly to medical devices, but one regulation that does impact the industry is the European regulation on animal by-products (ABPs). This regulation (EC) No 1774/2002 was developed in response to concerns over the spread of bovine spongiform encephalopathy (BSE), other animal diseases or chemical contaminants such as dioxins to the human population. The EU had already taken steps to regulate high risk animal by-products, or specific risk material, and exclude it from the food chain. However, a comprehensive approach to regulating ABP was seen by the EC as an essential for ensuring a high level of health protection in the EU. On 3 October 2002 the EU adopted Regulation (EC) No 1774/2002, which lays down strict animal and public health rules for the collection, transport, storage, handling, processing and use or disposal of all ABPs. These rules applied throughout the EU from 1 May 2003. The import, export, transit, and trade of raw and starting materials intended for medical device manufacture must therefore conform to this regulation. This regulation is applicable to intermediate products but it is not applicable to finished medical devices. As defined in the Regulation, materials used for the manufacture of medical devices must be category 3 material or equivalent, i.e. from animals fit for human consumption.

2.2.2 Directives

With regards to medical devices, the application of directives to the assessment of their suitability for purpose was a major step towards driving forward innovation and the uptake of new technology in the EU.

The first devices to be targeted by this new approach were active implantable medical devices, which are devices that are fixed within the human body and are powered by an energy source other than that of the body or by gravity. These devices were considered to be those that

posed the highest potential health risk to the patient through malfunction or side-effects than other types of device. As a result the Active Implantable Medical Devices Directive (AIMDD), EC Directive 90/385/EEC, was adopted by the European Council Ministers in June 1990 and came into effect on 1 January 1993 with a two-year period during which companies had a choice of applying the requirements of the AIMDD or following pre-existing national requirements. This period ended on 1 January 1995 and it became mandatory for the relevant devices to meet the requirements of the Directive.

The next group of devices to be considered by the EC were all other medical devices apart from in vitro diagnostic (IVD) devices, which were considered to pose the least risk to patients. The Medical Devices Directive (MDD), EC Directive 93/42/EEC, therefore came into force on 1 January 1995 with a transitional period up to 13 June 1998, after which all medical devices which were not IVDs or covered by the AIMDD, had to meet the requirements of the MDD in order to be marketed within the EU and EEA.

The publication of the final directive, the In Vitro Diagnostic Directive (IVDD), EC Directive 98/79/EC, occurred in December 1998 and came into effect on 7 June 2000 with a transition period for companies set to last for three and half years up to December 2003. There was therefore a span of eight years between publication of the AIMDD and the IVDD. During this period, a number of the generic elements of the directives changed, so it was logical that at some stage in the directives' lives, their requirements should be aligned. The opportunity for alignment came with the review time scale included in the MDD, article 11, paragraph 4. It required the EC to review the operation of specific aspects of the directive five years from the date of its entering into force. These aspects included four areas:

1. Adverse incident reporting.
2. Clinical investigations for class I and class IIa devices.
3. Design dossier examination by NBs.
4. Combination products.

The review of the MDD began in 2003, with the EC and member national CAs taking the opportunity to review all three directives at the same time. This review resulted in a revised directive, 2007/47/EC, which was published on 21 September 2007, with a mandate for transposition by 21 December 2008 and full implementation by 21 March 2010. This directive makes no changes to the IVDD (although IVDs are now specifically excluded from Directive 98/8/EC on Biocides, eliminating confusion as to which Directive applies).

2.2.3 Standards

European standards are the least powerful and least rigid of the three European documents. Whereas regulations have to be adhered to with immediate effect to the 'letter of the law', and directives have to be adopted into national legislation within a specified time frame, standards do not have to be followed, but it is highly recommended that they are in order to show compliance with the directives.

In a sense, where directives say what should be done, standards say how it should be done, and although the same result might be achieved in a number of ways, demonstrating that the various steps of a European standard have been followed presumes the fulfilment of the requirements of the directive to which it applies.

In essence, standards relate to products, services or systems and are no longer created solely for technical reasons, but have become platforms to enable greater social inclusiveness and engagement with technology.

A European standard (EN) is a document that has been adopted by one of the three recognized European standardization organizations: Comité Européen de Normalisation (CEN), Comité Européen de Normalisation Électrotechnique (CENELEC) or European Telecommunications Standards Institute (ETSI). An EN is available, in principle, in the three official languages of CEN (English, French and German).

A harmonized standard is an EN, prepared under the mandate of the EC or the EFTA Secretariat with the purpose of supporting the ERs of a directive. The mandate does not necessarily cover the complete standard, and it is possible to include other, additional provisions in the text of the standard, the application of which is not mandatory. When this is the case, distinction should be made between the regulated area of the standard, which 'supports' the requirements of the directive, and the voluntary area of the standard. This relation is explained in 'Annex Z' of every mandated standard.

In principle, the procedure of preparing and adopting a harmonized standard is the same as the procedure of adopting European standards. The difference being in that the role of CEN Consultant is included during public enquiry, who reviews the draft standard from the point of view of meeting the provisions given in the wording of the mandate and from the point of view of meeting the essential requirements of the corresponding European directives. It often occurs that a mandated standard supports more than one European directive. If this is the case, several CEN consultants will review the standard, each giving their report for the relevant field. Prior to formal casting of votes on the mandated standard, the CEN Consultant will be engaged again to confirm, within four weeks, the final text of the standard for voting. If the Consultant refuses to confirm the text, further coordination will be necessary

between the Consultant, the chairman and the technical secretary of the CEN Technical Committee who has prepared the draft.

When, in terms of the CEN/CENELEC rules, the result of formal voting is positive, the CEN Management Centre will send to its members the text of the standard to be transposed into their national standards systems. At the same time, the EC and the EFTA Secretariat will be notified. At this point, the mandated standard is still a 'candidate' for a harmonized standard. It is only after all member states have communicated, through the intermediary of the CEN Management Centre, to the EC and the EFTA Secretariat the title of the mandated standard translated into their national languages (e.g. the Spanish AENOR communicates the Spanish translation of the title, the Greek ELOT the Greek translation, etc.), that an announcement of the mandated standard is published in the Official Journal of the European Communities, together with the indication of the directive in whose support the standard has been prepared. Through this act, a mandated European standard becomes a 'Harmonized Standard'. From this point the standard may, and with some directives should, be applied in order to prove conformity with the requirements of the directive.

It should be noted that national 'ENs', e.g. BS EN are typically just a reproduction of the original document, denoting adoption by local/regional authorities, and they may therefore have a different issue date (year) from the original ISO version, while in fact they have the same content.

2.2.4 Guidelines

Guidelines are documents that are produced by the EC to help give a common approach by manufacturers and regulatory bodies to the processes involved in meeting the requirements of the directives. These guidelines are not legally binding and other approaches can be used to fulfil the needs of the directives, but they do provide a strong template for navigating the various processes involved.

Standards are repeatable, measurable and testable specifications that can be used as normative technical requirements. Any device claiming to conform to a standard can be tested by any lab and be found to either meet or not meet the requirements of the standard. Guidelines, however, literally provide guidance. An example of a guideline might be 'To stay healthy, a person should exercise at least 20 minutes a day', but what constitutes 'healthy'? Does this mean optimum health, a state of homeostasis, or just 'better than poor health'? Guidelines are therefore open to interpretation although some contain more strict and testable checklists than others.

2.3 Directives, standards and guidelines related to medical devices and clinical trials

In addition to those directives mentioned in 2.2.2 (the MDD, AIMDD, IVDD and 2007/47/EC) there are a number of other European documents that are relevant to medical devices and clinical trials that will be mentioned in this book:

- Directive 2001/83/EC *Medicinal products for human use*
- BS EN ISO 14155:2011, *Clinical investigation of medical devices for human subjects – Good clinical practice*
- EN ISO 25539-1:2009, *Cardiovascular implants. Endovascular devices. Endovascular prostheses*
- EN ISO 25539-2:2009, *Cardiovascular implants. Endovascular devices. Vascular stents.*
- EN ISO 10993 series, *Biological evaluation of medical devices Parts 1 to 20*
- EN ISO 14630:2009, *Non-active surgical implants – General requirements*
- BS EN ISO 14971:2009, *Medical devices. Application of risk management to medical devices*
- ISO 15223-1, *Medical devices – Symbols to be used with medical device labels, labelling and information to be supplied – Part 1: General requirements*
- EN 980:2008, *Symbols for use in the labelling of medical devices*
- GHTF/SG5/N3:2010, *Clinical investigations*
- GHTF SG5 N2R8:2007, *Guidance on clinical evaluation*
- MEDDEV 2.1/3 Rev. 3, *Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative*
- MEDDEV 2.7.1 Rev. 3, *Evaluation of clinical data: A guide for manufacturers and notified bodies*
- MEDDEV 2.4/1 Rev. 9 June 2010, *Medical devices: Guidance document – Classification of medical devices*
- MEDDEV 2.7.2, *Guide for competent authorities in making an assessment of clinical investigation notification*
- MEDDEV 2.7.3, *Clinical Investigations: Serious Adverse Event Reporting*
- MEDDEV 2.7.4, *Guidelines on Clinical Investigations: A Guide for Manufacturers and Notified Bodies.*
- MEDDEV 2.12-1 Rev. 7, Jan. 2012, *Guidelines on a Medical Devices Vigilance System*
- MEDDEV 2.12-2 Rev. 1, Jan. 2012, *Guidance on Post Market Clinical Follow-up studies, a guide for manufacturers and Notified Bodies*
- *The Declaration of Helsinki*

2.3.1 Recent major changes

Three major changes have occurred to European legislation in recent years that have had a major impact on the conduct of clinical trials for medical devices. These changes involve:

1. A directive (2007/47/EC)
2. A guideline (MEDDEV 2.7.1 Rev. 3) and
3. A standard (EN ISO 14155:2011).

3 The Medical Devices Directive 93/42/EEC

Before a discussion on the import of the recent changes of this directive is undertaken, it is important to understand the principles of the MDD and the significance of the structure of the European directives. This consists of recitals, articles and annexes, for example, the MDD consists of 22 recitals, 23 articles and 12 annexes.

3.1 Recitals

The 'recitals' in directives are preliminary statements that introduce the main parts of the directive. They give details of relevant earlier positions leading up to the present directive and they explain the background of the directive. Recitals always begin with the word 'whereas'.

The number of recitals depends on the complexity and length of the legislation in question. However, it should be noted that the style of drafting is to make the entirety of this opening section (i.e. the statement of the powers and the recitals) into one long sentence. This can add to the difficulty of understanding the text, although each recital is intended to deal with a separate topic.

With regards to the MDD, four of the recitals provide important information on its application, with the fourth recital making it clear that the Directive only addresses the safety regulations of the member states. The seventh and eighth recitals provide advice on the interpretation of the ERs and the sixteenth recital indicates that a contact person, responsible for the device, should be available for the authorities to contact.

3.2 Articles

The substantive provisions of directives are divided into 'articles'. Usually the opening provisions define terms used in the legislation, and deal with general obligations and definitions. Later articles deal with specific provisions and these may be divided into parts to make it easier to follow the meaning of the text. In particular, technical matters (e.g. scientific

lists, categories of plants and animals, and lists of values) may be dealt with separately in annexes, to make it easier to follow the text.

The articles cover general items such as scope and definitions, placing devices on the market and putting them into service, free movement of CE marked goods in Europe, reference to harmonized standards, vigilance and incident reporting, conformity assessment procedures, appointment of an authorized representative, consequences of wrongly-affixed CE marking, confidentiality, etc.

The 23 articles of the MDD provide definitions, define the rules and routes for compliance, describe the classification of medical devices and direct the reader to the 12 annexes that provide the detail. However, some of the articles are of more relevance than others to clinical trials and these are described briefly below:

Article 3: All medical devices must meet the (applicable) ERs of the directive, which are defined in Annex I.

Article 5: Describes that all standards are voluntary, but a manufacturer's compliance with a harmonized standard must be accepted by a notified body as an indication of conformity with relevant ERs.

Article 8: Referred to as the Safeguard Clause, gives member states the authority to restrict or prohibit the placement of devices or withdraw them from the market if they fail to meet the ERs, or if there has been incorrect application of the standards referenced in Article 5, or if there has been shortcomings in the standards themselves.

Article 9: Differentiates medical devices into classes I, IIa, IIb and III

Article 11: Describes the conformity-assessment procedures required for various classes of devices. These classes are described in Annex IX of the MDD.

Article 20: Stipulates that confidentiality is required for all information obtained in application of the directive.

3.3 Annexes

The annexes of a directive provide the detail to the stipulations in the recitals and articles. For example the 12 annexes of the MDD provide the details of the Directive and describe the rules, requirements and assessment routes that need to be followed to bring a medical device to the EU market and are therefore pertinent to clinical investigations. With regard to the MDD:

Annex I: In practical terms this is one of the most important sections of the Directive as it lists the 14 ERs, which are grouped into six general requirements and eight concerning design and construction and 54 subsets.

Annex II: The EC Declaration of Conformity. If a manufacturer has obtained full quality system registration, this is the most commonly used conformity route with the ERs. The manufacturer's quality system should be registered to the applicable EN ISO 13485:2003 and be subject to routine surveillance assessments. EN ISO 9001:2008 can also be used but EN ISO 13485 is complementary to EN ISO 9001:2008 and applicable to medical devices and many medical device companies are registered to both standards.

Annex III: EC Type-Examination. An NB is required to test and evaluate a representative sample of the device to ensure that the device fully complies with the MDD's applicable requirements and the appropriate technical standards. When the Annex III route is used, it is in conjunction with the procedures defined in Annex IV or Annex V.

Annex IV: EC Verification. The manufacturer must lodge with the NB an application for examination of the design dossier relating to the product, which it plans to manufacture and to declare that the product conforms with all appropriate MDD requirements and applicable technical specifications.

Annex V: EC Declaration of Conformity (Production Quality Assurance). A conformity assessment procedure for the quality system of the manufacturer excluding the design phase of new devices but including all other aspects of conformity with the MDD; this conformity assessment procedure is the most suitable procedure for sterile class IIa devices, if the manufacturer does not choose the Annex II as the basis of certification; it may also be applied to class IIb and III devices in combination with Annex III; the manufacturer may base their quality system on the harmonized standard EN ISO 13485:2003. It also includes a requirement for manufacturers to institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase and to implement appropriate means to apply any necessary corrective action.

Annex VI: EC Declaration of Conformity (Product Quality Assurance). A conformity assessment procedure for the quality system for manufacturers of devices of which the relevant properties can be assessed in the final inspection. This conformity assessment procedure is not suitable for devices involving special manufacturing processes requiring validation, like sterilization; Annex VI may not be used for the assessment of class III products.

Annex VII: EC Declaration of Conformity. A conformity assessment procedure in which the manufacturer themselves declares the

conformance of their devices with the MDD; suitable for class I devices, and required for class IIa devices in combination with one of the Annexes IV, V, or VI. An illustration of the various routes to compliance in accordance with 93/42/EEC is shown in Figure 1.

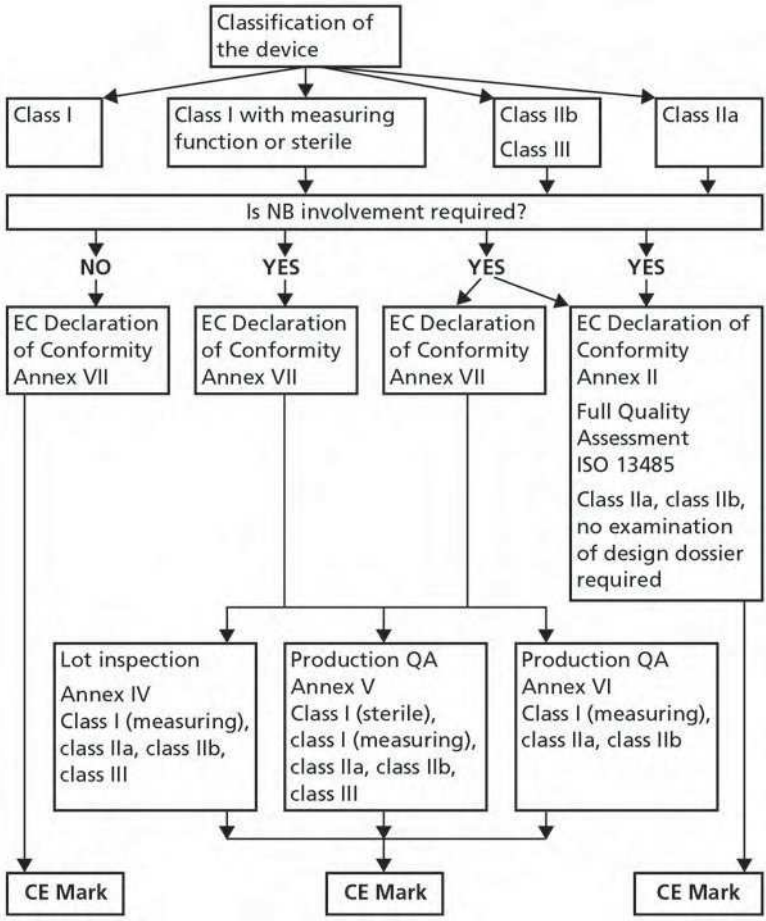

Figure 1 – Routes to conformity according to 93/42/EEC

Note that Directive 2007/47/EC now also permits manufacturers to use Annex II to obtain CE marking for class I measuring and sterile devices, in addition to the previous annexes (IV, V and VI). Only the manufacturing aspects concerned with the sterility or manufacturing related to conformity with the metrology measuring function, needs to be assessed by the NB.

Annex VIII: Statement Concerning Devices for Special Purposes. This applies to custom-made devices or devices designed for CI. The manufacturer must provide specific documentation relative to the intended use of the product including product identification information and data and a statement declaring that the device is intended for use by a specific patient, as well as the identification of the patient.

Annex IX: Classification Criteria. This section gives rules for defining which risk based class a device falls into.

Annex X: Clinical Evaluation. This section details the requirements for devices intended for clinical investigations.

Annex XI: Criteria to Be Met for the Designation of Notified Bodies.

Annex XII: CE Marking of Conformity. It defines the physical dimensions and appearance of the CE Mark.

3.3.1 Essential requirements

Annex I of the MDD is perhaps the most important of the annexes as it contains the ERs and these are the requirements that must be met by a device in order to receive marketing approval. Within the MDD the 14 ERs are grouped into six general requirements and eight concerning design and construction and 54 subsets, while the ERs contained within the AIMDD are similar to those of the MDD, but consists of 16 ERs grouped into five general requirements and eleven concerning design and construction. For the purpose of brevity, and because the MDD covers a broader range of devices, only the ERs of the MDD will be described in this Section, but it should be noted that, as described in Chapter 4, Directive 2007/47/EC has brought the AIMDD more into line with the MDD.

3.3.1.1. General requirements

The general requirements of the MDD are summarized below:

1. When used for their intended purpose and under the intended conditions of use, the devices will not pose a risk to either patients or other users and will maximize the risk benefit ratio and be safe to use.
2. Safety principles must be used in the design and construction of the device and should take account of the generally acknowledged state-of-the-art technologies.
3. The devices must meet all claimed performance criteria.

4. The devices must continue to function as intended for the lifetime of the device, without compromising safety or health, under normal conditions of use.
5. The devices must not be adversely affected during defined transport and storage conditions.
6. Any undesirable side-effects must constitute an acceptable risk when weighed against the intended performance and benefit to the patient.

3.3.1.2. Design and construction requirements

There are a number of subsections to the design and construction ERs that provide detail to the main points, but each of the main points refers to a main area of potential risk, as summarized below:

1. Chemical, physical and biological properties, should all be proved to be safe and this includes any product defined as a medicinal product, as defined by Directive 2004/27/EC (amending Directive 2001/83/EC), which has an ancillary action to the device.
2. Infection and microbial contamination risks should be minimized. This covers the sterilization of products and the prevention of transferring infections. Related to this is Directive 2003/32/EC on medical devices manufactured using animal tissues originating from bovine, ovine, caprine, deer, elk, mink and cat species, which aims to reduce the risk of Transmissible Spongiform Encephalopathies (TSEs) through use of a device.
3. The construction and environmental properties of the device should not create any risk either by itself or in combination with any other equipment which it is intended to be used with or near.
4. Devices with a measuring function must be designed and manufactured so that they provide sufficiently accurate and stable results and those results should be should be sufficiently easy to monitor and display and be presented in legal units.
5. Radiation exposure should be limited as far as possible taking into account the intended use of the device.
6. There should be protection against electrical, mechanical, thermal or noise risks, and there should be systems in place to warn of essential mechanical, electrical or power failure.
7. Labelling requirements and instructions for use (IFU). Specific instructions on labelling and IFU requirements are included in the MDD, but no IFU need to be provided for devices in class I or IIa if they can be used safely without such instructions. In addition different language requirements may be asked for by different member states.
8. If applicable demonstration of conformity with the ERs must be based on clinical data.

In summary the general requirements include the safety principles that must be used for design and construction: the devices must function continuously, under normal conditions of use without compromising safety or health and any undesirable side-effects must constitute an acceptable risk when weighed against intended performance and benefit to the patient, and the design and construction requirements are that safety is assured through risk management applied to the physical and biological properties of the device.

4 Directive 2007/47/EC

Directive 2007/47/EC came into force on 21 March 2010 and it has often been reported on as if it has replaced the MDD (Directive 93/42/EEC) and the AIMDD (Directive 90/385/EEC). This is not the case; it has only revised certain sections of these directives and therefore an unofficial name for 2007/47/EC is the 'amending Directive'.

Changes of major import that the directive has made are as follows:

- The ERs in Annex I of the MDD have been amended by the addition under the General Requirements of 'Demonstration of conformity with the ERs must include a clinical evaluation in accordance with Annex X'. This additional ER removes all doubt regarding the need to conduct a clinical evaluation for all classes of devices. In addition, the design and construction requirements have been changed so that when certain phthalates, which are mainly used as plasticizers, are an integral part of the medical device material formulation (i.e. not including contaminants or residues), and they are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, in accordance with Annex I of Directive 67/548/EEC, and the device is intended to administer and/or remove medicines, body fluids or other substances to or from the body or they are devices intended for transport and storage of such body fluids or substances, specific labelling is required.
- Annex II has been changed so that, in order to declare conformity the NB should be supplied with, 'Data stipulated in the part of the quality system relating to design, such as the results of analyses, calculations, tests, pre-clinical and clinical evaluation, post-market clinical follow-up (PMCF) plan and the results of the PMCF, if applicable, etc.' This therefore requires that clinical data should be supplied, which previously was not a defined requirement.
- Annex V (Production Quality Assurance) has been amended so that, in order to declare conformity there must be, 'An undertaking by the manufacturer to institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase, including the provisions referred to in Annex X.' This reference to Annex X therefore refers to clinical data.
- Annex VI (Product Quality Assurance) has also been amended in a similar manner to Annex V so that clinical data is also required.
- Annex X (Clinical Evaluation) has had many new elements added to it by 2007/47/EC, including a definition of what constitutes clinical data,

and changed it so that it no longer include references to implantable devices and devices in class III. Thus, it clarifies that appropriate clinical data are required for all classes of devices, not just those in higher risk categories.

There are no requirements under the MDD for labelling and IFU to be provided for devices in class I or IIa if they can be used safely without such instructions. However, according to the 2007/47/EC, where certain phthalates are an integral part of the medical device material formulation (i.e. not including contaminants or residues), and they are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, in accordance with Annex I of Directive 67/548/EEC, and the device is intended to administer and/or remove medicines, body fluids or other substances to or from the body or devices intended for transport and storage of such body fluids or substances, specific labelling is required.

Overall the major implications of 2007/47/EC on the conduct of clinical trials for medical devices are:

- the definition of clinical data has been improved so that it can be based on:
  - clinical investigations of the device concerned
  - clinical investigations or other studies of a similar equivalent device reported in scientific literature
  - published and/or unpublished reports on other clinical experience of either the device in question or a similar equivalent device
  - a combination of the above
- confirmation of conformity with the ERs concerning characteristics and performances of a device, the evaluation of potential side-effects and of the acceptability of the benefit-risk ratio must be based on clinical data;
- characteristics and performances that need to be confirmed with clinical data have been expanded and include:
  - reducing, as far as possible, the risk of error due to the ergonomic features of the device and the environment in which the device is intended to be used
  - consideration of the technical knowledge, experience, education and training and where applicable the medical and physical conditions of intended users.
- clinical data is required for all classes of devices, not just those in higher risk categories. Therefore, a clinical evaluation is required for all device classes;
- clinical investigations will need to be performed with implantable devices and devices in class III unless it is duly justified to rely on existing clinical data;
- it is required to document the clinical evaluation and its outcome, and this documentation must be included and/or fully referenced in

the technical documentation of the device and must follow a defined and methodologically sound procedure;
- it is required to actively update the clinical evaluation and its documentation with data obtained from the post-market surveillance;
- where PMCF as part of the post-market surveillance plan for the device is not deemed necessary, this conclusion must be duly justified and documented;
- where demonstration of conformity with essential requirements based on clinical data is not deemed appropriate, this needs to be adequately justified;
- member states may authorize the start of a clinical investigation before the expiry of 60 days, if the relevant ethics committee has issued a favourable opinion based on a review of the clinical investigation plan (CIP);
- where a clinical investigation is refused or halted by a member state, the member state must communicate its decision and the grounds for the decision to all other member states and the EC. In addition, when a member state has called for a significant modification or temporary interruption of a clinical investigation, the member state must inform the other member states concerned about its actions and the grounds for the actions taken;
- for custom-made devices and for devices intended for clinical investigations new information included in the official statement includes the investigator's brochure (IB), confirmation of insurance of subjects and the documents used to obtain informed consent (IC). In addition, a statement indicating whether the device incorporates, as an integral part, a medicinal substance or human blood derivative is required;
- active PMCF should be performed and the manufacturer must supply the NB with relevant information such as documentation on the quality system and not only the design data that were previously described such as the results of analyses and calculations, but also the preclinical and clinical evaluations, PMCF plan and the results of the PMCF, if applicable;
- manufacturers will need to develop careful justification for not conducting PMCF studies. Manufacturers should also be prepared for evaluations of compliance with PMCF requirements during NB assessment and quality system audit activities.

4.1 Summary of major changes

A summary of the main changes, with respect to clinical data, to sections of the MDD is given below:

1. Article 1, 14a and 15
2. Annex I – deletion of Section 14 insertion of 6a

3. Annex X – 1.1 Risk/Benefit
4. Annex X – 1.1 Defined & Methodologically Sound Procedure
5. Annex X – 1.1 Critical Evaluation
6. Annex X – 1.1a Clinical Investigations on Implantable Devices
7. Annex X – 1.1b Evaluation Shall be Documented
8. Annex X – 1.1c Evaluation Must be Actively Updated
9. Annex X – 1.1d No Clinical Data should be justified by evidence of risk management
10. Annex X – 2.3.5 Adverse Events to All Competent Authorities
11. Annex VIII – Devices for Clinical Investigation

Without reference to the relevant sections in the directives the main implications of the amending Directive for the medical device industry are:

- the AIMDD (90/385/EEC) was brought more into line with the MDD and IVDD in terms of structure;
- Authorized Representative (AR) – The appointment of an AR for all classes of devices is explicit. The AR has an explicit mandate to act, and be contacted, in lieu of the manufacturer in terms of meeting the obligations of the Directives;
- central circulatory system – This definition was changed to include the vessels of the aortic arch (*arcus aortae*) and descending aorta (*aorta descendens*) to the aortic bifurcation (*bifurcatio aortae*). Any device that comes into contact with these vessels is now considered to be a class III device;
- clinical data – All devices require clinical data, including class I devices. Stronger definitions have been provided on what constitutes clinical evidence;
- combination devices:
  - whether a product is a drug or device is determined by the Principal Mode of Action rather than by the intended use
  - if a medicinal product, as defined in Article 1 of Directive 2001/83/EC, is used 'in such a way that the device and medicinal product form a single integral product which is intended solely for use in the given combination and which is not reusable, that single product is governed by Directive 2001/83/EEC
- conformity assessment – class I Sterile and Measuring devices now have more flexibility to select a route to compliance, as they have been given the option to select a full quality assurance conformity assessment module;
- continuous use – The definition of this now includes situations in which a device, upon discontinuation or removal, is replaced immediately by the same or with an identical device;
- custom-device manufacturers – Are subject to a post market production review system involving incident reporting to the authorities;

- European databank – Data related to clinical investigations will now be collected for the European databank and shared among CAs. The databank will also include information on registration, AR, certificates and vigilance data. The data must be submitted in a standardized format, yet to be determined. At this time, the European databank is not operational;
- human tissue – Devices that incorporate medicinal products derived from human tissue, blood or plasma will be considered class III and are subject to consultation with the European Medicines Agency;
- increased transparency – Certain non-confidential summary information on devices will now be publicly available. Manufacturers of class IIb and class III devices will be required to submit a summary of information and data related to the device;
- IFU – Manufacturers must clearly indicate the date of issue or the latest revision of the IFU;
- In Vitro Diagnostics – IVDs are now specifically excluded from Directive 98/8/EC on Biocides, eliminating confusion as to which Directive applies;
- outsourced design and manufacturing – If the design or manufacturing of a device is done by a third party, it must be demonstrated that there are adequate controls in place to ensure the continued efficient operation of the party's quality system. This can be achieved through audits, receiving inspections or other means;
- NBs – These are required to perform an inspection of design documentation for a representative sample of devices using industry standard statistical techniques and 'commensurate' with the risk of the device;
- post-market surveillance – Custom devices require a post-market surveillance system that is reportable to Competent Authorities;
- records retention – Records must be maintained for inspection by the CAs for the 'useful life of the product' or five years from date of manufacture, whichever is greater. For the manufacturers of implantable devices this period is 15 years;
- single use devices – Manufacturers must provide information on known characteristics and technical factors known to the manufacturer that could pose a risk if the device were to be re-used. A manufacturer's indication of single use must be consistent across the EU and the information must be made available to the user upon request;
- software – Is considered an active medical device, whether integral with the device or as a stand-alone product. Software validation is also an ER.

5 MEDDEV 2.7.1 Rev. 3

MEDDEV 2.7.1 Rev. 3 *Evaluation of clinical data: A guide for manufacturers and notified bodies*, was released in December 2009 and aligns the EU guidance on clinical evaluations with the Global Harmonization Task Force (GHTF) guidance document, SG5/N2R8:2007, which was released in May 2007. The format and layout of the new revision is very different to the previous version it superseded, for example consisting of 46 pages compared to the previous version's 19 pages. While for the most part the content is similar, the wording has been changed to reflect the wording in the GHTF document, and minor changes have been made. Six appendices are now included, including a template for the Clinical Evaluation report, and Appendix F, provides a detailed example of a checklist that could be used by a NB to assess whether or not the clinical data provided by a manufacturer is sufficient.

A failure notice from a NB is shown in Table 1 (from which identifiable information of the device and the company involved have been removed) and demonstrates the problems that companies have had when not adjusting to the changes made through the implementation of Revision 3.

From the checklist shown in Table 1, it can be seen that MEDDEV 2.7.1 Rev. 3 has many strong ties to Directive 93/42/EEC as amended by 2007/47/EC. A major point shared by both, that has had the effect of increasing the number of clinical trials that are being conducted by medical device companies, is the need to have and stipulate a plan for the collection of post-market data. This has resulted in an increase in post-market clinical studies. In addition, there is a requirement to provide strong justification of why no clinical trial is necessary. Therefore, situations have arisen where, companies assessing this justification have realized that the clinical data they have accumulated through searches of the literature are insufficient to provide as evidence of suitability to market to NBs and have therefore quickly progressed to taking the clinical trial route. This process is in line with the advice provided by MEDDEV 2.7.1 Rev. 3 for the completion of a clinical evaluation: that the clinical evaluation is based on a comprehensive analysis of available pre- and post-market clinical data relevant to the intended use of the device in question. This includes clinical performance data and safety data together with data specific to the device in question as well as any data relating to devices claimed as comparable by the reviewer.

Table 1. Notification from a Notified Body on failed fulfilment of the requirements of MEDDEV 2.7.1 Rev.3

		Yes	No	Comments
1. General				
1.1.	Chosen route:			
	1. route without clinical data **OR** 2. clinical investigation route **OR** 3. literature route	x		Sections 4; 5; 6; 7; 8 shall be checked
1.2.	Demonstration of performance and safety is based on			
	– Literature	x		
	– Bench tests	x		e.g. dynamic & static testing
	– Pre-clinical studies	x		Reactivity experiment
	– Clinical data (clinical experience, clinical study)	x		
1.3.	Explanation and detailed justification for each step of chosen route?	x		Risk analysis
1.4.	Detailed justification, if no clinical trial is performed?		x	
2. Literature Route				*o Literature review (to be checked by sections 4.1; 4.2.) is required for any clinical evaluation* *o The "Literature route" may also include pre-clinical testing (e.g., bench tests, animal studies)*
4.1. Document check				
Literature search protocol (= plan)				
4.1.1.	Search protocol available?		X	
4.1.2.	Clearly defined objective of literature review?	x		

4.1.3.	Specification of types of studies to be included in review?	x		
4.1.4.	No concerns that all relevant publications are included (highquality data and low-quality data)?		x	
Literature search report				
4.1.5.	Search report available?		X	
4.1.6.	Are sources of data/ extent of search/ other sources specified?	x		
4.1.7.	Rationale for selection/relevance of literature available?	x		
4.1.8.	Have reasons been identified for believing that all relevant references, both favourable and unfavourable, are included?	x		Negative literature included.
4.1.9.	Criteria for exclusion of particular references + justification?	x		Ranking of literature acc. to scientific quality
4.1.10.	Detailed description of the different stages of literature search (identification, appraisal, analysis, conclusion)?	x		
4.1.12.	Copies of the publications referenced in the CER available?	x		
4.1.13.	Literature search report is a separate document, i.e. not included in CER?		x	Unclear
4.1.14.	Literature review up-to-date?	x		Existing; Procedure: every five years if no problems occur.
4.2. Evaluation of publications				
4.2.1.	Each single selected publication evaluated separately?		x	Not in the report
4.2.2.	Assessment of relevance of the author´s background and expertise in relation to the particular device/medical procedure?	x		Implicit: Acceptance by peer-reviewed journals
4.2.3.	Assessment whether author´s conclusions are substantiated by the available data?	x		Implicit: Acceptance by peer-reviewed journals
4.2.4.	Assessment whether literature quoted in publication reflects current state-of-the-art?	x		Recent publications: this is described in the relevant procedure

4.2.5.	Assessment whether references in the publication taken from recognized scientific publications?	x		Peer-reviewed journals only are accepted (procedure)
4.2.6.	Assessment whether publication is outcome of a study according to scientific principles?	x		Implicit: Acceptance by peer-reviewed journals
4.3. Issues to be addressed in the CER				
4.3.1.	Detailed justification for chosen literature route available?	x		Grade of detail shall be extended
4.3.2.	Description of extent to which the literature relates to the characteristics and features of the device under assessment?		x	Not detailed in the report, not formalized in the past
4.3.3.	Demonstration of equivalence in case the device under assessment is not identical with the device which is subject of the publication(s)?			
		x		
	– Clinical AND technical AND biological equivalence (all aspects must be met)? – In case of differences: Demonstration of significance of differences on safety and performance available? – In case of differences: Have gaps/differences been covered?			
3. CER in general				
5.1.	Author of CER suitably qualified in the relevant field?	x		
5.2.	Justification by the manufacturer for choice of author of CER?		x	
5.3.	CER approved by a second expert knowledgeable in the stateof-the-art and able to demonstrate objectivity?	x		
5.4.	Scope of clinical evaluation outlined?	x		
5.5.	Stages of clinical evaluation according to MEDDEV 2.7.1 Rev 3?	x		*Yes, although some areas lacking*
	Justification of any deviation?		x	NA
5.6.	Device description included?	x		

5.7.	Description of claims (including formal Intended Use, indications, contraindications) included?	x			Missing contraindications
5.8.	Proofs that all data (i.e., favourable and unfavourable) were analyzed in the CER?	x			Implied in objective
5.9.	Proofs that performance as claimed by Intended Use was demonstrated in the CER?			x	Unclear for all indications
5.10.	Analysis of all identified clinical risks and safety measures?			x	*Including severity and probability of each risk*
5.11.	If applicable: experience from prior clinical use of the device taken into consideration?	x			Existing device
5.12.	Description of methods of weighting of different papers and statistical methods of analysis (assessment methods, type/ duration of study, heterogeneity of the study population)?	x			
5.13.	Analysis of post-market experience of the same/ similar devices?	X			
5.14.	List of referenced publications attached?	x			
5.15.	Conclusion (including justification) of positive risk-to-benefit ratio taking into account the state-of-the-art?	x			State of the art to be pointed out more clearly (one article did)
5.16.	Can state-of-the-art taken into consideration be considered upto-date?	x			
5.17.	Signed and dated by the author?	x			
5.18.	Critical evaluation of methodology and results of all preclinical/ clinical tests and literature review?		x		
5.19.	All clinical risks evaluated in the CER included correspondingly in the labeling (IFU)?	x			To be pointed out more clearly
5.20.	Are all labeling claims regarding safety and performance substantiated by clinical data?	x			

5.21.	Evaluation performed in a systematic, thorough, critical and objective manner?	x		
5.22.	CER easily comprehensible for third-party review?	x		Depends on education level of 3rd party reviewer
4. Post-market surveillance				
7.1.	Appropriate plan for Post market clinical follow-up (PMCF) (MEDDEV 2.12-2) available? Adequate justification in case no PMCF plan is available?		x x	
7.2.	Adequate post-market surveillance in place?	x		
7.3.	Commitment to inform NB of significant updates to clinical evaluation based on post-market experience or scientific publications?	x		
7.4.	Documented post-market experience acceptable?	x		

The clinical evaluation is expected to address the significance of any risks that remain partially addressed after the manufacturer's risk management. The scope of this evaluation varies according with the outputs raised from the risk management.

There are four discrete stages in the clinical evaluation process:

1. Identification of pertinent clinical data. This information can be sourced from the literature or clinical investigation(s) or both. In the first case, the process of data searching and gathering is called a literature search.
2. Appraisal of the data, in terms of its relevance, applicability, quality and clinical significance.
3. Analysis of the data, whereby it is to determined if the data demonstrates the clinical performance and safety of the device in relation to its intended use.
4. Assessment at completion of the clinical evaluation process in which a report is compiled that outlines the various stages and details conclusions on the safety and performance of the device.

A schematic representation of the clinical evaluation process according to MEDDEV 2.7.1 Rev. 3 is shown in Figure 2.

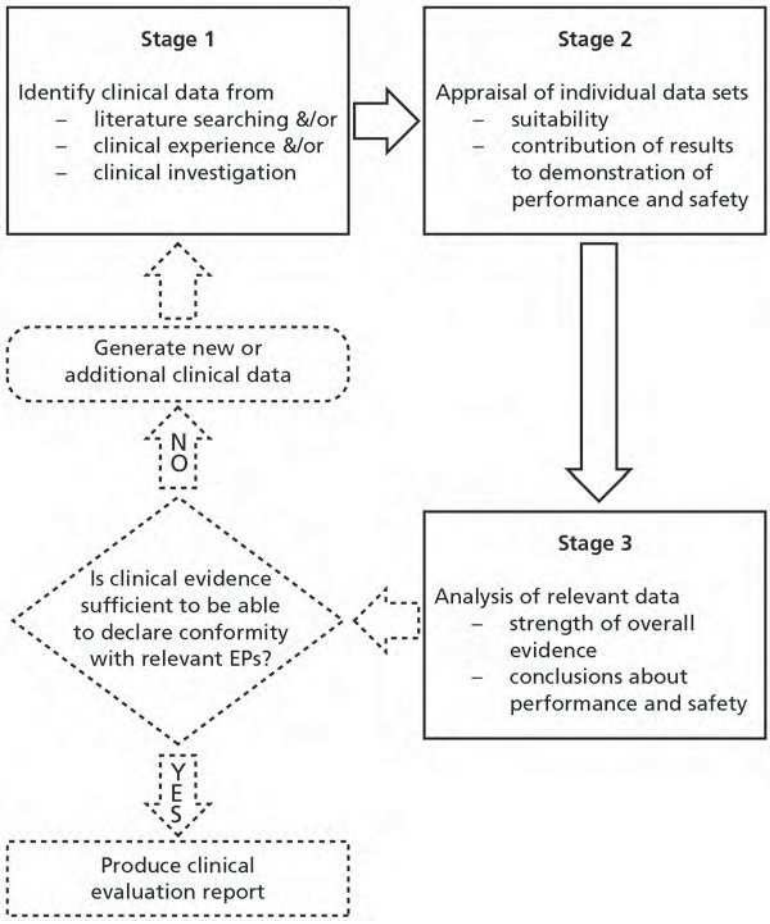

Figure 2 – Stages of clinical evaluation

Source: European Commission MEDDEV. 2.7.1 Rev. 3. December 2009

6 BS EN ISO 14155:2011

A clinical trial (called a clinical investigation when referring to medical devices) is one route that can be taken as part of a clinical evaluation to create clinical data.

Factors that affect the need to conduct a clinical investigation are the degree of novelty represented by the device. To be more precise:

- Is the device a completely new device of which the components, features or methods of action are previously unknown?
- Is it an existing device, which has been modified and the modification might affect the safety or performance significantly?
- Is this a new indication that is being proposed for the device?
- Does the device utilize new materials?
- Is it made from known materials but is to be used in a previously untried location?
- Will the device be used for a longer term than previously demonstrated?

If one or more of the above-mentioned conditions apply, the manufacturer, frequently the Clinical Affairs Department should consider arranging a clinical investigation in order to establish whether the performance capability of the device corresponds to the objective proposed and whether, under normal use, any unwanted side-effects constitute acceptable risks in relation to the effective benefit for the patient.

Documents that can be of assistance in determining whether a clinical investigation is necessary are the GHTF clinical investigation document: GHTF/SG5/N3:2010, which also provides guidance on what type of clinical investigation should be conducted and MEDDEV 2.7.4 *Guidelines on Clinical Investigations: A Guide for Manufacturers and Notified Bodies,* which indicates the type and quality of the clinical investigation information that NBs should be looking for.

A provision in the standard operating procedures (SOPs) of many medical device companies referring to clinical investigations is that they must be conducted as described in the harmonized standard on clinical investigations. Prior to 2011 this standard was published in two parts: BS EN ISO 14155-1:2009 – *Clinical investigation of medical devices for human subjects – Part 1: General requirements* and

BS EN ISO 14155-2:2009 – *Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plan*. Both parts of this standard (abbreviated to 14155:2009 for convenience in this book) were identical to Parts 1 and 2 of ISO 14155:2003 and superseded Parts 1 and 2 of BS EN ISO 14155:2003 to harmonize the standard against the revised directive.

In 2011, a new standard was published, which replaced the two part clinical investigation standard: BS EN ISO 14155:2011, *Clinical investigation of medical devices for human subjects – Good clinical practice*. This provides more detail on key aspects of clinical study planning, execution and documentation, and addresses topics such as quality systems for clinical research, as well as better fulfilling the legal requirements of the MDD and AIMDD. This standard will be abbreviated to 14155:2011 for convenience in this book.

The document has been organized so that users can walk through the steps of a clinical study sequentially from first concept to the final report. Sections also summarize the responsibilities of each key participant (i.e. sponsor, investigator). Annexes provide detailed suggestions for the content of protocols (CIPs) and final reports. Other annexes summarize the range of forms used in clinical studies and suggest a flow chart for assessing adverse events.

6.1 Major changes introduced by BS EN ISO 14155:2011

6.1.1 Scope

The scope of the amended standard has been revised and expanded. It states that 14155:2011 addresses good clinical practices for the design, conduct, recording and reporting of clinical investigations carried out on human subjects to assess the safety or performance of medical devices for regulatory purposes. It also states that, 'The principles set forth in this International Standard also apply to all other clinical investigations and should be followed as far as possible, depending on the nature of the clinical investigation and the requirements of national regulations.' This stipulates, therefore that the standard should not only be used when clinical studies are needed for the generation of clinical study data for regulatory purposes, but also when studies are conducted for other reasons, such as the generation of data for marketing purposes.

6.1.2 Structure

There are nine clauses, which form the major headings of the amended standard, instead of the 15 that were in the previous version, and eight

annexes instead of four. The eight annexes include two normative annexes, one for the CIP and the other for the investigator's brochure, which provide details for the contents and layout of these two documents. Six informative annexes cover case report forms (CRFs), the clinical investigation report, essential clinical investigation documents, an adverse event classification tree, the relationship with the MDD and the relationship with the AIMDD.

The titles of some of the clauses of the amended standard have remained the same as the previous version, such as 'Ethical considerations', while others have been changed subtly but importantly. For example, where the previous version had a clause entitled 'Justification for a clinical investigation' the amended standard has a sub-clause entitled 'Justification for the design of a clinical investigation'. The amended standard therefore places more emphasis on the integrated role of clinical investigations in generating clinical data as part of the clinical evaluation process.

The standard also includes new titles on clinical investigation planning, clinical investigation conduct, clinical investigation suspension, termination and close out, responsibilities of the sponsor, and responsibilities of the principal investigator and the annexes.

In general, the text in the amended standard is much clearer than its predecessor and while some definitions have been revised, new clearer definitions have been added: audit, blinding/masking, contract research organization, source documentation and others. There are 44 definitions in the amended standard compared to 23 in the previous version.

Although it is stated that the ethical principles of a clinical investigation, as before, should be based on the principles of the Declaration of Helsinki, the ethical considerations have been considerably extended in ISO 14155:2011. For example it is explicitly stated how the sponsor and investigators should avoid improper inducement of any individuals involved in a clinical investigation, and includes a whole new section (Section 4.5) on 'Communication with the ethics committee'. This is a very useful section, for those who are unused to dealing with rigorous ethics committees as it details the information that may be asked for. In Annex B of 14155:2009, information that 'can be of relevance for the ethics committee' was listed, such as an assessment of the scientific merit and justification of the clinical investigation project and of the investigational plan proposal. In sub-clause 4.5.2, of the amended standard clearer indications of the minimum specific documents that should be submitted to the ethics committee are provided. This information includes the CIP, IB or equivalent documentation; IC form and any other written information to be provided to subjects; procedures for recruiting subjects and advertising materials; and a copy of the CV of the principal investigator(s). In the event that an EC does not ask for this information, it is useful to prepare it anyway in the event of queries being raised at a

later date. Especially in light of the new addition to the standard, which in sub-clause 8.2.2(a), clarifies that the sponsor is responsible for preparing the documents required for EC submission. This was not specifically stated in 14155:2009.

Sub-clause 4.5.3 states that, 'Prior to commencing the clinical investigation, the sponsor shall obtain documentation of the EC's approval/favourable opinion identifying the documents and amendments on which the opinion was based'. This is a significant change to 14155:2009 as the failure to notably identify the documents upon which the opinion is based can, and has, caused delays to the submission of clinical study documentation to regulatory authorities. This can particularly occur if any of the documents have been amended before submission to the EC resulting in confusion about which version the EC based their opinion on.

The responsibilities of the sponsor have been extended considerably in the amended standard. Specifically, the sponsor shall, 'Implement and maintain written clinical quality procedures to ensure that the clinical investigation is designed, conducted and monitored, and that data are generated, documented, recorded and reported in compliance with this International Standard, the CIP, any subsequent amendment(s), and any other applicable standards and regulatory requirements.' This therefore means that whereas previously it could be stated that a clinical evaluation had been conducted in compliance with the standard, it is now essential that documentary proof should be made available that backs up this claim. In addition, whereas 14155:2009 merely stated that it was the sponsor's responsibility to 'Ensure that all adverse events and all adverse device effects are reported and reviewed with the clinical investigator(s) and, where appropriate, that all serious adverse events and all serious adverse device effects are reported to the relevant authorities and ethics committee(s) and/or safety monitoring committee(s)', the new Standard significantly expands on this. In sub-clause 8.2.5 it states that the sponsor is responsible for the classification of adverse events and the ongoing safety evaluation of the clinical investigation and expands the safety evaluation and reporting requirements, listing eight actions that are required to be taken. Notably amongst these actions is sub-clause 8.2.5(b), which requires that the sponsor should review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect. Such qualification and quantification of device deficiency is new in regard to the management of clinical studies, but is a very valuable aid towards the successful compilation of the final clinical evaluation report.

6.2 Summary

Many of the changes in the regulations and the guidance documents will only be apparent in the implementation and conduction of a clinical investigation and the following chapters will discuss these processes.

1. Clearer definitions of adverse events, adverse device effects, and unanticipated device effects.
2. A new definition, recording, and reporting requirements for device deficiencies.
3. Requirements for recording and reporting adverse device effects in persons other than subjects.
4. Implied requirement for a clinical research quality management system.
5. Requirement for Risk Analysis Report.
6. Requirement for a Clinical Evaluation Report to justify the study design.
7. Required content for a protocol (CIP).
8. Required content for an IB.
9. Suggested content and organization for CRFs.
10. Discussion of data monitoring committees.
11. Requirements for document and data control.
12. Requirements for electronic data systems.
13. Auditing recommendations.
14. Procedures for suspension or premature termination of a trial.
15. Procedures for working with vulnerable populations.
16. An extensive list of the documents essential for a clinical trial.
17. Omission of the annex discussing how to conduct a literature review.
18. Two different attempts at adverse event classification.

7 Preparing and conducting a clinical investigation

The process of initiating, conducting and reporting on a clinical investigation can be split into several phases, all of which have been affected by the development of 14155:2011, MEDDEV 2.7.1 Rev. 3 and 2007/47/EC. These phases are termed planning, preparation, implementation and closing. However, before a device can ever be tested on a human being its biocompatibility needs to be assured and the other aspects of the ERs relating to the safety and performance of the device, addressed as fully as possible through bench and animal testing. Using a coronary stent as an example, a bench test might include testing its radial strength, bend strength, crimping conformity, fatigue resistance and in vitro toxicity. Animal studies would then be conducted, in animal vessels of a similar size to that in which they would be used in humans, to assess other biocompatibility factors, therapeutic effects and overall safety. To aid in these processes a number of standards are available such as the ISO 10993 series of 19 standards for evaluating the biocompatibility of a medical device.

If it appears that the results of the bench and animal testing are going to be encouraging, the planning phase of the clinical investigation can then commence based on the intended performance of the device and potential risks identified through a review of the literature and information identified in preclinical testing. Information relating to risk analysis and how it should be documented can be found in Clause 5 of 14155:2011, which recommends that risk should be assessed according to BS EN ISO 14971:2007, *Application of risk management to medical devices*.

7.1 Planning

There are several procedures that need to be conducted in the planning phase and these include:

- classifying the device;
- preparing the budget;
- preparing the study design;
- selecting the clinical investigation team and appointing a project leader;

- obtaining management approval;
- writing the CIP.

The first three procedures in the above list are not conducted in isolation to each other as each influences the other, but, for the purpose of discussion, they will be addressed in turn.

7.1.1 Classification

Article 9 of the MDD, EC Directive 93/42/EEC, stipulates that medical devices should be differentiated into risk classes I, IIa, IIb and III and refers to Annex IX for classification guidelines. Class I devices are perceived to be those that pose the least risk to the recipient and class III devices are those that have the potential to cause the most harm either through their use or their failure.

The advent of devices that incorporate substances that are active on a pharmacological level has presented problems in terms of classification. The medicinal products for human use directive (EC Directive 2001/83/EC) defines a medicinal product as 'Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product.'

In deciding whether a product should be classed as a medical device or medicinal product, the intended purpose of the product should be taken into account and the method by which the principal intended action is achieved. As stated in Directive 2007/47/EC, a medical device is that, 'Which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.' Typically, a medical device function is fulfilled by physical means such as support of organs or the replacement of body functions, whereas the action of a medicinal product is generally achieved by pharmacological, immunological means or by metabolism. In the context of the directives, 'pharmacological' means an interaction between the molecules of the substance in question and a cellular constituent that either results in a direct response, or that blocks the response to another agent; 'immunological' is considered to be an action on the body that occurs through stimulation and action of cells or products involved in a specific immune reaction; 'metabolic' is an action that stops, starts or changes the speed of the normal chemical processes participating in, and available for, normal body function. The fact that a product is itself metabolized does not imply that it achieves its principal intended action by metabolic means.

Products are classed as medical devices if they use medicinal products but achieve their primary function through physical means, but if the pharmacological, immunological or metabolic action is more than ancillary then the product will be classed as a medicinal product.

To help with the classification of borderline products there is a guidance document MEDDEV 2.1/3 Rev. 3, *Borderline products, drug-delivery products and medical devices incorporating, as an integral part, an ancillary medicinal substance or an ancillary human blood derivative*. If the technology does not fall into the classification of a medical device, 14155:2011, the directives and the guidance documents mentioned in this book will not be applicable.

7.1.2 The budget

For the purpose of gaining CE mark approval the undertaking of a clinical investigation is normally determined by the fact that there is insufficient evidence from other data sources to support the claim that a device is safe and performs as intended. Therefore, the purpose of the clinical investigation is to fill in the gaps of the clinical evaluation, and therefore, to a certain degree, the extent of the clinical investigation will be determined.

Clinical trials can vary in size from a single centre in one country to multicentre trials in multiple countries and the cost associated with them rises accordingly. There are many advantages of multicentre trials: faster recruitment of the required number of patients, results that take account of differences in clinical practice and are thus more convincing and whose acceptability by peers, NBs and journals is higher, due to the patient sample of multicentre trials being more representative of the market environment. However, multicentre trials require a high input in terms of quality assurance concerning admission, treatment and follow-up and therefore a highly developed coordinating centre is also needed. A large multicentre clinical investigation can therefore cost well over a €1 million while a single centre investigation may cost only tens of thousands. Therefore, in order to prepare a budget, the potential expenditure should be broken down into specific areas: direct costs and indirect costs.

Direct costs are the expenditure specifically related to conducting the clinical investigation and include:

- manufacturing costs of the clinical trial devices, which should include 25 per cent more than the target number of subjects to be recruited;
- the cost of any comparator devices which should also include 25 per cent more than the target number of subjects to be recruited;
- personnel costs, which should include that of the Principal Investigator, research assistants, secretarial support, database and statistical support. In order to achieve this, there should be a

breakdown of the time involved in each of their duties, multiplied by their hourly rate. However, some centres have a standard fee schedule and a typical one for an NHS site is shown in Figure 3;

Chief Investigator set-up fee of £1200 to cover the work performed by the Chief Investigator for ethics submissions and all site set-up activities – that is in addition to the per patient fees. This is non-refundable in the event that the study is cancelled prior to patient recruitment commencing.

Investigator set-up fee of £900 payable on signature of the CTA to cover the work performed by the investigator and his team prior to recruitment – that is in addition to the per patient fees.

The R&D fee is £1000 – this is to cover the work done by the R&D department in processing, review and approval of projects.

Medical Physics set-up fee of £500 – to cover the work done by the Medical Physics team to complete the IRAS application documentation.

Pharmacy costings and payments are made separately with the appropriate Pharmacist and are based on the Standard Industry template, version of an hourly staff rate of £49.15. A simple dispensary study will involve 900 minutes.

Per Patient fees – consultant hourly rate at £68.75 all medical staff irrespective of grade £25.87 per hourly rate on top of Agenda for Change band 3 at £11.79. The admin rate will only be used for studies which require specific data entry or other discrete/defined tasks, by an admin assistant. It is not to be used for calculating general admin duties such as consultants' secretarial costs. Direct staff costs (e.g. consultant hourly rate = £68.75), will have 70% overheads and 20% capacity building added.

Patient travel expenses should be paid pro rata in addition to the per patient fee and overheads are not applied.

Figure 3 – Costs involved at a UK NHS clinical investigation site

- patient-related costs – the payment of costs for travel to and from the investigation site are frequently paid, but anything above this may be seen as inducement of the subjects. Some countries, such as Spain and Italy, are more acceptable of such payments whereas other countries, such as the UK are not;

- miscellaneous costs – biostatistical or other analytical costs, equipment maintenance, shipping and postal costs, laboratory and specialized equipment supplies;
- insurance – previous versions of BS EN ISO 14155 stated that insurance for compensation to subjects in the event of injury and 14155:2011 (Subclause 8.2.2 d) states that it is a responsibility of the sponsor that they 'Take out insurance covering the cost of treatment of subjects in the event of injuries caused by the clinical investigation, in accordance with the national regulations if applicable.' However, this should now be a requirement of national regulations as, although the previous medical device directives had no requirement for insurance coverage, Directive 2007/47/EC states that the directives should be amended so that 'For devices intended for clinical investigations' there should be 'the confirmation of insurance of subjects'.

Indirect costs for the study include all administrative charges for a particular site, and may include such things as office space, telephone, fax, copying machine, lights and heat. Overheads are specific to each institution, and generally range from 20 per cent to 40 per cent of the total direct costs.

By adding the direct and indirect costs for each site together and including those costs incurred by the sponsor and any Clinical Research Organisation (CRO) in administration of the clinical investigation, a total budget for the investigation can be determined. It will then be required that the return on the investment of the clinical investigation be determined by assessing the first six months or first year profits of marketing the product. If the return on investment is too low, it may therefore be worthwhile adjusting the size of the clinical investigation in terms of the number of patients recruited and the number of sites involved.

Another aspect that should be factored into the budget is the cost involved in undertaking certain administrative activities, which could include training, investigator meetings, central lab recruitment, data and safety monitoring boards and steering committees.

It should be noted that the costs involved in conducting a clinical investigation varies between countries (see Figure 4), and the calculations should be made for each country to be involved. In addition, a multinational trial involves a number of extra overheads. One such overhead is translation and, although sponsors are relying increasingly on English as a global language, local physicians' work with patients in their native languages. The cost implications of this dichotomy include the cost of translating protocols, IC forms, questionnaires, source data, adverse event reports and even training content. A second factor that can have a major effect is value-added tax (VAT) as, if trials are conducted in countries where a company does not have a presence, it could limit the

ability to receive a refund of any VAT incurred on the value of the devices imported for the trial and on the services performed under the study. With VAT rates ranging from 10 per cent to 20 per cent on top of customs and duty rates, this could represent a significant hidden cost of conducting the trial.

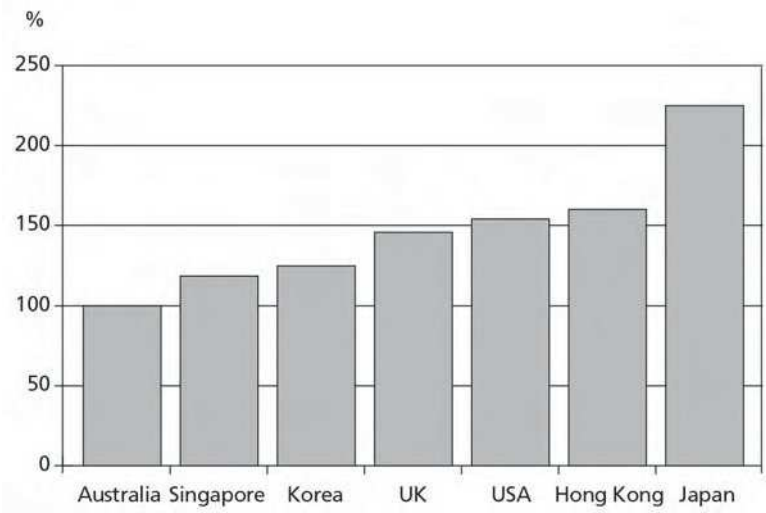

Figure 4 – Percentage of overall expenditure on medical device clinical investigations using Australia as the base

Once the budget is determined, a payment schedule should be established that includes:

- a non-refundable initial payment that include ethics committee approval and other start-up costs;
- regular payments with realistic milestones, such as the enrolment of the first subject;
- final payment made upon closure at site;
- invoicing permitted for other costs (i.e. auxiliary equipment and procedures).

Very importantly, the final budget and schedule should be agreed on by all parties and signed off before commencement of the project. In practice, however, it is frequently the case that the sponsor sets the budget internally, agrees on the fees informally with the investigational site before commencing ethics committee approval, and then signs the clinical investigation agreement once this is underway.

7.1.3 Preparing the study design

Sub-clause 5.3 of 14155:2011 states that the justification for the design of a clinical investigation should be '…based on the evaluation of pre-clinical data and the results of a clinical evaluation,' and an efficient study design is vital to the successful implementation and completion of a clinical investigation. Steps that should be undertaken include:

- the study hypothesis – is the device safe, comparable to a predicate device etc;
- endpoints – occurrence of adverse events, extent of revascularization etc;
- type of study – prospective, randomized, case series etc;
- subject inclusion and exclusion criteria – age, sex, disability etc;
- sample size – this should be calculated by a statistician or by a review of similar studies;
- study duration – this should be based on the timescale of the primary endpoints and validated by a statistician or by a review of similar studies, but also the dynamics of the treated condition and subject population should be taken into consideration, e.g. there is little point in planning a five year follow-up if the expected complications will be resolved in one month;
- study sites – the number and location;
- randomization of subjects – if randomization is required, the various methods should be examined to see which is most appropriate, such as a centralized telephone randomization or randomization by envelope. It also has to be considered whether randomization is appropriate in certain patient populations, the same as with a drug study where it might not be ethical to place seriously ill patients in a placebo group;
- blinding – no blinding, single or double blinding, analytical blinding;
- minimal data sets required per subject – this should this should be calculated by a statistician and include the planned response to missed data points;
- dissemination of safety and performance criteria – how this will be achieved, especially in response to serious adverse events etc;
- data collection – schedule of data collection;
- monitoring procedures – frequency etc;
- data storage – not only how it will be stored, but where it will be stored and for how long;
- data analysis – the statistical analysis that will be conducted and who it will be conducted by;
- publication and dissemination of the results – how this will be achieved and by whom.

Some of the above points are not vital to the immediate initiation of a clinical investigation, but they can be very helpful in preventing delays later on. For example not all European ethics committees have the same requirements, and in one multinational study where ethics committee

approval had been given in Italy and Germany the trial was almost delayed in the UK because it was required that the data storage details be provided and the identity of the statistician conducting the analysis.

Changes to the standards and directives have had little impact on this stage of the clinical investigation process, however, there has been clarification of some issues. For example, with regards to vulnerable populations previous versions of BS EN ISO 14155 merely stated that in the case of juveniles etc., that are unable to give their IC 'Informed consent can only be given by the legal guardian or representative.' 14155:2011 not only gives a definition of what constitutes a vulnerable person, but also states, 'Clinical investigations shall be conducted in vulnerable populations only when they cannot be carried out in non-vulnerable populations and shall follow the additional EC procedures where applicable. These clinical investigations shall be designed specifically to address health problems that occur in the vulnerable population, and offer the possibility of direct health-related benefit to the vulnerable population.'

7.1.4 Selecting the clinical investigation team

It is obviously important to attempt to recruit the best team possible for a clinical investigation and some of the areas that should be covered include: clinical affairs, data management, manufacturing, marketing, medical expertise, management, regulatory affairs, R&D and statistical support. For the first time 14155:2011 states that the sponsor can transfer any or all of its duties and functions relating to a clinical investigation to an external organization (such as a CRO or individual contractor), but ultimate responsibility for quality and integrity remains with the sponsor. However, the sponsor must specify in writing any duty or function assumed by the external organization and those that it retains for itself.

Another factor that has changed in the amended standard is that there is a stipulation for checking the qualifications of monitors of the study so that they are, familiar with the Standard and qualified in all areas covered by it; they are knowledgeable about the use of the investigational device and IC procedures and are trained in the sponsor's quality assurance and quality control systems. This essentially means that they are sufficiently well acquainted with the device and how it should be used to instruct investigators and also be well acquainted with all safety procedures. If they undergo any training this should also be documented, and is worth mentioning to demonstrate that due vigilance has been adhered to.

At this stage, it is also worth considering who will be responsible for compiling the results of the clinical investigation and placing them within the context of a clinical evaluation or using the results of post-marketing studies to create articles and publicity materials. With regards to creating

a clinical evaluation a change introduced by MEDDEV 2.7.1 Rev. 3 is that the clinical evaluation must be 'Written by a person suitably qualified in the relevant field, and reviewed and approved by an expert knowledgeable in the 'state of the art' and able to demonstrate objectivity.' This gives a certain freedom to the sponsor in that it stipulates that the clinical evaluation can be written by a medical writer, which only has to be reviewed by an expert, rather than an expert having to be found who has the time to author the entire clinical evaluation.

7.1.5 Writing the Clinical Investigation Plan

ISO 14155:2011states that the CIP is the, 'document or set of documents that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation. NB The term 'protocol' is synonymous with 'CIP'. However, protocol has many different meanings, some not related to clinical investigation, and these can differ from country to country. Therefore, the term CIP is used in this International Standard.' It should also be noted that the CIP is also a legal document that acts as a contract.

For the first time ISO 14155:2011stipulates, in detail what the contents and ideal layout of the CIP should be. This is provided in Annex A of the Standard and it contains 18 level one headings, 11 level two headings and over 110 bullet points to be followed. What none of the documents clarify, however, is how the CIP should be written. It is therefore important to remember that the CIP has not only to be understood by the members of the investigational team, but also by members of the NB and the ethics committees. ECs are composed of laypeople in addition to members of the medical and scientific community and therefore, whilst every aspect of the clinical investigation should be covered, including the background, justification and the methodology, it should be written in such a way that it is self-explanatory to the majority of educated readers with a Flesch Reading Ease test score in the region of 40 to 65.

7.1.6 Writing the case report forms

The CRFs should be written at the same time as the CIP, and should reflect its requirements. There are no real guidelines to the required contents of a CRF in 14155:2009, but Annex C of 14155:2011provides an overview of the format of a CRF.

Elements that should be included within it are:

- name of sponsor;
- reference number of the CIP;
- version number of the CRF (footer or header);

- name of the investigation, reference number (footer or header);
- investigator's signature and date;
- CLINICAL INVESTIGATION reference number on each page (footer or header);
- date of visit (footer or header);
- subject identification (footer or header);
- investigational site/investigator number (footer or header);
- page number and total number of pages (footer or header);
- medical history;
- eligibility;
- vital signs;
- medication;
- physical examination;
- specific laboratory test;
- concomitant medication;
- specific questions;
- informed consent;
- device procedure;
- subject withdrawal;
- AEs.

The wording of the CRF should be as simple and clear as possible, and the amount of data to be entered should be limited to the essential information and continuity of form should be maintained throughout. In addition, it should take into account that it should enable the required data to be analysed. There have been instances where the CRF has failed to incorporate questions for recording the required endpoints.

If they are on paper the forms should be printed on three-part carbonless paper and grouped in binders, one complete set of blank forms for each subject to be enrolled and it should be ensured that there is adequate margin for binding.

In creating a CRF, it should be remembered that it has to fulfil the requirements of a number of roles:

- the investigator who enters the information;
- the database designer, who designs a database application to receive the data;
- the data entry person who transcribes the information from the paper form into the database.

These people can therefore help with affirming that the final format of the CRF is fit for purpose and points that are worth bearing in mind in its formulation are:

- tick box entries are the preferred format for database entry as deleting, circling or underlining answer formats can lead to confusion.

- in questions that could have a number of answers, the answers should be mutually exclusive and the most common answer should be placed first in the list.
- visual analogue scales should preferably be 10 cm in length and clearly labelled with their minimum and maximum values. This length allows the easy measurement and translation of responses.
- the entries on the CRF should be ordered so that the data can be collected and recorded chronologically. Separate sheets should be used for each visit the form records.
- a separate form should be designed for adverse events, and this should include questions about the severity of the event, the date of onset, the date of resolution, any treatment that was required, and whether the event is device related.

7.2 Preparation

Procedures that should be conducted in the preparatory phase include: preparing all the required documentation, preparing the labelling and IFU, gaining insurance, confirming the selection of the investigation sites and personnel, gaining ethics committee approval and obtaining regulatory approval.

7.2.1 Documentation

In addition to the CIP documentation required for a clinical investigation trial should include the CRFs, the IB, ethics committee approval, subject screening log, subject identification code list, subject enrolment log, clinical investigation agreement, initials/signatures list, adverse event form, device accountability log, patients' IC and possibly a patient information sheet.

Although all of these documents will need to be prepared, the documents that may be required first are the IC and the patient information sheet, as, apart from the CIP these are frequently the only documents that an ethics committee is required to examine. The information required to be included in an EC has changed little due to implementation of the amended standard and regulations, with the major requirements still being that it should be explained that participation involves research, is voluntary and that choosing not to participate will not influence their standard of care. Major sections that should be covered include:

- the title of the study;
- the sponsor of the study;
- name and contact details of the principal investigator;

- the invitation to take part—this is a major section where the reasons for the invitation are given (including the fact that it is involves research and what aspects are experimental), the voluntary nature of their participation, and the consequences of their participation;
- description of the procedures – including time scale etc;
- possible risks, problems or unwanted effects – including an estimation of likelihood and potential severity An estimation of the risks involved should be conducted in accordance to BS EN ISO 14971:2009 – application of risk management to medical devices;
- possible benefits – to themselves directly and the community. No promises should be made and it should be indicated whether they might be in a placebo group;
- alternatives to participation – other standard treatments or procedures;
- personal expenditures – the costs that the participant may have to cover;
- compensation – what they may receive for participation, this can include repayment of costs such as for travel;
- confidentiality – describe how their personal data will be stored, used and disseminated;
- contact points – if the participant has any concerns or queries who they can contact at any time;
- the right to withdraw – if for any reason, at any time, the participant wished to withdraw from the study they may do so without fear or risk of compromising their care;
- the consent statement – in which the patient signs that they have understood all of the above points and they are willing to participate in the study.

7.2.1.1 The Investigator's Brochure

The IB is a compilation of the clinical and non-clinical data on the investigational product that are relevant to the clinical investigation. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for the key features of the protocol, such as the methods of use and safety monitoring procedures, and encourage their compliance. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make their own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person and representatives of the disciplines that generated the described data should generally participate in the editing of an IB, but the contents of the IB should be approved by the sponsor.

As described by 14155:2011 the IB should contain:

- a summary of the literature and an evaluation supporting the rationale for the intended use of the device and the design of the clinical investigation;
- a general description of the device and its components in accordance with the descriptions described for the CIP;
- a description of the mechanism of action of the device, along with supporting scientific literature, including, if relevant, the manufacturer's IFU and installation;
- possible risks, contra-indications, warning etc., for the device;
- a description of the intended clinical performance;
- a description of the materials used;
- a description of preclinical studies, which should include:
  - design calculations,
  - in vitro tests,
  - mechanical and electrical tests,
  - reliability tests,
  - validation of software relating to the function of the device,
  - any performance tests,
  - ex vivo tests
  - an evaluation of biological safety in accordance with Standard ISO 10993-1
- a summary of relevant previous clinical experience with the device and with other devices with similar characteristics;
- a list of the standards complied with in full or in part;
- results of the risk assessment

When writing the IB the authors should:

- write the IB for investigators, who are not specialists within all areas of the IB;
- focus on the main issues;
- ensure that the structure and content are clear;
- keep it short and simple. It is recommended that it does not exceed 50 pages;
- handle confidential information, such as technological innovations, with care, to protect intellectual property;
- use tables and figures whenever possible;
- ensure that consistent information is provided between sections;
- include actual values, not only relative changes or differences;
- provide per section a listing of citations for source documents.

The new directive and standard do not make any major changes as to how the documents required should be structured, but there is the addition of considerable help to understanding and categorizing adverse events, which could be used in the formulation of adverse event reporting forms. This information takes the form of a classification tree in Annex F of 14155:2011

Making a checklist of all the documents that are required throughout the study can be helpful in tracking documentation, and this could look like the example in Figure 5.

7.2.1.2 Clinical investigation agreement

The clinical investigation agreement is a complex document and varies from site to site and between nations, however, major headings that frequently can occur within these documents are:

- parties – Names and addresses of responsible health institution, sponsor and CRO;
- definitions;
- investigator and investigation site team members;
- clinical investigation governance;
- obligations of the parties and the investigator;
- liabilities and indemnity;
- confidentiality, data protection and freedom of information;
- publicity;
- publication;
- intellectual property;
- financial arrangements;
- term;
- early termination;
- relationship between the parties;
- agreement and modification;
- force majeure – This section should occur in every agreement and typical wording is:

> No Party shall be liable to another Party or shall be in default of its obligations hereunder if such default is the result of war, hostilities, terrorist activity, revolution, civil commotion, strike, epidemic, accident, fire, wind, flood or because of any act of God or other cause beyond the reasonable control of the Party affected. The Party affected by such circumstances shall promptly notify the other Parties in writing when such circumstances cause a delay or failure in performance ('a Delay') and when they cease to do so. In the event of a Delay lasting for four (4) weeks or more the non-affected Parties shall have the right to terminate this Agreement immediately by notice in writing to the other Parties.

- notices;
- dispute resolution;
- survival of clauses – This refers to what parts of the agreement, such as intellectual property, will remain in place and valid once the term of the agreement has expired;
- governing law;
- signatures.

Document Checklist

Document	Version	Notes	Prepared	Delivered
CIP			☐	☐
IB			☐	☐
CRF			☐	☐
Ethics committee submission		For which sites	☐	☐
Ethics committee approval			☐	☐
Competent Authority letter of no objection			☐	☐
Subject screening log			☐	☐
Subject identification code list			☐	☐
Initials/signature list			☐	☐
Adverse event form			☐	☐
Device accountability log			☐	☐
Informed consent		Translation into country languages and adaptation	☐	☐
Patient information sheet		Translation into country languages and adaptation	☐	☐
Letters from statistician on viability of the study			☐	☐
Insurance documents			☐	☐
Clinical investigation agreement			☐	☐
Letter to GP/personal doctor			☐	☐
CV of principal investigator			☐	☐
CVs of other investigators			☐	☐
Instructions for use		Translation of parts dedicated to persons who are not part of the investigation team	☐	☐

Figure 5 – Document checklist

7.2.2 Labelling and instructions for use

The amended standard has not changed the recommendations for the labelling of devices for clinical investigations and it simply states, 'The investigational device, the IFU or the packaging shall indicate that the investigational device is exclusively for use in a clinical investigation, if required by national regulations.' Labelling is required by various national regulations to be in different languages, as is shown in Table 2.

Table 2 – Language requirements for labelling and instructions for use

Country	Language	Other requirements
Austria	German	None
Belgium	Dutch + German + French (All three must be used for patient instructions)	None
Bulgaria	Bulgarian (English labels for professional use only)	Software may be in English.
Cyprus	Non-professional use devices in Greek. Professional use devices in Greek or English	It may be requested that labelling be in Greek characters for sterile devices, LOT, custom-made devices, investigational devices
Czech Republic	Czech	None
Denmark	Danish	None
Estonia	Estonian	None
Finland	Finnish + Swedish	None
France	French	Can request to check technical documentation/clinical trial information in French
Germany	German	None
Greece	Greek	None
Hungary	Hungarian	None
Iceland	Icelandic	None
Ireland	English	None
Italy	Italian	None
Latvia	Latvian – For professional use English or German is accepted	None
Liechtenstein	German	None
Lithuania	Lithuanian	None
Luxembourg	French	None
Malta	Maltese or English	None
The Netherlands	Dutch	A Dutch language waiver is possible upon application to Dutch Competent Authority
Norway	Norwegian	None
Poland	Polish	Devices for professional use only, upon written request, IFUs can be provided in other languages
Portugal	Portuguese	None

For guidance on labelling, ISO 15223-1:2007, Medical *devices – Symbols to be used with medical device labels, labelling and information to be supplied – Part 1: General requirements*, and ISO 15223-2:2010, *Medical devices – Symbols to be used with medical device labels, labelling, and information to be supplied – Part 2: Symbol development, selection and validation*, should be understood and the harmonized standard EN 980 allows for the presumption of conformity.

7.2.3 Insurance

As stated in Section 7.1.1, it is now a requirement of both the MDD and 14155:2011 that insurance is provided to subjects to cover the cost of treatment of subjects in the event of injuries caused by the clinical investigation. In addition, it is a requirement of many ethics committees to see a copy of the insurance certificate before they will grant approval for the clinical investigation to proceed. The insurance broker issuing the certificate must have a place of business registered in the EU and the policy must be in the national language.

7.2.4 Confirming the selection of the investigation sites and personnel

In the planning phase the investigation sites and the investigators that will conduct the trial will have been targeted, but before final selection occurs and contracts are arranged, a number of areas need to be checked. These include:

1. Investigators must be properly qualified and have adequate experience to conduct the trial.
2. An up-to-date CV will be required, which normally requires dating and signing, for the sponsor and submission to the ethics committee. These should normally be no more than two pages in length and experienced investigators will frequently have such an abbreviated CV already prepared.
3. CVs will also be required for any members of staff who see trial subjects, records data and obtains consent.
4. Other factors that should be taken into account are that the investigator must have sufficient time to conduct the trial including identifying the patients, conducting screening, performing the trial, meeting with the monitor and allowing for auditing. For this reason some of the busiest physicians are unsuitable as investigators unless they have a strong support infrastructure.

It should be noted that, although, ethics committees etc. always asked for the qualifications of the principal investigator to be proven through submission of a CV it wasn't stipulated in the old standards. The

amended standard also explicitly states that all key members of the investigational team should also provide CVs detailing their knowledge and competence to the sponsor. Both the old and the amended standard, however require that the investigators be 'Trained in the use of the investigational device under consideration.' Therefore, it is the responsibility of the monitor to ensure that the method of application of the trial device is according to the IFU, and particularly for a new device the sponsor should provide written instructions as well as hands-on training, which can include an observer or proctor being present during the first few cases. However, the presence of this person may have to be checked with the ethics committee and referred to in the patient information provided at consent. It should not be assumed that it is known how any piece of equipment should be used and therefore this should all be checked. Also in terms of multi-site investigations, it is important to check and train the users at all sites to ensure that the equipment is being calibrated, used and, if necessary, recorded from, in the same manner.

With regards to investigational sites it should be assessed whether there is sufficient throughput of appropriate patients and that the equipment and facilities provided by the site is suitable, regularly maintained with evidence provided through maintenance records and that the equipment will be available throughout the course of the trial. It can be the case, for example, that a Magnetic Resonance Imaging scanner is present, but it is unavailable for the investigation due to a high regular workload.

At the pre-site initiation the monitor should ensure that the investigator understands and accepts the obligations involved in the clinical investigation and understands how to use the investigational device and obtain IC. For this purpose, it is useful for the monitor to review a copy of the IC with the investigator to ensure they have a full understanding of the process. In addition, at the pre-site initiation visit, the monitor should understand their obligation to obtain EC review and approval of the clinical investigation before initiation of the clinical investigation and inform the sponsor of EC opinion. The monitor should also check that the site has access to an adequate number of suitable subjects, suitable facilities and time to conduct the investigation. It should be noted that any material used to advertise the clinical investigation to potential subjects should be approved by the ethics committee.

The monitor should also discuss the investigational site's subject recruitment strategy and ensure that a thorough feasibility assessment of the protocol, including retrospective and prospective analyses of their patient population has been conducted by the site. This may be done by conducting database searches and reviewing medical records over a five-year period to identify subjects who meet the eligibility criteria. This should be accompanied by a careful review of past enrolment performance metrics for the disease in question to evaluate what the

most successful strategies were for recruiting subjects in past and similar studies. It is very important to preserving patients' confidentiality while validating that the sites selected have credible access to the patient population of interest.

Another factor that should be taken into account is the frequent mismatch between the subject eligibility criteria and the available patient population. Making the inclusion criteria too strict can make it very difficult to enrol patients into a study. Therefore the monitor can gain input from the sites on the practicality of the inclusion and exclusion criteria of the CIP and feed this back to the sponsor. This is very important as having to amend the protocol, to broaden the inclusion criteria, once the investigation has been initiated is a very costly affair.

7.2.5 Ethics committee and competent authority approval

It is vital to gain ethics committee approval before any clinical investigation can take place. However, for a medical device that is CE marked and is being used in a post-marketing study, strictly within its intended approved use, then approval by the competent authority (CA) may not be required. Even though this may be the general rule however, some ethics committees may still require a statement of 'No Objection' from the CA before they will process an application.

The regulations vary between countries as to whether the submission to a CA is required before submission to the ethics committee or whether they can be submitted in parallel (Italy, Sweden and the UK).

A fee may also be payable for submission to the ethics committees and to the CAs. For example in the UK the CA requires that initial applications are made through the IRAS which captures the information needed by the CA. Users can print out the completed PCA1 and PCA2 forms and sterilization pro forma for signing before making the notification to the CA with the fee. The cost for low risk devices is £3,020 (initial application) or £2,120 (resubmission). For high-risk devices it is £4,240 (initial application) or £2,770 (resubmission), and one hard copy of the full submission and eight rewritable CD-ROMs are required. All information must be in English and, if any part of the supporting data consists of material in another language, this must be translated and one copy in the original language included.

According to Directive 2007/47/EC, clinical investigations for devices within class III and implantable and long-term invasive devices within class IIa or IIb, can commence after 60 days of notification to the CA unless the CA has issued a contrary decision or approval has not been given by the ethics committee. The CA can also issue approval prior to 60 days and for other classes of devices clinical investigations can commence

immediately after the date of notification, provided that the ethics committee concerned has issued a favourable opinion.

The time involved in waiting for CA and ethics committee approval can be used to ensure that any other documentation not required for the notification process is in place. A list of the documentation required and where it should be stored is given in Annex E of 14155:2011. However, for the first time the Standard makes special mention of the following:

- amendments to the CIP, IB, CRFs, IC and other subject information, or other clinical investigation documents should be tracked and a justification statement included with each amended section of a document, whilst the version number and date of amendments should be documented. Amendments to the CIP, IC and subject information documents should be notified and approved by the ethics committee;
- a subject identification log of all the subjects enrolled in the clinical investigation should be maintained by the investigation site and an identification code linked to their names, alternative subject identification or contact information;
- source documents should be created and maintained by the investigation site team throughout the clinical investigation.

7.3 Implementation

7.3.1 Traceability

Having checked that all the documentation is in place there should also be a check to ensure that there is a system of traceability. This is an important development, because although this was implied in 14155:2009 it was not implicit, whereas 14155:2011 states that, 'All documents and data shall be produced and maintained in a way that ensures control and traceability. Where relevant, the accuracy of translations shall be guaranteed and documented. All documents, and subsequent versions, related to a clinical investigation shall be identifiable, traceable and appropriately stored to provide a complete history of the clinical investigation. The investigator shall ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.' Further mention is also made of source documentation in 14155:2011 which states that the data reported on the CRFs should be derived from source documents and be consistent with those sources with any discrepancies explained in writing. This therefore also provides a more detailed description of the importance and correct method of use

of source data than 14155:2009, which simply states that it is the responsibility of the monitor and sponsor to ensure that, 'The data in the case report forms are complete, are recorded in a timely manner and are consistent with the source data.'

7.3.2 Audit

A correct approach to using source documentation is also highly important in auditing a clinical investigation, and whereas 14155:2009 simply stated that investigators should allow for auditing of their processes, 14155:2011 enters into much greater detail. The Standard 14155:2011 does not declare that an audit has to be undertaken, stating that 'Procedures for a clinical investigation audit shall be guided by the importance of the clinical investigation, the number of subjects in the clinical investigation, the type and complexity of the clinical investigation, the level of risk to the subjects and any identified problem(s).' However, the advantages of having an audit in place are that it can confirm the validity of the investigation, stop incorrect practices within the investigation before they totally invalidate the results and allow the NBs to quickly ascertain and track that correct practices were followed.

7.3.3 Equipment

In addition to a check on the documentation it should also be confirmed that all the other required resources are available, such as the investigational and comparative devices and storage facilities.

According to 14155:2011, access to investigational devices should be controlled and only used according to the CIP and therefore the sponsor should maintain records to keep track of all the devices, documenting the receipt, use, return and disposal of the investigational devices, as shown in Figure 6.

Details in the log should include the date of receipt, identification number, expiry date (if applicable), date of use, subject identification, date of return of device or explanation from subject (if applicable), and the date of return of unused, expired or malfunctioning investigational devices, if applicable. For ancillary devices it is also good practice to record their identification numbers, especially when they are in contact with the device during application.

At implementation of the clinical investigation the monitor should check that, in accordance with 14155:2011 (8.2.4.5 - n) 'Maintenance and calibration of the equipment relevant to the assessment of the clinical investigation is appropriately performed and documented, where applicable.' Therefore, the monitor should check the calibration of the

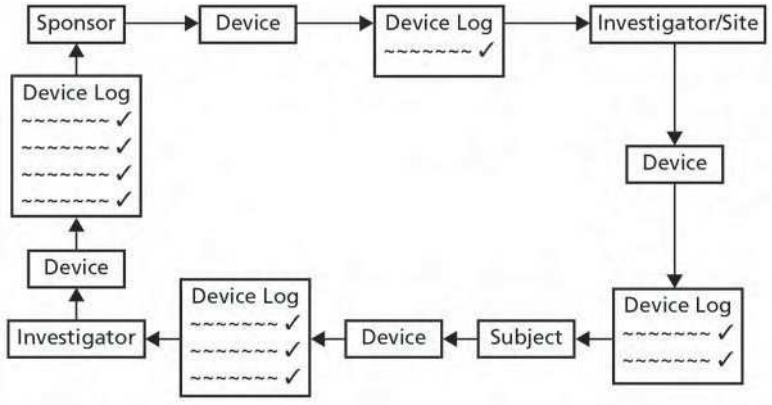

Figure 6 – Route of investigational device accountability

applicable instruments (spirometers, patient controlled analgesia equipment etc.) and the calibration records.

7.3.4 Recruitment and retention

Although a recruitment strategy will have already been formulated and the process approved by the ethics committees, recruitment of subjects cannot begin until ethics committee approval has been granted in writing.

The costs of recruitment can absorb 15 per cent to 18 per cent of the total budget of a clinical investigation and only 2 per cent to 20 per cent of screened patients may actually participate in it.

Enrolment can be increased by collating prospective patients into databases and the patients then approaching them and asking for their 'pre-consent'. Contacting patients by post, email or text is also being increasingly used to inform patients of future studies. In addition, incentive payments are increasingly being used to pay investigators, co-investigators and study nurses for high levels of recruitment, which often take the form of milestone payments. However, care has to be taken that this cannot be viewed as undue enticement and recruitment levels should be set to specified ceilings to ensure that in multicentre studies there is no undue bias or weighting to one site or population centre, as this could invalidate the results. A problem with such 'scatter-gun' approaches to recruitment is that it can lead to much more time involved in the screening process to sort the viable subjects from the non-viable, especially in cases where subjects are self-referring.

There are a number of reasons for screened patients not being admitted to a study and the main reason (approximately 50 per cent to 55 per cent of cases) is that they fail to meet the inclusion criteria, and the second major reason (35 per cent to 40 per cent) is that patients are unable to be available for all the required study visits. Once patients are enrolled into a study it is very important therefore that they continue to the end.

Patients may fail to complete a study for a number of reasons:

- they may fail to experience a benefit from the study and therefore do not wish to continue the study, but instead return to standard care;
- they may experience adverse effects and either be withdrawn from the study by the investigators or withdraw themselves;
- their other commitments may make it difficult for them to continue attending the follow-up study dates.

Subjects may therefore require continuous reassurance of the social benefits they are contributing to, and keeping in contact with them to remind them of appointments and motivate them. However, great care has to be taken to ensure that this cannot be viewed as coercion in any way or form.

In motivating the patient, it has to be remembered that the investigator is frequently not the patient's doctor, and it is the patient's relationship with their doctor that is likely to have the greatest influence on a patient's attitude to the investigation. This being the case it is advisable to have strong lines of communication with the subject's doctor in order to ensure the greatest compliance.

With regards to motivation, the use of mobile phones allows a strong method of direct communication and can be used to overcome the most common challenges with clinical studies. Mobile phone technology can allow the distribution of automatic reminders directly to the subject. Messages can be tailored to the individual to include information on the dosage of any medications they need to take in combination with the device and post-operative exercises. Delivery reports or interactive messages can be employed to ensure that the messages are received. Short messages can also be sent to motivate and enhance confidence in the study. Subject reporting via text messages can help to improve data quality and effectively determine the efficacy of a new device. Security and confidentiality are important considerations and all methods of data collection and evaluations must be developed in accordance with strict regulatory requirements (EU Directive 2002/58/EC on privacy and electronic communications). Subject consent should be obtained and an opt-out option should always be made available. All information must be encrypted and stored on a secure database in order to ensure full compliance with the EU data privacy act.

7.3.5 Monitoring

The purpose of clinical investigation monitoring is to verify that the conduct of the clinical investigation complies with the CIP, approved by the CA and ethics committees, any subsequent approved amendments, 14155:2011 and all other relevant regulatory requirements. Checking that the investigational team are working from the correct version of the CIP may seem obvious, but it can be overlooked. Research nurses, for example, may have received version 1 of a CIP, but objections from the ethics committee or ancillary bodies, such as radiological protection, may have led to a revision of the CIP being submitted and approved. It is therefore very important to check that all sites and personnel within those sites are working from the same document.

With regards to the qualifications a monitor should have 14155:2009 simply stated that, 'All parties participating in the conduct of the clinical investigation shall be appropriately qualified by education and/or experience to perform their tasks.' however, 14155:2011 goes into more detail and a monitor need not be a person qualified to diagnose and treat the disease or other condition for which the test article is under investigation, but somewhere in the direct line of review of the study data there should be a person so qualified. However, the monitors appointed by the sponsor should be:

- appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented;
- knowledgeable on the use of the investigational device(s) and relevant requirements, the CIP, the IC process and any other written information to be provided to subjects;
- trained in the sponsor's clinical quality assurance and quality control system and able to carry out the responsibilities of a monitor effectively and efficiently.

The number of monitors required for a clinical investigation varies depending on the circumstances, such as:

- the number of investigators conducting the study;
- the number and geographic location of the investigational sites;
- the type of product involved in the study;
- the complexity of the study;
- the number of parameters that need to be measured and monitored.

In general, there is a need for on-site monitoring, before, during, and after the trial and factors that should be covered at the initiation visit include:

- the complexity of the study;
- the number of parameters that need to be measured and monitored;

- confirmation that the investigators have received and understood all the correct documentation including the CIP, IB, IC, CRFs, IFUs and agreements;
- checking that sufficient numbers of the investigational devices have been received to commence the clinical investigation;
- confirming that the investigators have received sufficient training in the use of the investigational device and how the investigation should run;
- confirming that the investigators are aware of their responsibilities in terms of their contract and duty of care towards the subjects.

For subsequent monitoring visits an example of a monitoring form that would meet the requirements of 14155:2011 is shown in Figure 7.

Section 1

Date..... Investigation site.....

Monitor..... PI.....

Section 2

The facilities are fit for purpose?
Yes ☐ No ☐

If No, explain why .....

The CIP and IB are being followed?
Yes ☐ No ☐

If No, explain why .....

Accurate and complete records are being maintained? Yes ☐ No ☐

If No, explain why .....

All responsibilities of the PI are being conducted and not being delegated?
Yes ☐ No ☐

If No, explain why .....

Section 3 – Investigational devices

The return of unused investigational products complies with regulatory requirements? Yes ☐ No ☐

If No, explain why .....

The receipt, use, and return of the investigational devices are controlled and documented adequately?
Yes ☐ No ☐

If No, explain why .....

Storage facilities for the investigational device are fit for purpose?
Yes ☐ No ☐

If No, explain why .....

Storage times and conditions are acceptable? Yes ☐ No ☐

If No, explain why .....

Supplies are sufficient for the investigation? Yes ☐ No ☐

If No, explain why .....

Devices have been supplied only to eligible subjects and in accordance with the CIP? Yes ☐ No ☐

If No, explain why .....

Subjects have been provided with appropriate instruction on use, storing, and returning the device?
Yes ☐ No ☐

If No, explain why .....

Section 4 – Recruitment

How many patients have been screened?.....

How many subjects have been recruited?.....

Have only eligible subjects been recruited? Yes ☐ No ☐

If No, explain why .....

Subject recruitment rate?.....

Have any subjects missed study dates?
Yes ☐ No ☐

If Yes, what are the subject identifiers?

.....

Section 5 – Reporting

Has the data required by the CIP been reported on the CRF? Yes ☐ No ☐

If No, explain why .....

Figure 7 – Example of a monitoring form in compliance with the requirements of BS EN ISO 14155:2011

Section 5 *(continued)*

Is the data reported on the CRF consistent with the source data/ documents? Yes ☐ No ☐

If No, explain why .....

Are any therapy modifications documented for each subjects? Yes ☐ No ☐

If No, explain why .....

Are adverse events, concomitant medications, and intercurrent illnesses reported in accordance with the CIP on the CRFs? Yes ☐ No ☐

If No, explain why .....

Are any failed study visits or required tests reported in the CRFs? Yes ☐ No ☐

If No, explain why .....

Are withdrawals and dropouts of enrolled subjects reported in the CRFs? Yes ☐ No ☐

If No, explain why .....

Are the CRFs accurate and legible? Yes ☐ No ☐

If No, explain why .....

Have corrections, additions or deletions made to the CRFs, been dated, justified and initialled by the principal investigator or by their authorised designee? Yes ☐ No ☐

If No, explain why .....

Section 6 – Adverse events

Have all adverse events and device deficiencies been reported to the sponsor? Yes ☐ No ☐

If No, explain why .....

Have all serious adverse events and device deficiencies that could have led to a serious adverse device effect been reported to the sponsor without unjust delay? Yes ☐ No ☐

If No, explain why .....

Have all serious adverse events and deviations been reported to the EC, if required? Yes ☐ No ☐

If No, explain why .....

Section 7 – Conclusion reporting

Summary of what was reviewed, significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.

.....

.....

.....

.....

.....

Section 8

Signature ..... **Date** .....

Figure 7 (continued)

7.3.6 Adverse events

The regulations relating to adverse events encountered within clinical investigations originate within the directives. The AIMDD Annex VII 2.3.5 stipulates that all adverse events must be recorded, whilst the MDD Annex X 2.3.5 states that all adverse events, such as those specified in Article 10 must be fully recorded and notified to the CA. Directive 2007/47/EC expands upon this to state that 'All serious adverse events must be fully recorded and immediately notified to all CAs of the member states in which the clinical investigation is being performed.' The reporting of adverse events is backed up by 14155:2011, which states that the sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and expands the safety evaluation and reporting requirements, listing eight actions that must be taken:

1. Review the investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the investigational device; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties.
2. Review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties.
3. Report or ensure the reporting to the ethics committee by the principal investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or the CIP or by the EC.
4. Report to regulatory authorities, within the required time period, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or the CIP.
5. Report all relevant safety information to the data monitoring committee, if established, according to written procedures.
6. In the case of a multicentre clinical investigation, inform all principal investigators in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor, and ensure that they are reported to their EC, if required by national regulations or the CIP or by the EC, whichever is more stringent; this information shall be sent to all the principal investigators within a time frame established according to the perceived risk as defined in the risk analysis report.
7. Ensure that the EC and the regulatory authorities are informed of significant new information about the clinical investigation.

8. In case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether risk analysis needs to be updated and assess whether corrective or preventive action is required.

Despite such legislation and guidance documents, such as MEDDEV 2.7.1 Rev. 3 that indicates how risks and adverse events should be monitored and reported, the process of reporting adverse events appears to be one that sponsors might be failing in.

In order to help resolve these problems it is important for the sponsor to bear in mind that one of the objectives of the clinical investigation is to monitor all side-effects that the device might have in normal use. Therefore, if an adverse event does occur in the course of the investigation, it should be clearly recorded and reported to the sponsor for evaluation and to determine if this event was related to the device. This will help to prevent the occurrence of a potentially catastrophic serious adverse incident when the device is on the market.

When an adverse event occurs with a non-CE marked device in the course of a clinical investigation the method of reporting the event should be conducted according to the guidelines on clinical investigations. However, if a clinical investigation is being conducted with a CE marked device, used within its intended indication, it is important to evaluate whether the event should be reported within the vigilance system.

7.4 Closing

There are several procedures that need to be conducted in the closing phase and these include:

- notifying;
- collecting;
- filing;
- analysing;
- reporting.

7.4.1 Notifying

From the planning phase the investigators should have been made aware of the proposed duration of the study and this will have been confirmed in the CIP. The regulatory bodies should have been informed of the proposed date of the study termination from the preparatory phase and the subjects from the time of screening. Therefore, on termination of the study the subjects, investigators, monitors, the involved ethics committees, and CAs should be notified of the closure of the investigation.

7.4.1.1 Subject notification

As subjects may be recruited in phases, some subjects may have completed their follow-up visits before the full termination of the study. Therefore, the subjects should be made aware at their penultimate and final visit that their part in the study is coming to completion and they should be provided with information for their continuing care and contact details for any queries that arise as a result of their having taken part in the study.

If the study is terminated early because of a high incidence of adverse effects then the subjects should be informed and they will continue to be monitored for the remaining period of the planned study duration and, if required, stop using the device or have it explanted.

If the subject themselves suffers from serious adverse device effects that necessitates them having to be withdrawn from the study the subject will be notified of this and of the planned remedial action and continuing care that they will receive.

7.4.1.2 Routine close-out

Routine close-out occurs when all the required subjects have been recruited and all subjects have completed their follow-up visits.

The sponsor, normally through the monitor, will therefore notify the investigation sites that termination is about to take place and book a time for a close-out visit.

The investigation site will then have to notify the ethics committee and the CA, if required.

7.4.1.3 Suspension

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when instructed by the regulatory authorities, the sponsor must suspend the clinical investigation while the risk is being assessed. In addition, the participation of a particular investigation site or investigator may be suspended by the sponsor if monitoring or auditing identifies serious or repeated deviations from the CIP.

If suspension occurs, the sponsor should justify its decision in writing and ensure that all parties in direct contact with the investigation site(s) are informed of the decision.

When the sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor must inform the principal

investigators, the ethics committees, and, where appropriate, the regulatory authority of the rationale and provide them with the relevant data supporting this decision. Resumption can occur if the ethics committees and other regulatory authorities notified before the clinical investigation agree that it can resume. The principal investigator or authorized designee shall then inform the subjects and explain the reasons for the resumption.

7.4.1.4 Early termination

If the investigation is terminated earlier than anticipated a detailed explanation of the reasons for the early termination should also be provided.

Hopefully the reason for closing a clinical investigation is that it has successfully run its course but they may have to be prematurely terminated for other reasons. Such a reason can be evidence of major deviations from the protocol, but the most common cause is an unacceptably high incidence of adverse effects. In such a circumstance, it is vital that such evidence is rapidly acted upon. This is not only to prevent further risk to subjects and for ethical reasons, but if the NB witnesses that prompt action has been taken then they will have a more favourable opinion of the sponsor which could be to their benefit in subsequent clinical investigations (note that this should not officially be the case, but NBs are composed of people and each NB has its own characteristics, which is one of the reasons why companies frequently have their favoured NB).

At termination the sponsor will inform the investigator, who will inform the EC and the subjects, and the sponsor will also inform the CA. Funds should also be immediately made available by the sponsor for the investigator to treat the affected subjects and follow-up the others.

If only one site is closed down, notifications will have to be sent to the other sites if the reason for the closure is for safety concerns.

7.4.2 Collecting

At the closure of the trial all the devices that have not been used and those that were used, but were detailed in the CIP to be collected at the end of the investigation, must be gathered by the investigator and recorded by the monitor. The monitor should then make a written report to the sponsor that can take on the form of that shown in Figure 8.

Section 1

Date..... Investigation site.....

Monitor..... PI.....

Section 2 – Final patient recruitment status

Screened: .....

Screen fails: .....

Enrolled: .....

Discontinued or withdrew (for any reason): .....

Completed: .....

Lost to follow-up: .....

Enrolment violations: .....

Section 3 – Protocol and investigational sites

Have facilities remained adequate?
Yes ☐ No ☐ N/A ☐

If No, explain why .....

Has the staff remained the same?
Yes ☐ No ☐ N/A ☐

If No, explain why .....

For change of investigators, all regulatory paperwork must be completed – Investigator Agreements, CV, financial disclosure form(s), etc.

Have deficiencies/action items from previous monitoring visit been corrected? Yes ☐ No ☐ N/A ☐

If No, explain why .....

Have today's deficiencies/action items been discussed with the Investigator and staff (if any)?
Yes ☐ No ☐ N/A ☐

If No, explain why .....

Are GCP, CA and ethics committee requirements being met by the investigator and staff?
Yes ☐ No ☐ N/A ☐

If No, explain why .....

Was source documentation sufficient?
Yes ☐ No ☐ N/A ☐

If No, explain why .....

Discuss plans for final study report, publications and presentations and clarify roles and responsibilities of investigators.

Other: .....

Section 4 – Regulatory

Did the monitor meet with the PI at this visit? Yes ☐ No ☐

If No, indicate how monitor will follow up .....

Was the monitoring visit log signed?
Yes ☐ No ☐

If No, indicate how monitor will follow up .....

Final signed protocol/Investigator Agreement(s) copies present in regulatory files? Yes ☐ No ☐

If No, explain why .....

Figure 8 – Example of a close out monitoring form in compliance with the requirements of BS EN ISO 14155:2011

Are CVs of the investigator, sub-investigators and study personnel (if applicable) and current and present?
Yes ☐ No ☐

If No, explain why .....

Has the PI submitted the final (close out) report to the ethics committee?
Yes ☐ No ☐

If No, explain why .....

Collect copy of submission and any final ethics committee correspondence/acknowledgment.

Compare the master list (from sponsor) of adverse events to those in the site's regulatory books.

List any missing documents and remind investigator of their obligation to review these reports and submit to the ethics committee per the ethics committee's policies and procedures.

Have there been any changes or updates to any of the following? If yes, collect copy of new documents.

Investigator CVs Yes ☐ No ☐
Investigator medical licences Yes ☐ No ☐
Investigator Agreements Yes ☐ No ☐
Laboratory certifications Yes ☐ No ☐
Laboratory normals Yes ☐ No ☐
Radiation licence Yes ☐ No ☐
Mammography certification Yes ☐ No ☐

Communications between site and sponsor

Collect originals of the following documents (leave copy at site):

Protocol and/or Amendment Signature Page(s)

Final Site signature log

Final Monitor Visit Log

Final Device Accountability Log(s)

Describe where study records will be archived. Did the CRA/sponsor discuss requirement for length of study document storage; and the investigators need to gain approval in writing from the sponsor prior to destroying any study documents.

Per directive 2007/47/EC on retention period, an investigator or sponsor shall maintain the records required for a period of 15 after the date on which the investigation is terminated or completed.

Section 5 – Regulatory documents at site with version and dates

Protocol
Version..... Date.....

Amendment(s)
Version..... Date.....

CRF Version..... Date.....

CRF Instructions
Version..... Date.....

IFU Version..... Date.....

IB Version..... Date.....

Laboratory Manual
Version..... Date.....

Ethics committee approval
Version..... Date.....

Memos from sponsor
Version..... Date.....

Other Version..... Date.....

Figure 8 (continued)

Section 6 – Conclusion reporting

Action items resolved from prior visits:

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Action items still pending from prior visits:

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New action items for site:

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New action items for sponsor:

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Comments

List all comments that would add information to report (not mentioned above). Detail important discussions with investigator and /or staff.

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Significant findings

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Deviations

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Deficiencies

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Conclusions

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Section 7

Monitor

Signature ..... **Date** .....

Principal investigator

Signature ..... **Date** .....

Sponsor

Signature ..... **Date** .....

Figure 8 (continued)

A copy of the monitoring report or a summary of key findings shall be shared with the principal investigator in writing.

In addition, all the forms and data associated with the investigation must also be collected and filed appropriately. A list of the documentation required and where is should be held is given in Table E.3 – Essential clinical investigation documents after clinical investigation in 14155:2011.

To cover these requirements a section that is frequently included in clinical investigation agreements is: 'At close-out of the Investigation Site following termination or expiration of this Agreement the Board shall immediately deliver, and shall make sure that the Investigator delivers to the sponsor or CRO and at the sponsor's expense, all confidential information and any other unused materials and/or equipment provided to the Investigation Site (named) and/or the Investigator pursuant to this Agreement.'

7.4.3 Filing

In accordance with Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data, there are certain criteria that stipulate how the information on the subjects of clinical investigations should be kept and protected. The subjects of a trial should be informed that their data shall be kept confidential, will be entered into a computer and will be stored on an electronic database, which may be transferred from one site to another e.g. from the site of the original manufacturer of the device to a later manufacturer of the device. In addition the subjects should be informed that they have the right to access this information, modify the information or, at any time, to withdraw their information from the database.

This is sometimes an area that is forgotten when conducting an investigation and it is also a policy that does not exist in some countries e.g. the U.S. Therefore, if the data is transferred to a country that does not have equivalent regulations to the EEC on data protection then this can cause problems. These regulations and problems also apply to data that is stored in other forms such as paper records.

Since the U.S. has not established comprehensive legal regulations corresponding to the EU member states' data privacy standards, the EC collaborated with the U.S. Department of Trade to compile the framework for the Safe Harbor Program. The transfer of personal data to a U.S. company is permitted, and deemed as adequately protected, within the framework of this structure. The prerequisite is that the U.S. company is a signatory of the U.S. /EU Safe Harbor Agreement. In 2000 the EU recognized that an adequate level of personal data privacy was provided by the Safe Harbor Program signatory companies.

Electronic data is more frequently being transferred between locations by the internet, but it is commonly known that the internet is not a completely secure medium. Therefore, sponsors should ensure that if they wish to transfer their data in this manner, firewalls and other security measures are taken to ensure that the data is not hacked or modified in transmission.

7.4.3.1 Database

It is essential to have a well-constructed database to allow correct data entry and restricted access.

A key part of database design is database validation to provide brief descriptions of the validation strategies and activities to outline test procedures and document validation results with written assurance that the system is fit for purpose and to identify key personnel and their responsibilities as part of the validation process.

It is important to ensure that any individuals who will require access to the database and/or be responsible for data input, are given training for the database system by the database developer. The training sessions provided should be logged in the individual's training log.

The designated statistician should receive a full and dated download of the database, with a complete, clean and accurate dataset used for analysis. This should be retained separately from the live database to allow reproducible analyses. This is sometimes referred to as 'database lock.' It is a controlled procedure that freezes the data in a particular format securing the trial data and preventing further changes. There is a requirement to ensure all the trial data have been received, verified, fully coded and cleaned for analysis with all queries resolved before locking the database for further analyses. Unlocking of the database should be strictly controlled and documented.

When storing data it is important:

- to ensure that for electronically stored trial data (lap top, PC hard drive, and server) there is routine and adequate back-up provided;
- to ensure that data are anonymized by using patient trial numbers where possible and that the database as well as the lap top and/or PC are password protected;
- for data to be stored on any mobile disks (i.e. CD-ROM, USB stick, memory cards etc) that there is sufficient encryption and back-up of data in case of loss of memory disks;
- to document when the database is backed up; where it is stored; how it can be accessed if necessary; and who has access to the back-up;

- to outline the disaster recovery plan. Whether there is a hard copy or CD-ROM of the data stored in a secure separate location (e.g. fireproof cabinet) and how often this is done.

It is important to maintain procedures and records related to access. There should be clearly defined responsibilities for database security such as:

- security strategy and delegation;
- management and delegation of privileges;
- levels of access for users and for infrastructure (firewall, back-up, reboot)

There should be procedures in place for recovery of the database following a breakdown, routine back-up and disaster recovery. These entries should be recorded using a log.

Where data are transferred there should be a documented record of data transfers and measures in place for the recovery of original information after transfer. The receiver must acknowledge receipt of the data and password protection should be used at all times.

7.4.4 Analysis

The analysis of the data obtained from the clinical investigation must be carried out in accordance to the original method detailed in the CIP.

The object of the clinical trial is to collect data concerning the safety and effectiveness of a device in a sample of the target population. Statistical analysis is then used to infer relevant information concerning properties of the target population from the observations of those same properties in the trial sample. These inferences require that the research questions be translated into numerical statements of relationships of those population properties. Tests of the stated hypotheses should provide unequivocal answers to the research questions.

For example, if the research question is 'For some disease, is the mean value of a critical outcome variable after prescribed treatment, greater for the device-treated group than for the control group?' Two hypotheses would be formed: A null hypothesis that states that the mean value of patients post-treatment in the treatment group is equal to (or worse than) that in the controls; and an alternative (or research) hypothesis that states that the mean value post-treatment in the treatment group is greater than that in the controls. There are two types of decision errors that can be made by inferring results from a sample to the population. If the sample indicates that the mean is greater in the device treated group than in the controls (i.e. rejecting the null hypothesis) when in the population there is no difference between means, a Type I error (also

called an Alpha error) is made. If, on the other hand, the sample indicates no difference between means (i.e. accepting the null hypothesis), when the device mean is actually greater, then a Type II error is made. The probability of making a Type II error is also known as Beta error and statistical power is defined as 1-Beta.

The probabilities of these two types of errors factor heavily into all sample size calculations for hypothesis tests. Usually these probabilities are fixed in advance, giving more weight to the error with the more serious consequences.

For example, a Type I error occurs if the aim of the trial is to show that the test device is 'better than' the control, and we falsely reject the null hypothesis, and conclude that the device may be better than the comparison device, when in fact it is equivalent or even worse than the control. Conversely, if the object of the trial is to show that the device mean survival is 'as good as' ('no worse than') that of the control, then it would be more serious to accept a false null hypothesis (a Type II error). Additionally, clinical trial hypothesis tests should involve clinically meaningful differences, that is, those differences in the outcome variable(s) determined by experts in the medical community to be clinically significant. The most common sample size formulas include an estimate of the variability of the clinically meaningful difference in the numerator and an estimate of the clinically meaningful difference to be detected in the denominator. Thus, for a given outcome variable, the larger the variability, the larger the sample size that will be required. Similarly, for a given variability, the smaller the clinical difference to be detected, the larger the sample size.

7.4.5 Reporting

Reporting and publishing the results and conclusions of a clinical investigation is one of its major aims. However, the process should be regulated quite closely and the terms should be written into the clinical investigation agreement, as in this example: 'The sponsor recognizes that the Investigation Site and Investigator have a responsibility to ensure that results of scientific interest arising from the clinical investigation are appropriately published and disseminated. The sponsor agrees that the Investigator shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the clinical investigation, subject to this clause and any publication policy described in the CIP. If the clinical investigation is multi-centred, any publication based on the results obtained at the Investigation Site (or a group of sites) shall not be made before the first multi-centre publication. If a publication concerns the analyses of sub-sets of data

from a multi-centred clinical investigation the publication shall make reference to the relevant multi-centre publication(s).

Upon completion of the clinical investigation, and any prior publication of multi-centre data, or when the clinical investigation data are adequate (in sponsor's reasonable judgement), the Investigator may prepare the data derived from the clinical investigation for publication. Such data will be submitted to the sponsor for review and comment prior to publication. In order to ensure that the sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the sponsor for review at least sixty (60) days (or the time limit specified in the CIP if longer) prior to submission for publication, public dissemination, or review by a publication committee.

It is agreed that the Investigator shall ensure that all reasonable comments made by the sponsor in relation to a proposed publication by the Investigator will be incorporated by the Investigator into the publication.

The sponsor or CRO may present at symposia, national or regional professional meetings, and publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the clinical investigation and in particular, but without limiting the foregoing, post a summary of study results in (an) on-line clinical trials register(s) before or after publication by any other method. In the event the sponsor or CRO coordinates a multi-centre publication, the participation of the Investigator as a named author shall be determined in accordance with the sponsor's or CRO's policy and generally accepted standards for authorship. If the Investigator is a named author of the multi-centre publication, such person shall have access to the clinical investigation data from all clinical investigation sites as necessary to participate fully in the development of the multi-centre publication.

During the period for review of a proposed publication, the sponsor shall be entitled to make a reasoned request to the Investigator that publication be delayed for a period of up to six (6) months from the date of first submission to the sponsor in order to enable the sponsor to take steps to protect its proprietary information and/or Intellectual Property Rights and Know How and the Investigator shall not unreasonably withhold their consent to such a request.'

For review by the regulatory authorities the results and conclusions of the clinical investigation should be brought together in the Clinical Study Report (CSR). In brief, the CSR integrates the clinical and statistical descriptions, presentations, and analyses into a single report, incorporating tables and figures. Appendices contain such information as the protocol, sample CRFs, investigator-related information, technical

statistical documentation, related publications, patient data listings, and related computer printouts from the clinical study database.

In writing the CSR it is extremely important not to just look at the object of the study but to consider who will evaluate or examine the data. The NB will review and need data on safety and performance, whilst the CA will want to see that issues that were raised in the initial risk analysis have been addressed and health technology assessment organizations such as the National Institute for Health and Clinical Excellence will, in addition, wish to see its efficiency compared to other potential treatments.

It is often a good idea if the person writing the CSR is someone who was not directly involved in the clinical investigation. This is because someone who has worked on the study may have become so accustomed to the study that they may fail to notice deficiencies in the way the data is reported that will be glaringly obvious to the objective medical writer. Some manufacturers stipulate in their SOPs that the author should be a physician qualified in the condition being treated by the investigational device. However, this can not only be unnecessarily costly but also counterproductive, as their own views may infiltrate into the report.

Theoretically, the writer of the CSR should be able to prepare the document from the CIP and a set of tables and listings, which accurately record all the data collected in the study in an easy-to-understand format, however this is rarely the case and the objective professional writer can help in this respect. For example, a data listing may be provided that doesn't contain a mention of height and weight data, despite the CIP indicating that these variables would be recorded. If this was because the statistician forgot to list the data, the omission can easily be rectified. However, if the investigator failed to record height and weight data the sponsor will need to be informed and if it is because the CIP was changed that change will have to be noted, but if the omission occurred because the investigator forgot to record height and weight then the situation may be more difficult to solve. In each case, the writer provides an objective check to the data and has the potential to spot problems in the investigation before the intended audience does. In addition, the professional writer can greatly add to the clarity of the CSR. For example the statistician may provide tabulated data for the report that is technically correct but difficult to understand and the medical writer should be able to liaise with the statistician to develop a less confusing way of presenting the data.

With regards to the content and layout of a CSR, Annex D of 14155:2011 provides a suggested format with some explanation of the purpose of the contents. However, although the Annex states that the signatures should include those of the sponsor and coordinating investigators or principal investigators to indicate their agreement with the contents of the report and although 14155:2011 does state that ultimate

responsibility for the clinical investigation resides with the sponsor, it is worthwhile to also obtain the signature of any CRO that was involved as they were the 'front line' body responsible for organizing the running of the clinical investigation.

8. Industry examples

This chapter will examine some real-life case scenarios of the clinical investigation procedure.

8.1 The need for a clinical investigation

Case study – Device for gastro-oesophageal reflux

A U.S. company developed a device to treat severe *gastro-oesophageal reflux* – a condition that in its milder forms, is generally treated with drugs or, for persistent severe symptoms, by surgery to 'tighten' the lower oesophagus. Following bench testing and a few human implants, the company decided to initiate a randomized clinical trial against surgical treatment in centres in the U.S. and Europe. This route was chosen because there was no predicate device that could be used for proof of equivalence. The data generated from the trial was sufficient for CE mark approval and subsequently the company initiated a one and two year follow-up study of the device to test measure effectiveness and its ability to reduce the need for medication and increase patients' satisfaction with their condition.

Case study – Implant for drug-device combination product

Another U.S. company wished to gain European approval for an implant, which was a drug - device combination product. The implant had already received CE mark approval as had the drug, and the principal intended action of the drug – device combination was still mechanical and therefore would still be classified as a class III medical device. The company therefore assumed that a clinical evaluation based on a review of the literature would be sufficient to prove compliance with the ERs. However, it was the NB's opinion that the function of both the device and the drug could be significantly affected by their combination. In addition the mode of delivery of the drug would be altered from its approved route and therefore a literature survey would not be sufficient and a full clinical investigation was called for.

8.2 Notifications

Case study – Ensure all agreements are in place

A U.S. company had set up a multicentre trial in five EU countries to gain post-marketing experience of a CE marked implant device. Because the device was already approved there was no legal requirement to gain CA approval of the study and therefore no CA opinion was sought. At one centre however, signature of the clinical trial agreement had been delayed until after ethics committee approval had been granted. Once ethics committee approval had been granted, however, the site said it would not be able to go ahead with the study until a letter of 'No Objection' was received from the CA or approval was indicated by there being no contrary objection within 60 days. This meant that, at this late stage of the investigation process, the CA had to be contacted, and the initiation of the investigation delayed by 60 days. This therefore demonstrates the importance of gaining a thorough knowledge of the investigation site's requirements in the planning stage of the process and not assuming that all European sites will have similar requirements.

Case study – Maintaining an evidence trail

The 60 day CA approval period can also be misleading. For example, in Italy, a submission was made to the CA and, as there was a positive ethics committee decision and no objection was raised by CA the study went ahead. However, the CA then stopped the trial and said that they had not received the submission. The sponsor then showed that they had written proof that the submission had been delivered and the CA managed to find the documents. However, they ruled that the study would have to be stalled for another 60 days or until they reached their decision. This highlights the importance of gaining evidence of document delivery and of continuing to check on the decision process.

Case study – Procedure approval

Ethics committee notifications also frequently run into difficulties. An example of this was a company that had, in accordance with the details in the CIP, set out in its application to the German authorities the procedures that needed to be conducted on its mastectomy subjects, which included the standard imaging that is required by any mastectomy patient. Because it was a procedure related to standard care, a review of the radiological exposure was not conducted and approval by a radiology expert not sought and gained approval from. The ethics committee, however, stated that as the procedure was listed in the CIP it was part of the protocol and therefore required assessment and approval. The implications of this resulted in the CIP being rewritten and a new version submitted and distributed that removed the stipulations for these particular procedures and instead replaced them with wording that, 'Subjects will receive all care and procedures associated with normal standards of care.' Unfortunately, the ethics committee opinion on this version was that as the CIP later stated that measurements would be taken from the radiographic images obtained through standard imaging the imaging process had to be considered an investigation procedure. This resulted in another CIP version being produced, and opinions and approval being sought from radiology experts. This demonstrates the importance of realizing that, especially under the guidance of MEDDEV 2.7.1, Rev. 3 and 14155:2011, any procedure listed in a CIP or measurement taken from a procedure will require ethics committee approval.

Case study – National differences

A further factor that should be taken into consideration with ethics committees is their national structure. In the UK for example, a foreign company made the assumption that it would be able to apply for approval at the next meeting date of the ethics committee situated closest to the investigation site. However, in the UK there is a central booking service and there are speciality ethics committees so therefore the Central Allocation System (CAS) will direct the company to the nearest ethics committee and meeting date that specializes in medical devices.

In France, it helps if the sections of the protocol that concern data collection and data processing are clearly delineated as data protection issues are considered separately to the ethics committee by the National Consultative Committee on the processing of information in the health sector and then referred for approval to the Data Protection Supervisory Authority.

8.3 Monitoring

Case study – Standard operating procedures

A developer of a new wound care product wished to test its effect on postoperative wound care in terms of healing rate and resistance to infection compared to the standard wound dressing. Due to a lack of training and vigilance of the monitor at one site, however, the nurses, as part of their standard postoperative wound care protocol, changed the dressing after one day and applied a topical antimicrobial gel, which negated the results for all those subjects at the site. This demonstrates the importance of the monitor checking on what the SOPs are at an investigation site and ensuring that anyone involved in the study and the support workers are aware of the required procedures.

Case study – Sampling

In another study, at the interim visits, a monitor conducted spot checks on the records of a sample of patients, however, at closure it was discovered that the monitor had selected the same patients for review at each of the interim visits and one of the patients that had not been selected had been implanted with the wrong device. This occurred because although the CRF stated that the correct device had been used it did not tally with the source documentation and a thorough review of that subject's records had never been undertaken. This indicates the need for differential sampling at each visit and a detailed match of CRF to source data.

Case study – Adverse events

In another case a monitor noticed that there were adverse events noted in a patient's notes but not on the CRF. The reason for this was that such events were frequent occurrences with the operative procedure being undertaken and were not considered by the physicians to be related to the clinical investigation. The monitor rectified the anomaly and educated the investigation team that any adverse event occurring to a subject involved in a clinical investigation should be recorded on the CRF.

8.4 National issues and other considerations

The following examples have been provided by Factory-CRO for Medical Devices, which is a full service European Contract Research Organization that has been specializing in medical device trials for over twenty years and has a great deal of experience in how legislation can affect the implementation of studies involving medical devices. Overall the company views the development of 14155:2011 as a very positive move. As Dr Joris Bannenberg, Chief Operating Officer of Factory, stated, 'The new standard is much more detailed than the previous version, and anybody that follows it will conduct a good study. It is also aware of combination products and electronic data management and the definitions and language are much more harmonized with ICH-GCP, so it is much more up-to-date. Of course the major problem is that although it tells you what to do, it doesn't tell you how to do it. For example, the Standard will tell you that you should submit it to the ethics committee and notify the CA, but that is where the problems can start, because it is then that the major differences between countries begin to show. For example whether you should you use a paper submission, whether you should fill out a form to accompany the submission, whether the submission to the ethics committee and the CA can be done in parallel, are any payments required and when should they be made, are there any limitations to when submissions can be made, such as in Spain where they are accepted only during the first five days of the month, etc'. National differences in gaining approval for medical device investigations in Europe are a major problem area for many companies. For example one company that intended to conduct a run a clinical study in multiple EU countries came to Factory when they experienced problems with ethics committee submissions in different countries, especially with regard to deciding which site should be the central ethics committee and how local ethics committees should be approached.

The main problems that companies usually experience is that local language is either required or expected, as it facilitates communication between the EC and CA, and that they usually underestimate how knowledge of the local culture can aid navigation of the approval processes.

In addition, other problems that companies face are that detailed documents are frequently needed rather than those listed in 14155:2011. For example, member states may vary in the type of insurance they require and the amount of indemnity that is needed and the requirements for structure of IC documents might also vary. Other national differences include:

- Germany now requires a much more extensive IB, which should include a very thorough and detailed risk-benefit analysis. This is similar to the UK;
- radiation exposure levels are sometimes reviewed by ethics committees by their own expert, while in Germany approval is needed from the Federal Office for Radiation Protection (BfS) for any radiation exposure that is therapeutic or above standard of care, and, in the UK an accredited medical physics expert is needed at the site to assess exposure levels;
- payment for devices can differ and, in Italy for example, ethics committees often require that in post-marketing randomized studies the sponsor also pays also for the costs of the control-device.

Differences can also occur within regions of the same country and even between institutions. For example, Factory has found that universities are more costly, because of their claimed overheads and regional hospitals require a longer time to approve contracts, but it is advisable that all investigators are paid the same amount as increased ease of communication is making negotiations much more transparent, and no investigator would wish to be paid less than another.

Overall the clinical investigation environment is changing rapidly and it is Factory's experience that the whole method of how to conduct a submission might change within the space of six months. In addition, with the development of new laws and regulations, it is often the case that, because companies and people are hesitant about how to interpret them and what the practical consequences of them are, they will frequently prefer to do nothing at all. It therefore takes a while (at least six months) before a common practice is evolved.

9 Conclusions

Figure 9 illustrates the pathway that should occur from device conception to gaining market approval in regulatory terms; however, it does not take into account the many other actions that should occur such as researching and establishing a price for the new device. In addition it has not taken into account that in submission for market approval the NB will wish to see clear evidence for a plan of post-market surveillance, which may well lead to a requirement for further clinical studies to be conducted (post-market clinical follow-up - PMCF).

In many ways the publication of 14155:2011 and the other recent documents, such as MEDDEV 2.7.1 Rev. 3, will not require major changes in the SOPs of those companies that are well acquainted with conducting European clinical investigations and seeking CE mark approval, as the fundamentals have remained the same. What has been eradicated, however, are many of the former areas of uncertainty with greater detail being added and stipulations that create 'black and white' directions where previously there were many shades of grey. This has the advantage that it should increase the uniformity of approach by both companies and regulatory bodies across Europe and this should improve the quality of data that form the basis of regulatory judgements and also provide better safeguards for clinical subjects. Therefore, device safety is therefore enhanced both within the environment of a clinical investigation and within the market should the device receive CE marking approval.

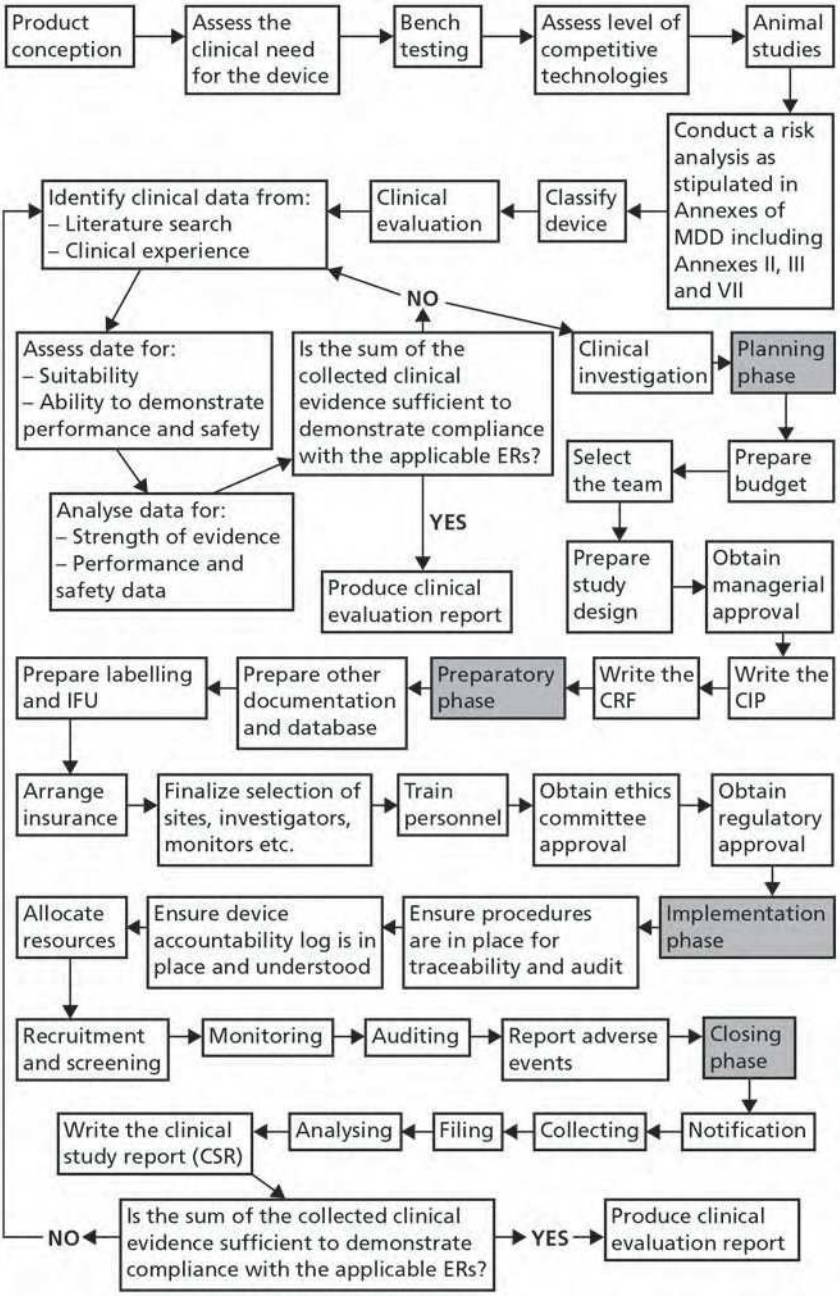

Figure 9 – The clinical investigation route

Glossary

Authorized Representative – When a manufacturer is based outside the EC, the CAs need to be able to contact a legally appointed entity or person who is based within the EC, and who will act on behalf of the manufacturer. This is the Authorized Representative.

Case Report Form – The form on which each subject's results for each study visit are recorded.

Clinical Investigation Plan – One of the main documents of a clinical investigation which sets out the objective(s), design, methodology, statistical considerations and organization of a clinical investigation.

Competent Authority – The government bodies in Europe who are responsible for the appointment of NBs and the administration of the medical device directives. The CA must be approached when planning a clinical study to obtain a CE mark.

Conformité Européenne – Mandatory European marking for industrial products including medical devices to indicate conformity with the health and safety requirements set out in European Directive.

Essential Requirements – The essential elements that have to be demonstrated by a medical device to prove conformity with the medical device directives.

European Economic Area – This was established in 1994 to allow Iceland, Liechtenstein and Norway to participate in the EU's internal market without a conventional EU membership. In exchange, they are obliged to adopt all EU legislation related to the single market, except laws on agriculture and fisheries. Switzerland has not joined the EEA.

European Free Trade Area – This was established in 1960 to create free trade among members and to seek a broader economic union with other countries of Western Europe. Current members are Iceland, Liechtenstein, Norway and Switzerland.

European Union – An economic and political union or confederation of 27 member states.

Good Clinical Practice – A set of guidelines that helps make sure that the results of a clinical investigation are reliable and that the patients are protected.

Investigator – A doctor or a person following a profession agreed in the member state for investigations because of the scientific background and the experience in patient care required. The investigator is responsible for the conduct of a clinical investigation at a trial site. If the study is conducted by a team of individuals the leader responsible for the team and may be called the principal investigator.

Investigator's Brochure – The document that provides instructions to the investigator on how the study should be conducted.

Informed consent – The process of gaining consent from an individual for their participation in a clinical investigation.

Member state – A country that is part of the EU.

Notified Body – A public or private organization that has been accredited to validate the compliance of a medical device to the European Directives.

Phthalates – A group of industrial chemicals used to make plastics more flexible or resilient. They are in widespread use and are present in many items including food packaging, vinyl flooring, adhesives, detergents and shampoo. However, phthalates have been found to disrupt the endocrine system.

Guide to European Medical Device Trials
and BS EN ISO 14155

The book explains, in clear terms, how to comply with BS EN ISO 14155:2011, which was formed by the revision and merging of BS EN ISO 14155:2009, Parts 1 and 2. It highlights the differences between the old standards and the new one and how BS EN ISO 14155 relates to other standards, directives and guidance documents for medical devices.

The book describes in detail the regulations, directives and standards governing medical devices and clinical trials, including Directives 93/42/EEC and 2007/47/EC, and MEDDEV 2.7.1 Rev. 3, as well as documenting the major changes introduced by BS EN ISO 14155:2011. Following this, it describes the process of initiating, conducting and reporting on a clinical investigation, with supporting industry examples of where problems can arise. It provides an invaluable reference as to how clinical trials of medical devices should be conducted.

It is a priceless guide for new researchers and a worthy reference source for experienced researchers, whilst providing an insight into the area of clinical trials for anyone involved in the production or marketing of medical devices.

About the Author

Duncan Fatz is an independent healthcare consultant and writer specializing in medical devices. As a clinical trials co-ordinator for the UK's North West Thames Health Authority, a researcher for the Medical Research Council and independent consultant and lecturer, Duncan has been guiding medical device companies and their products through the clinical trial process and on to subsequent reimbursement approval in the major European markets for almost 20 years. He has written two reports on conducting medical device clinical trials for PJB Publications, and two courses for Informa Healthcare.

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