European Clinical Trial Medical Device Regulation and the Protection of Human Participants

By

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Declaration

"I hereby declare that this project is entirely my own work and that it has not been submitted for any other academic award, or part thereof, at this or any other education establishment".

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Abstract

The focus of this research is in the area of European clinical trial regulation for medical devices to determine if the health and welfare of human participants is protected. There were four questions to be addressed: 1) Evaluation of clinical trial history to determine the evolution and lessons learned from the past 2) Evaluation of European medical device regulation to determine if it adequately protects the welfare of human participants in clinical trials 3) Evaluation and review of a real-life case study to identify if weaknesses exist in the medical device clinical trial regulation and process which would put human participants at risk 4) Identify what other factors affect the protection of human participants in medical device clinical trials. These research questions were addressed by applying various research methodologies which included an in-depth literature review of European regulation, in-depth personal interviews and a case study analysis.

The research produced a number of key findings. Clinical research has evolved and advanced significantly and has brought benefits to patients and society as a whole. European medical device regulation has evolved to protect the health and well-being of human participants in clinical trials. However, regulation does not cover every conceivable scenario, and challenges still exist with ensuring that the regulations are followed.

The research recommended several changes that could address the current weaknesses which put human participants lives at risk during clinical trials, such as; the merging of regulations for medical devices and drugs for clinical trials into one regulation; having the presence of representatives from the ethics committee, competent authority and clinical experts when informed consent is being processed to ensure that no bias or undue force is exercised to any participant; regulation updates every three years to keep in line with scientific and technological advances; mandatory quarterly audits by the competent authority and ethics committee for clinical trials initiated by physicians or hospitals; legally binding contracts for the publication of clinical trial results to prevent inaccurate or inconsistent information reaching the public domain and any conflicts of interest could be declared to the authorities with the clinical trial submission.

Key Words: ‘Clinical Trial’, ‘Medical Devices’, ‘Regulation’, ‘Europe’, ‘Ethics’, ‘Informed Consent, ‘Medical Journals’

Chapter 1: Introduction

Clinical trials, which aim to improve medical knowledge, patient care and provide hope for future generations, would not be possible without the involvement of human participants. As stated by the World Health Organisation:

> ‘a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc’ WHO (2018).

Further definitions of a clinical trial/investigation include the following examples:

> As stated in the Medical Device Regulation (EU) 2017/745 (MDR): ‘clinical investigation’ means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device’ European Commission (2018a).

> As stated in The Clinicaltrials.gov database:‘assigned to groups that receive one or more intervention/treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study's protocol. Participants may receive diagnostic, therapeutic, or other types of interventions’ (Clinicaltrials.gov).

Medical devices are regulated in Europe via the Medical Device Directives (MDDs) and the MDR in order to protect patients and users. Included in the MDR in Article 64, with regard to clinical investigations, is precise reference to the adherence to ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good clinical practice) European Commission (2018a).

Adherence to regulations ensures that products used on/in humans and placed on the market meet the safety, regulatory, and quality standards required.

1.1 What is a Medical Device?

A medical device is defined in the MDR as:

> ‘ any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, — diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability, — investigation, replacement or modification of the anatomy or of a physiological or pathological process or state, — providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means’ European Commission (2018a).

The following products shall also be deemed to be medical devices:- ‘devices for the control or support of conception; — products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point’ European Commission (2018a).

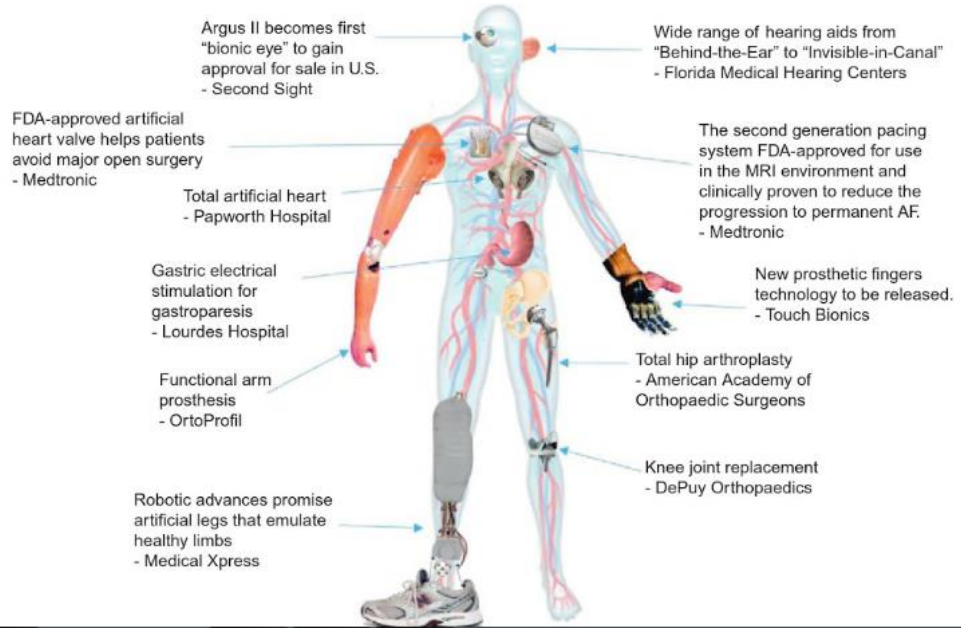

Figure 1: Examples of Medical Devices for the Human Body (Ramakrishna *et al.* 2015 p.5)

1.2 The Medical Device Industry in Europe

The medical device industry in Europe helps to ensure the health and well-being of European citizens and covers a wide range of products and is a significant employer in Europe European Commission (2018b). The key factor is to ensure that, through the regulatory system, only products which meet and satisfy the regulation requirements are placed on the market. Whilst innovation is key to the future in enhancing healthcare, it must be balanced by the primary goal of protecting the people involved in clinical investigations to test new technologies and products prior to being placed on the market.

The medical device industry, due to it's diversity and innovativeness, makes a significant contribution to the safety, quality and efficacy of European healthcare. The industry covers a wide range of products from simple bandages to sophisticated equipment, such as X-ray equipment. The sector plays a significant role in diagnosing, preventing, monitoring and treating diseases which also provides improvement to the quality of life for people with disabilities (European Commission 2018b).

The medical devices sector helps save lives by providing innovative health care solutions regarding diagnosis, prevention, monitoring, treatment, and alleviation of disease.

> 'The sector has become increasingly important for the healthcare of EU citizens and an influencer of expenditure. The medical devices industry is a major employer in Europe, employing 575,000 people in the EU. Total sales amount to EUR 100 billion. The sector represents some 25,000 companies, of which 95% are Small and Medium-sized Enterprises (SMEs)' European Commission (2018b).

Pharmaceuticals and medical devices have their own regulatory systems, as they are very different industries. Research and development models also vary.

> 'Driven by technology, device improvements are typically available to users and patients within 18-24 months of previous iterations. Medicinal products on the other hand, are pharmaceutically based and tend to have longer product lifecycles with improvements measured in decades' Medtech Europe (2018).

When it comes to requiring the same type of clinical data for devices as for drugs, it is worth highlighting that,

> 'unlike in pharmaceuticals, randomised clinical trials are not the 'gold standard' on how to assess effectiveness and safety in medical devices because: Most devices cannot be evaluated with randomised clinical trials as it is hard to blind and randomise devices due to strong ethical and practical issues in the choice of the 'comparator' (e.g. what would have been a comparator for an implantable cardiac defibrillator?). Device impact depends heavily on clinician training and experience, patient selection and the care delivery setting' Medtech Europe (2018).

In contrast to the MDD, in order to be compliant with the MDR, which comes into effect in May 2020, manufacturers will be required to provide much more clinical evidence in order to attain a CE mark. This will be a time consuming exercise, as, together with the increased scrutiny imposed by notified bodies, it is expected that the time to market will lengthen considerably from the current average of 18-24 months, as outlined above, European Commission (2018a).

1.3 Medical Device Regulation in Europe

The task of harmonising requirements and regulating medical devices is handled by the European Commission in close cooperation with Member State Competent Authorities. Legislation covers implantable, non-implantable, and in vitro diagnostics medical devices. The MDDs have been replaced by the MDR, which were approved on 5th April 2017. The distinction between a Directive and a Regulation is important. Directives have been ratified by the EU Parliament and transposed into national law by each member state, whereas Regulations have very clear and defined rules that are binding across all member states. Manufacturers of currently approved medical devices will have a transition time of 3 years, until May 26, 2020, to meet the requirements of the MDR and 5 years, until May 26, 2022, for manufacturers of IVDRs (In-Vitro Device Regulations) European Commission (2018c).

As stated by the European Commission:

> 'The new Regulations contain a series of extremely important improvements to modernise the current system. Among them are: Stricter control for high-risk devices via a new pre-market scrutiny mechanism with the involvement of a pool of experts at EU level. The reinforcement of the criteria for designation and processes for oversight of Notified Bodies. The inclusion of certain aesthetic devices which present the same characteristics and risk profile as analogous medical devices under the scope of these regulations. The introduction of a new risk classification system for in vitro diagnostic medical devices in line with international guidance. Improved transparency through the establishment of a comprehensive EU database on medical devices and of a device traceability system based on Unique Device Identification. The introduction of an "implant card" containing information about implanted medical devices for a patient' European Commission (2018c).

The reinforcement of the rules on clinical evidence, including an EU-wide coordinated procedure for authorisation of multi-centre clinical investigations are described below:

> 'The strengthening of post-market surveillance requirements for manufacturers. Improved coordination mechanisms between EU countries in the fields of vigilance and market surveillance. The MDR aims to provide greater focus on transparency and traceability. In particular, the emphasis on clinical evidence and the standardisation of European procedures to ensure a more co-ordinated approach to approving clinical trials. The focus on post market surveillance will ensure the product remains scrutinized throughout the device lifecycle' (European Commission 2018c).

1.4 Reasons for the Change from Medical Device Directives to Medical Device Regulation

1.4.1 Change from Directives to Regulation

Among the significant changes that have been introduced in the MDR are more precise requirements relating to clinical data and investigations. Clinical justifications based on device equivalence has been a standard practice in the past, but with the MDR, equivalence is going to be less accepted, particularly for higher risk devices. As such, the manufacturer will have to demonstrate equivalence by having access to equivalent device data, and the MDR requires a contract between the manufacturer and the equivalent device manufacturer to access the technical documentation of that device. This will mean that equivalence can only be claimed for devices for which a manufacturer has access to technical documentation European Commission (2018a).

As stated in the MDR:

> 'The notified body shall, in circumstances in which the clinical evidence is based partly or totally on data from devices which are claimed to be equivalent to the device under assessment, assess the suitability of using such data, taking into account factors such as new indications and innovation. The notified body shall clearly document its conclusions on the claimed equivalence, and on the relevance and adequacy of the data for demonstrating conformity. For any characteristic of the device claimed as innovative by the manufacturer or for new indications, the notified body shall assess to what extent specific claims are supported by specific pre-clinical and clinical data and risk analysis. The notified body shall verify that the clinical evidence and the clinical evaluation are adequate and shall verify the conclusions drawn by the manufacturer on the conformity with the relevant general safety and performance requirements. That verification shall include consideration of the adequacy of the benefit-risk determination, the risk management, the instructions for use, the user training and the manufacturer's post-market surveillance plan, and include a review of the need for, and the adequacy of, the PMCF plan proposed, where applicable' European Commission (2018a).

In the past, it was common to have risk management files and clinical evaluations as separate, stand-alone documents. The MDR requires risk management and clinical evaluation are interdependent processes, in order to confirm compliance with the essential requirements and ensure the safety and performance of the device on the market. Clinical risks will be addressed in clinical investigations, clinical evaluations, and post-market clinical follow-up European Commission (2018a).

As stated in the MDR::

> ‘The risk management system should be carefully aligned with and reflected in the clinical evaluation for the device, including the clinical risks to be addressed as part of clinical investigations, clinical evaluation and post-market clinical follow up. The risk management and clinical evaluation processes should be inter-dependent and should be regularly updated’ European Commission (2018a).

Eudamed, the European database on medical devices, will become a public tool. Up until the MDR, the Eudamed database was an information tool, accessible to national competent authorities and the European Commission, and used by European authorities for post-market surveillance. Clinical evidence is not a new requirement, but the MDR has introduced extensive new clinical investigation requirements. Under the MDD, lower risk devices were required to have clinical evaluation reports (CERs) and higher risk devices needed clinical data. CERs still are required but the content and acceptability has changed. The first line of Annex XIV of the MDR states: ‘To plan, continuously conduct and document a clinical evaluation’ European Commission (2018a).

Manufacturers will have to adopt a life-cycle approach and continuously update the CER. As stated in the MDR, new requirements for CERs include:

> ‘an indication how benefit-risk issues relating to specific components such as use of pharmaceutical, non- viable animal or human tissues, are to be addressed; and — a clinical development plan indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF as referred to in Part B of this Annex with an indication of milestones and a description of potential acceptance criteria.’ European Commission (2018a).

In addition to CERs, as stated in Article 32 of the MDR, a public summary of safety and clinical performance is now required for certain types and classes of devices. Class III and implantable devices are expected to have clinical data derived from clinical investigations that were conducted under the supervision of a sponsor European Commission (2018a).

The changes to existing laws in Europe are mostly due to a widespread demand for increased patient protection. European Commission (2018b) ‘In the past, high-risk devices, such as implants, have, on average, undergone significantly shorter approval processes, when compared to the United States’ Van Norman (2016).

Figure 2 provides a comparison of device approval processes between Europe (MDD) and the United States. The differences in the time to approval are based on clinical data and evidence requirements.

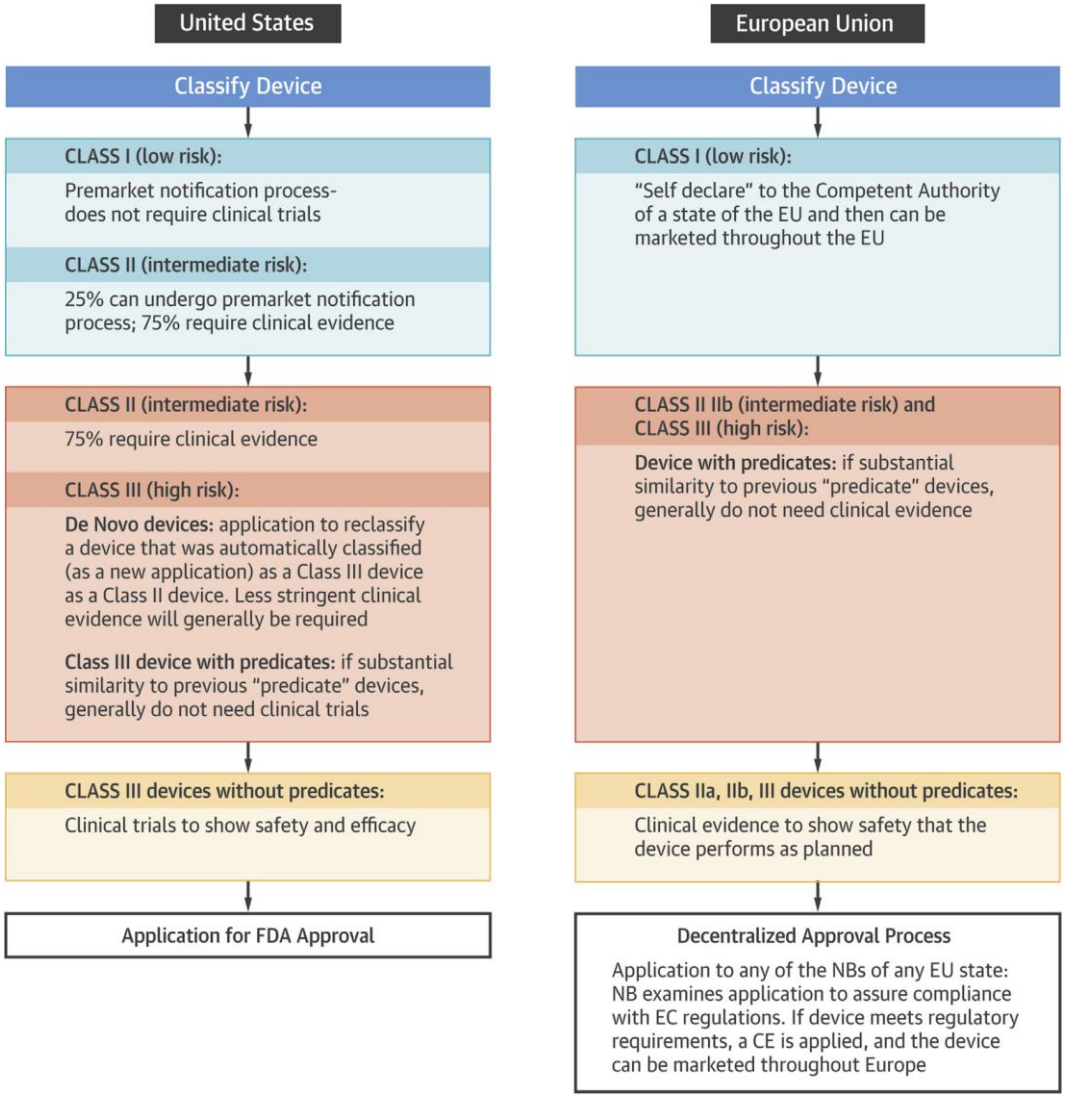

Figure 2: Comparison of Device Approval Processes in the United States and EU (Van Norman 2016)

In Europe, devices attain the CE mark if they meet the essential requirements and perform as intended. Clinical trials are required based on the level of risk. In contrast, in the U.S., high risk devices must demonstrate reasonable safety and effectiveness in clinical trials before they are used by patients. This has led to many high-risk devices being approved faster in the EU than in the US, resulting in questions over their safety Van Norman (2016).

Examples of weaknesses in the regulatory system were identified in cases such as Poly Implant Prothèse (PIP) breast implants and metal-on-metal hip replacements. A review of the device approval and post-market surveillance system were prompted by the events surrounding the silicone breast implant company. The company was issued with a CE mark in 1991 but was found to have switched from a medical grade silicone to industrial grade silicone and over 30,000 women who had received these implants were at risk of systemic toxicity and cancer Van Norman (2016).

The industrial silicone was not approved for use:

> 'The silicone-based scandal came about when PIP implants made from a cheaper, industrial-grade silicone (that was not approved for medical use) were rupturing at a rate that was double the industry average' IMARC Research (2017).

Further failures occurred in relation to the metal hip implants in 2010. DePuy, which is a subsidiary of Johnson and Johnson had to recall it's ASR (articular surface replacement) hip prostheses from the market as the device had several defects. As the device began to wear, metal debris caused degradation of the soft tissues around the joint. The metal was released into the blood and cerebral spinal fluid in some patients Cohen (2011).

The ASR™ hip adverse events came to light during the collection of post-market surveillance as clinical trials were not conducted Wienroth, McCormack and Joyce (2014).

Furthermore, as described by Cohen (2011), in his review:

> 'The ASR is a "metal on metal" hip—the head at the top and the lining of the cup it fits into are made of cobalt chrome metal rather than ceramic or polyethylene. The devices come in different sizes according to the existing anatomy and there are forms for both total hip replacement (ASR XL) and hip resurfacing (ASR resurfacing). The conventional total hip replacement consists of a metal head with a polyethylene cup. But these joints don't last forever. Over time the plastic cup wears away against the hard metal head. Younger, more active people are especially likely to require early revision surgery to replace the worn out joint. Competition between manufacturers spurred DePuy to develop the ASR. Both forms of the DePuy ASR came on to the market in Europe in 2003. At the time, resurfacing prostheses were classed as a class

IIb device, which meant they didn't need to be tested in patients before entering the EU market'.

Figure 3 below provides a graphical overview of the difference between total hip replacement and resurfacing.

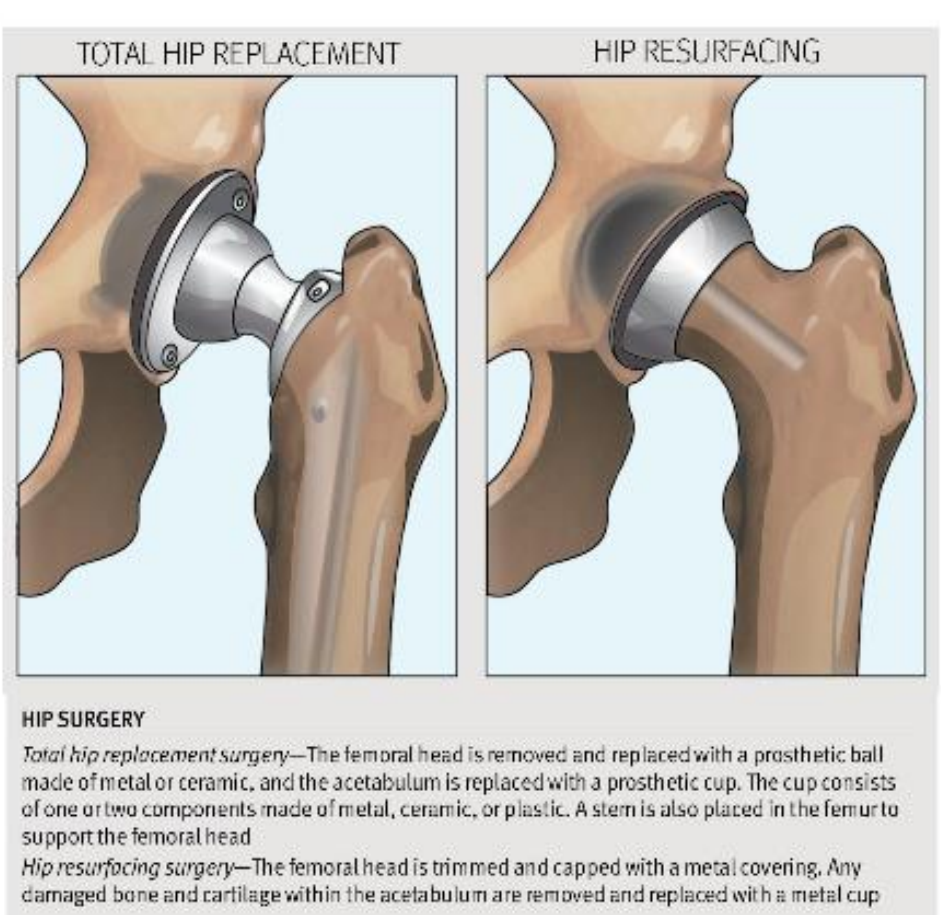

Figure 3: Hip Surgery (BMJ 2011)

As a result, primarily, of the above types of regulatory failures, regulatory standards in the EU received heavy criticisms. The Du Puy metal hip implant case is an example of how, if regulations existed requiring clinical investigations to be performed on class IIb devices, the device would not have been placed on the market. The MDR was designed to address these regulatory weaknesses.

1.5 Clinical Trial Designs

There are two main types of clinical trials: observational studies and experimental/interventional trials. Figure 4 provides a graphical overview of the different types of designs.

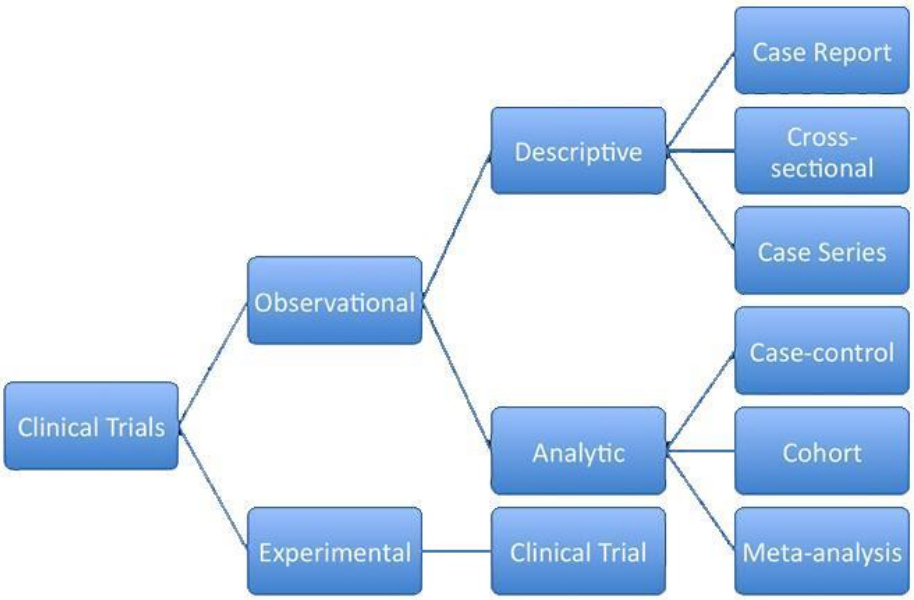

Figure 4: Clinical Trial Design: (Google Images – OrthoBullets, 2018)

1.5.1 Observational Studies:

In observational studies, participants are not asked to do anything different or test out any treatments. They simply involve researchers measuring certain things in groups of people, usually to help understand more about possible ways of preventing an illness. As stated below:

> 'The kinds of things researchers would be interested in measuring would vary a lot from study to study but usually include several aspects of people's general health and wellbeing as well as information on their daily activities such as diet and exercise. The researches might just need to measure these once or they might follow people up over time to see how the things they are measuring change over time or differ between different groups of people (for example a group of older people versus younger people or a group of people with asthma versus a group without asthma' London Imperial College (2015).

There are different types of observational studies, as presented in Figure 5.

Observational study design measures of disease, measures of risk, and temporality.

Study design	Measures of disease	Measures of risk	Temporality
Ecological	Prevalence (rough estimate)	Prevalence ratio	Retrospective
Proportional mortality	Proportional mortality Standardized mortality	Proportional mortality ratio Standardized mortality ratio	Retrospective
Case-crossover	None	Odds ratio	Retrospective
Cross-sectional	Point prevalence Period prevalence	Odds ratio Prevalence odds ratio Prevalence ratio Prevalence difference	Retrospective
Case-control	None	Odds ratio	Retrospective
Retrospective and prospective cohort	Point prevalence Period prevalence Incidence	Odds ratio Prevalence odds ratio Prevalence ratio Prevalence difference Attributable risk Incidence rate ratio Relative risk Risk ratio Hazard ratio	Retrospective only Both retrospective and prospective Prospective only

Figure 5: Observational study design measures of disease, measures of risk, and temporality (Thiese 2014)

1.5.2 Interventional Trials

Interventional study designs, as the name suggests, means that the researcher will intervene at different points of the study. Also called experimental study designs, the most common and strongest interventional study design is a randomised controlled trial. Other type of interventional studies include pre-post study design, non-randomised controlled trials and quasi-experiments Thiese (2014).

There is usually more than one way to try to prevent or treat a particular illness. However, doctors may not know what the best way is.

> 'The way we find out is by asking people to take part in a clinical trial to compare the benefits and potential risks of each approach and see which way works best (this is called an Interventional Trial). An interventional trial could be in any of the following areas:drug treatments, surgery – different surgical techniques or approaches, medical devices, nutrition, exercise or other lifestyle aspect' London Imperial College (2015).

1.6 Key Roles and Responsibilities in Clinical Trials

It is vitally important that the correct stakeholders are involved in clinical trials. Depending on the trial, other roles and responsibilities may be required. The following organisations and people are key to clinical trials conducted in Europe:

'The participant, or subject: This is the person taking part in the trial.

The sponsor: This is the organisation or person that is paying for the trial; they might be a pharmaceutical or medical device company, an academic, a doctor, or a hospital.

The principal investigator: This is the person who is leading the research team, usually a doctor or specialist in the disease.

The study coordinator: This is the person supporting the principal investigator, who is in charge of running the trial on a day-to-day basis and coordinating the different people or organisations involved in the study.

The Ethics Review Board/Investigational Review Board: This is an independent group that is responsible for protecting the rights, safety and well-being of people taking part in the trial. They approve information about how the trial will be conducted before it can go ahead' Raremark (2018).

1.7 Process for Conducting Clinical Trials for Medical Devices in Europe

When research is conducted on new drugs, a clinical trial is required in every case. Small changes to the composition of a drug may result in unexpected effects and will require clinical data before the changes can be conducted European Medicines Agency (2018a). In contrast, with medical devices, clinical trials are not always required, and whether or not one will be conducted depends on a risk assessment. For example, although an adhesive bandage is a medical device, it is a low risk to human subjects and therefore would not require a clinical trial. On the other hand, a drug-eluting stent, or a new material for a hip replacement are considered high risk and may require a clinical trial European Commission (2018f).

Figure 6 presents an overview of the clinical trial process for medical devices.

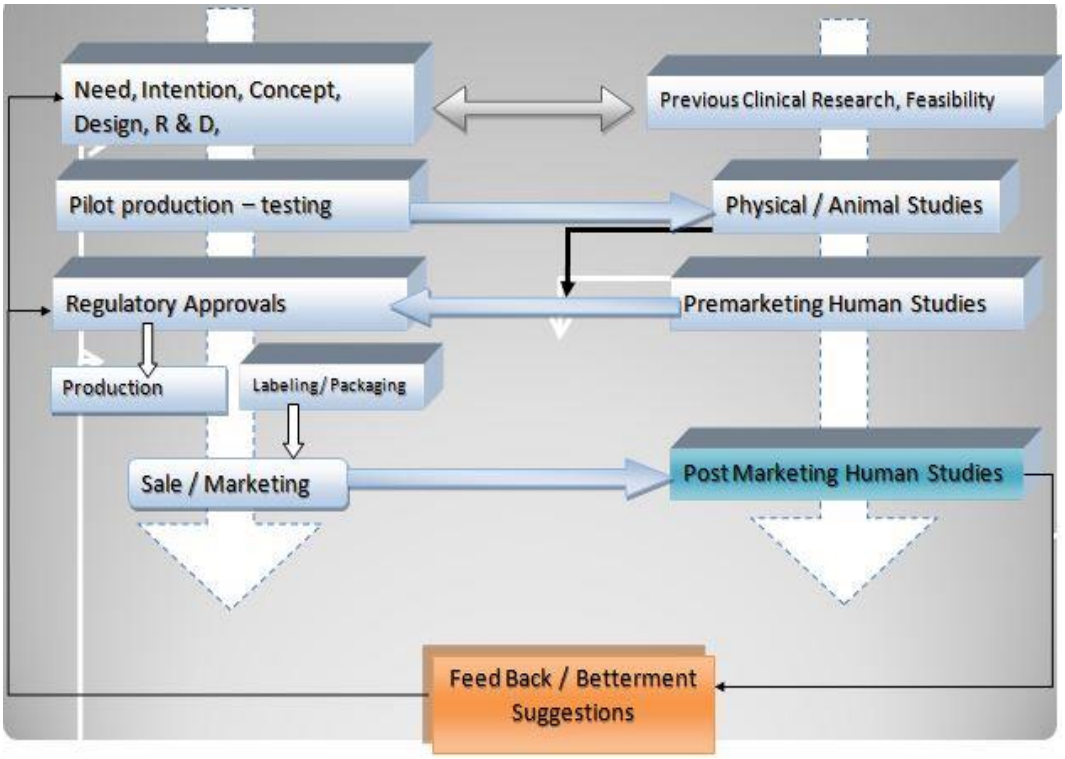

Figure 6: Clinical Research in Medical Devices – (Genelife Clinical Research,2014)

According to the MDR, for class III devices and implantable devices, to ensure a high level of safety and performance and compliance with the regulation requirements, it is necessary to conduct clinical investigations with responsibility for such investigations to be attributed to the legal manufacturer or sponsor European Commission (2018a).

As outlined in the MDD, in the case of devices falling within Class III and implantable and long-term invasive devices falling within Class IIa or IIb, a clinical trial can commence 60 days after notification to the competent authorities, unless a decision to the contrary has been notified based on public health or policy European Commission (2018d).

As outlined in the MDR, the member states will notify the sponsor within 45 days of it's decision, provided that there have been no negative opinions received from the ethics committee. The member state can extend the 45 days by a further 20 days if consultation required European Commission (2018a).

1.8 Classification of the Product

The first step in regulatory compliance in Europe is determining the classification that applies to the applicable product. Under the MDD and the MDR, classification is determined using a rule based approach. Those rules can be identified in Annex IX of the MDD and Annex VIII of the MDR, whereby: 'Devices shall be divided into classes I, IIa, IIb and III, taking into account the intended purpose of the devices and their inherent risks. Classification shall be carried out in accordance with Annex VIII' European Commission (2018a) and (2018d). According to the guidelines on medical device classification – as stated in MEDDEV 2. 4/1 Rev. 9 - June 2010 – Classification of Medical Devices:

> 'The classification of medical devices is a 'risk based' system based on the vulnerability of the human body taking account of the potential risks associated with the devices. This approach allows the use of a set of criteria that can be combined in various ways in order to determine classification, e.g. duration of contact with the body, degree of invasiveness and local vs. systemic effect' European Commission (2018e).

1.9 Determining what Type of Clinical Data will be required

In order to be able to CE mark any device, a manufacturer must demonstrate that the stated device complies with the relevant essential requirements of the MDD/MDR. Any new device in development should follow the requirements of the MDR in order to be compliant for approval when the MDR is implemented. To demonstrate such compliance, and depending on the classification of the product, it will be necessary to provide clinical data, which can consist of:

> 'a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where there is demonstration of equivalence of the device to the device to which the data relates and the data adequately demonstrates compliance with the relevant essential requirements or a critical evaluation of the results of all the clinical investigations made or a critical evaluation of the combined data provided' MHRA (2017).

Unless safety and conformance can be demonstrated by other means, a specifically designed clinical investigation will likely be required. Clinical investigations can be performed on the basis of an appropriate plan of investigation reflecting the latest scientific and technical knowledge and defined in such a way as to confirm or refute the manufacturer's claims regarding the safety, performance and aspects relating to the benefit-risk of devices.

As referred to in the MDR:

> 'the clinical investigations shall include an adequate number of observations to guarantee the scientific validity of the conclusions. The rationale for the design and chosen statistical methodology shall be presented as further described in Section 3.6 of Chapter II of this Annex' European Commission (2018a).

The manufacturer should specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements, as specified in the MDR:

> 'That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose. The clinical evaluation, its results and the clinical evidence derived from it shall be documented in a clinical evaluation report as referred to in Section 4 of Annex XIV, which, except for custom-made devices, shall be part of the technical documentation referred to in Annex II relating to the device concerned' European Commission (2018a).

Clinical investigations are required for Class IIb and III devices, unless there is sufficient clinical data justification available.

1.10 Notification to the National Competent Authority

In order to gain approval of a clinical trial, the manufacturer must notify the national competent authorities of the member states in which the clinical trial will take place, as stated in the MDD:

> 'In the case of devices intended for clinical investigations, the manufacturer or the authorised representative, established in the Community, shall follow the procedure referred to in Annex VIII and notify the competent authorities of the Member States in which the investigations are to be conducted by means of the statement mentioned in Section 2.2 of Annex VIII. 2. In the case of devices falling within Class III and implantable and long-term invasive devices falling within Class IIa or IIb, the manufacturer may commence the relevant clinical investigation at the end of a period of 60 days after notification, unless the competent authorities have notified him within that period of a decision to the contrary based on considerations of public health or public policy. Member States may however authorise manufacturers to commence the relevant clinical investigations before the expiry of the period of 60 days, insofar as the relevant ethics committee has issued a favourable opinion on the programme of investigation in question, including its review of the clinical investigation plan' European Commission (2018d).

In addition, as stated in the MDR:

> 'the clinical investigation is the subject of an authorisation by the Member State(s) in which the clinical investigation is to be conducted, in accordance with this Regulation, unless otherwise stated' European Commission (2018a).

The Competent Authority will then review the submission and make a decision on whether the trial can proceed.

The application to the Competent Authority must contain the following elements, which will be detailed below in full:

Table 1 Competent Authority (Meddev 2.7/2, Revision 2)

a) Application Form - Containing basic data on clinical investigations, to be included in the EUDAMED CI module by the MS, will have to be provided and should be preferably in an xml-format, to facilitate the upload by MS
b) sponsor's and manufacturer's name (if the manufacturer is not the sponsor) and contact points for communication (similarly for authorised representative in the EEA if applicable)
c) whether first submission or resubmission
d) if resubmission with regard to same device, previous date(s) and reference number(s) of earlier submission(s)
e) Member States and other countries participating in this clinical investigation as part of a multicentre/multinational study at the time of filing and the opinion available of the Member State or other countries
f) a EUDAMED Clinical Investigation identification number (CIV ID), when available
g) the application form signed by the sponsor confirming that:

- the information provided is complete;
- that submitted documents contain an accurate account of the information available;
- that the clinical investigation will be conducted in accordance with the clinical investigation plan;
- that serious adverse events, device deficiencies and related updates will be reported, in accordance with the applicable legislation (see MEDDEV 2.7.3);
- that appropriate safety measures have been taken for study participants/users and other persons;
- that the applicable fee for submission is accepted

h) copy of the Ethics committee opinion as soon as available according to national requirements
i) title of the clinical investigation
j) other relevant documentation according to national requirements

k) description of the current legal status of the investigational medical device and its intended use within the clinical investigation:

- CE marked and within intended use (esp. Directive 90/385/EEC or if national provision); manufacturer should give indication on amount and time of market exposure since first placing on the market;
- CE marked and not within intended use;
- not CE marked;
- if national provisions allow: simplified dossier, if the investigational medical device has previously been part of a clinical investigation in the Member State and investigational medical device and its use have not been modified since then at all'.
- Additionally, the following information is required to be submitted to the Competent Authority:
- 'data allowing identification of the device in question;
- the clinical investigation plan;
- the investigator's brochure;
- the confirmation of insurance of subjects;
- the documents used to obtain informed consent (usually CAs request translation into national language(s));
- a statement indicating whether or not the device incorporates, as an integral part, a substance or human blood derivative referred to in Section 10 of Annex 1 of Directive 90/385/EEC respectively section 7.4 of Annex I of Directive 93/42/EEC;
- a statement indicating whether or not the device is manufactured utilising tissues of animal origin as referred to in Commission Regulation 722/2012/EC;
- the opinion of the ethics committee concerned and details of the aspects covered by its opinion;
- the name of the medical practitioner or other authorized person and of the institution responsible for the investigations;
- the place, starting date and scheduled duration for the investigation;
- a statement that the device in question conforms to the essential requirements apart from the aspects covered by the investigation and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient European Commission (2018e).

Based on the outcome of the review of the documentation provided to the Competent Authority, the clinical investigation may be approved or rejected.

After the commencement of a clinical investigation, the Competent Authority may suspend a trial based on unacceptable risks to subjects. The Competent Authority will inform the Ethics Committee of its decision then European Commission (2018a).

1.11 Conducting the Clinical Trial

The clinical investigation should be performed, as per the guidelines outlined in the harmonised standard, EN ISO 14155: 2011 - Clinical investigation of medical devices for human subjects - Good clinical practice. EN ISO 14155:2011 is listed as a harmonised standard on the European Commission website European Commission (2018g). A harmonised standard is a European standard elaborated on the basis of a request from the European Commission to a recognized European Standards Organisation (CEN, CENELEC or ETSI) to develop a European standard that provides solutions for compliance with a legal provision Cenelec (2017). Such a request provides guidelines that requested standards must respect to meet the essential requirements or other provisions of relevant European Union harmonization legislation. As such:

> ‘Compliance with harmonised standards provides a presumption of conformity with the corresponding requirements of harmonisation legislation. Manufacturers, other economic operators or conformity assessment bodies can use harmonised standards to demonstrate that products, services or processes comply with relevant EU legislation’ Cenelec (2017).

ISO 14155:2011 provides precise requirements for the design, conduct and reporting of clinical investigations which involved human participants. Published originally in 1996, there have been extensive revisions over the past 20 years in order to effectively address the specific investigation requirements for medical devices, and to better align its requirements with those of the Good Clinical Practice (GCP) guidelines developed by the International Conference on Harmonization (ICH). The current version of the standard, ISO 14155:2011, which replaced ISO 14155:2003 Parts 1 and 2, is now closely harmonised with GCP guidelines. These guidelines have served as the basis for regulatory requirements applicable to clinical investigations of pharmaceutical products and medical devices UL Life and Health Sciences (2017).

ISO 14155:2011 consists of nine separate clauses and six annexes that provide specific requirements applicable to clinical investigations for medical devices. The details of the key clauses are described in Appendix 3.

1.12 Clinical Trial Guidance Documents for Medical Devices

The European Commission provides a range of guidance documents to assist stakeholders in implementing directives and regulation related to medical devices. The MEDDEVs promote a common approach to be followed by manufacturers and Notified Bodies that are involved in conformity assessment procedures. The MEDDEVs are drafted by authorities charged with safeguarding public health in conjunction with all stakeholders; industry associations, health professionals associations, Notified Bodies and European Standardisation Organisations. This is in accordance with the relevant annexes of the directives. According to the European Commission:

> 'MEDDEVs are carefully drafted through a consultation process with all interested parties and are subject to a regular updating process. These documents have particular reference codes and are endorsed at the Medical Devices Expert Group (MDEG) plenary meetings. The guidelines are not legally binding. However, due to the participation of the aforementioned interested parties and the experts from competent authorities, it is expected that the guidelines be followed, ensuring the uniform application of relevant directive provisions' European Commission (2018e).

In relation to clinical trial and data, the following are the MEDDEVs available that provide guidelines for manufacturers, notified bodies, and competent authorities to be followed when performing clinical evaluations and trials.

1. Meddev 2.7/1 – Clinical Evaluation: Guide for manufacturers and notified bodies;
2. Meddev 2.7/2 - Guidelines for Competent Authorities for making a validation/assessment of a clinical investigation application;
3. Meddev 2.7/3 – Clinical investigation: Serious adverse event reporting;
4. Meddev 2.7/4 – Guidelines on clinical investigation: A guide for manufacturers and notified bodies;
5. Meddev 2.2/2 – Guidelines on post-market clinical follow up;
6. NBOG – Checklist for audit or notified body review of clinical data/evaluation European Commission (2018e).

1.13 Informed Consent

Any human subject who participates in a clinical trial must be provided with all the information, including risks and benefits pertaining to that clinical trial. Thus, it is vitally important that the participant fully understands all aspects of the clinical trial and that they have chosen, voluntarily, to participate.

In particular, vulnerable groups must have the capacity to consent. In this regard then, according to the MDR:

> ‘informed consent means a subject's free and voluntary expression of his or her willingness to participate in a particular clinical investigation, after having been informed of all aspects of the clinical investigation that are relevant to the subject's decision to participate or, in the case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical investigation’ European Commission (2018a).

Specific requirements are detailed in the MDR which include the fact that informed consent must be written, dated and signed by the person performing the interview and by the human participant. Where a participant is not able to give consent, a legally designated representative will sign on their behalf . If a participant is unable to write, consent can be provided through appropriate alternative means in the presence of at least one impartial witness. In this case, the witness will sign and date the informed consent. All information provided to the participant or legal representative should enable complete understanding of the nature, objectives, benefits, implications, risks and inconveniences involved in the clinical trial. It should also include the participants rights and guarantees regarding protection and in particular, the right to refuse to participate or withdraw from the trial. Additionally, the conditions and duration of the trial, treatment alternatives and any follow up measures if the trial is discontinued should be explained. The information provided to the participant should be comprehensive, concise, clear, relevant and understandable to the participant or legal representative. The information must be provided in a prior interview with a member of the trial investigating team who is appropriately qualified under national law. All information should be prepared in writing and verification is required that the participant has understood all the information provided European Commission (2018a).

As stated by Mallia (2018):

> ‘The autonomy of patients participating in research means that a proper informed consent process must take place. This means that information must be given according to a reasonable person standard implying what legally and ethical a reasonable person participating in the research would want to know’ Mallia (2018).

The research must assure that the patient has understood all the information given and that a voluntary choice has been made. This means that no form of coercion must take place and that information must not be manipulated in such a way as to influence the participant.

> ‘No undue pressure or persuasion must either occur. Particular attention must be paid to vulnerable groups and participants must be competent and have the capacity to consent. Where necessary the use of a proxy to act on behalf of a patient who does not have legal capacity must be used and the best interests of the patient must be asserted. In research consent must always include a signed consent form which again is duly explained and authorised by the research ethics committee’ Mallia (2018).

Ensuring the informed consent of the trial participant is an important step in conducting a clinical trial. In addition to the MDD and MDR requirements, EN ISO 14155, should be followed in this regard. It is vitally important to ensure that information is presented in an accurate and understandable format. Risks and benefits must be clearly outlined by an appropriately qualified person in an interview prior to the clinical trial. It is equally important that the participant be informed of any alternative options available so that he/she can make an informed decision about participation. Documented evidence of signed and approved consent must also be recorded prior to commencement of the clinical trial.

1.14 Differences between medical device and drug clinical studies

Both medical device and drug clinical studies should be approved by an Ethics committee and clinical investigations shall be subject to scientific and ethical review. As stated in the MDR:

> 'The ethical review shall be performed by an ethics committee in accordance with national law. Member States shall ensure that the procedures for review by ethics committees are compatible with the procedures set out in this Regulation for the assessment of the application for authorisation of a clinical investigation. At least one lay person shall participate in the ethical review' European Commission (2018a).

Regarding ethical review for pharmaceuticals, as stated in the medicines - Regulation No. 536/2014:

> 'The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7 as appropriate for each Member State concerned' European Medicines Agency (2018b).

Furthermore, the essential documents for a medical device investigation are similar to the ones required for a pharmaceutical study. The term Clinical Investigation Plan is generally used to refer to the study protocol in the case of a clinical investigation of a medical device. Regulatory requirements for clinical investigations of medical devices are different to pharmaceuticals and this affects the design of their clinical investigations.

> 'There is no legal requirement to demonstrate the efficacy of the device to obtain CE marking. The objective of the clinical investigation is to demonstrate the safety and performance (conformity with claims) of a medical device. In a pharmaceutical study the objective is to demonstrate the safety and efficacy of the medicinal product. One consequence is that case numbers in a medical device investigation are usually lower than in pharmaceutical studies. The stage of a clinical investigation which needs to be satisfactorily completed for CE marking may therefore be likened to Phase II in drug development, where evidence of clinical activity of a drug is sought, rather than Phase III. Since efficacy does not need to be demonstrated, randomised controlled trial designs for medical devices are rarely necessary and therefore proof of statistical significance may not be necessary. Interim analysis of study data may be feasible, provided it has been written into the investigation plan. In comparative pharmaceutical studies the most robust comparator is a placebo control, which is often applied and generally required by authorities' Cromsource (2015).

In a medical device investigation, a placebo control is usually not possible. This is particularly the case with implantable devices, where placebo control groups (involving sham surgery) are not possible. However, studies comparing a medical device with standard therapy are possible, although in some cases there may be no standard therapy available which is similar enough to warrant comparison, especially for novel devices. In addition, the user (usually a healthcare professional) often cannot be blinded to the study intervention.

> 'A specific feature of medical device investigations is that product performance may be influenced by user. Furthermore, the use of a medical device may sometimes be associated with a learning curve for the user, where the outcomes improve with experience. Another feature is that adverse events, in particular adverse device effects, may not only concern the investigation subjects but also third parties, such as users of the device. In contrast, adverse events in pharmaceutical studies are only monitored for the clinical study subjects. Due to the wide range of types of device, testing methodologies vary widely. Some performance data might simply require user handling feedback; other data might be more analytical. Medical devices often create large amounts of data that are transmitted, processed and stored via specific software interfaces. For such data sets, specific monitoring rules have to be established focusing on supervising data processing rather than individual data points. Moreover, medical devices are subject to frequent incremental innovation . Results from long-term clinical studies with predicate devices may no longer be relevant to improved products and medical procedures' Cromsource (2015).

Clinical trials for medicines are regulated by the Directive 2001/20/EC, which will be repealed by regulation EU No 536/2014. Although the regulation entered into force on 16 June 2014, the timing of its application depends on the development of a fully functional EU clinical trials portal and database, which will be confirmed by an independent audit.

In relation to this:

> 'The Regulation becomes applicable six months after the European Commission publishes a notice of this confirmation. The entry into application of the Regulation is currently estimated to occur in 2019. The Regulation will ensure a greater level of harmonisation of the rules for conducting clinical trials throughout the EU. It introduces an authorisation procedure based on a single submission via a single EU portal, an assessment procedure leading to a single decision, rules on the protection of subjects and informed consent, and transparency requirements. It will also make it easier for pharmaceutical companies to conduct multinational clinical trials, which should increase the number of studies conducted within the EU' European Medicines Agency (2018b).

The portal will be a single entry point for submission of all clinical trials and will be publicly available. There will be secure workspaces available for sponsors and competent authorities, which will provide full access to all information pertaining to clinical trials.

Outlined in Table 2 and 3, below, are the key differences between medical device and drug clinical trials.

Table 2: Clinical Trial Classification of Drugs and Devices (Chittester, 2014)

Drugs	**Devices**
Phase 1 • Aimed at safety and tolerance • Healthy volunteers (20-100 subjects) • Determine dosing and major adverse effects	Pilot: • Smaller population with disease or condition (10-30 subjects) • Determine preliminary safety and performance information
Phase 2 • Aimed at safety and effectiveness • Small population with disease or condition (50-200 subjects) • Confirm dosing and major adverse effects	Pivotal: • Larger population with disease or condition (150-300 subjects) • Determine effectiveness and adverse effects
Phase 3: • Aimed at safety and effectiveness • Large population with disease or condition (100s to 1000s of subjects) • Determine drug-drug interactions and minor adverse effects	Not Applicable
Phase 4: • Post approval study • Collect long-term data and adverse effects	Post-Approval Study: • Collect long-term data and adverse effects

Table 3: Clinical Trial Design of Drugs and Devices (Chittester, 2014)

Drugs	**Devices**
• Randomisation is common • Control group • Large populations Includes placebos • May compare to other approved therapies • Ability to “blind” • Difficult to visualise	• Often no randomisation • Control group • Small populations • Rarely uses placebos • May compare to other approved therapies • Difficult to “blind” • Visualisation often included

A small change to a drug could result in unanticipated outcomes. Medical devices clinical trials may not always be required and will depend on risk assessment. In that regard, an example would be a tongue depressor or adhesive bandage which pose little risk, and therefore a clinical trial would not be required. Compared to a drug-eluting stent or a new material for a hip replacement, as they introduce higher risks, a clinical trial may be required Chittester (2014).

Figure 7 below presents a summary of key differences in medical device and drug trials:

Aspect	Medical devices compared to drugs
Principal mode of action	Not by pharmacological means
	Less interaction with human body
	Some devices work exclusively outside the human body
Development	More technical, involves engineers
	Faster development cycle
	Less patients required in clinical studies
	More frequent product updates
Clinical studies	Commonly no studies in healthy volunteers
	Blinding is often not possible
	No classification in Phase I, II, III, and IV studies, but:
	-Feasibility,[9] Pilot-, First-in-Men-, First-in-Human studies are similar to Phase II studies
	-Pivotal-, Premarket-, CE-mark studies are similar to Phase III studies
	Postmarket studies, registries are similar to Phase IV studies[11]
Miscellaneous	Success of treatment may be related to physician's skills, particularly for invasive devices such as implants
	Often smaller companies, requiring an "all-rounder" mentality

Figure 7: Main differences between medical devices and drugs at a glance (Doerr, Whitman and Walker, 2017)

1.15 Aims and Objectives

The aim of this research is to evaluate European clinical trial history, regulations, and a real-life case study to determine if the health and welfare of human participants in medical device clinical trials are protected.

The research aims to address the following:

1. Evaluation of clinical trial history to determine the evolution and lessons learned from the past.
2. Evaluation of European medical device regulation to determine if it adequately protects the welfare of human participants in clinical trials.
3. Evaluation and review of a real life case study to identify if weaknesses exist in the medical device clinical trial regulation and process which would put human participants at risk.
4. Identify what other factors affect the protection of human participants in medical device clinical trials.

1.16 Value of the Research

The clinical trial regulation and process, particularly by regulatory affairs professionals, is not widely known, as it is a specific function that seldom crosses over into Post Market/Vigilance Surveillance activities. Therefore, this research will be a valuable study for understanding how clinical trials are conducted, the regulation that applies, and the importance of this process in ensuring that medical devices placed on the market have been sufficiently tested to ensure their safety and effectiveness. Additionally, from the literature research, the topic of clinical trials and the protection of human participants, as a combined topic, revealed that significant research literature is not readily available on this important subject.

Clinical trials are crucial in answering specific scientific questions and are necessary to determine the benefits and risks of a new medical treatment to patients and to society in general. However, this research cannot be conducted without the involvement of human volunteers and participants. History has demonstrated that some weaknesses in our regulatory framework have resulted in patient injury and death. Therefore, the research examines the major changes that have occurred in the regulation of clinical trials and how that regulation has evolved in protecting the health and welfare of human participants.

1.17 Conclusion

Clinical trials improve medical knowledge but would not be possible without human participants. The medical device industry in Europe aims to protect the health and well-being of European citizens, covers a wide range of products and is a significant employer in Europe. The European medical device regulatory system is in place to ensure that products placed on the European market meet and satisfy the regulation requirements. The MDDs have been replaced by the MDR, which were approved on 5th April 2017. The MDR was developed to address failures in the system which resulted in cases such as PIP and DuPuy. Among the significant changes that have been introduced are more precise requirements relating to clinical data and investigations. Clinical Evaluation Reports (CERS) will now adopt a life cycle approach and will need to be continually updated based on post market data. Class III and implantable devices will require clinical data derived from clinical investigations. European medical device regulation and guidelines provide precise instructions as to how clinical trials are to be conducted. Differences exist in clinical trial design between medical devices and drugs. In order to obtain the CE Mark for medical devices the clinical trial must demonstrate the safety and performance of the device whereas in a pharmaceutical study, the trial must prove the safety and efficacy of the drug. A clinical trial will not always be required for a medical device, depending on classification, whereas a clinical trial is always conducted for medicines. One of the key factors in conducting clinical trials which involves human participants is ensuring that informed consent has been obtained which includes ensuring that the participant fully understands all risks and benefits pertaining to the clinical that they are involved in.

Chapter 2: Literature Review

2.1 Introduction

This literature review examines the evolution of clinical trials and European clinical trial regulation as it pertains to medical devices.

The research aims to address the following:

1. Evaluation of clinical trial history to determine the evolution and lessons learned from the past.
2. Evaluation of European medical device regulation to determine if it adequately protects the welfare of human participants in clinical trials.
3. Evaluation and review of a real-life case study to identify if weaknesses exist in the medical device clinical trial regulation and process which would put human participants at risk.
4. Identify what other factors affect the protection of human participants in medical device clinical trials.

In order to address the above objectives of this study, a review of the following major categories of literature with respect to Clinical Trials was performed:

- History of Clinical Trials
- European Clinical Trial Regulations for Medical Devices
- Clinical Trial Ethics
- Clinical Trials with Vulnerable Participants
- Real Life Case Study
- The Role of Medical Journals in Clinical Trials
- Conflict of Interest

2.2 History of Clinical Trials

Advances in the field of medicine are often dependent on the quality of research that is conducted. Ensuring accurate and credible data from clinical trials and protection of human subjects is essential and the price for compromise is high. Human curiosity has been the driving force in the advancement of science and medicine since these disciplines came into existence. In addition, human subjects have been used to validate the theories of those innovators involved in the pursuit of this knowledge.

The first accounts of clinical trials outlined below identified that clinical trial evolution was primarily related to drug therapies, thus, a history of medical device inventions was researched.

As described in the New York Times (2012):

> 'René Laënnec (1815) - French physician, invented the stethoscope, in order to hear the heart beat of a very overweight lady.
>
> Dr. Albert S. Hyman (1936) developed a heart pacemaker. Dr. Hyman advised that the device had been used in seven cases,and had shown success in only two.
>
> Claude Beck (1947), successfully defibrillated the heart of a 14-year-old boy during cardiac surgery, which effectively brought a dead person to life. This was stated to be the first successful clinical application.
>
> Henry Opitek (1952), was operated on using an artificial heart, the Dodrill GMR heart machine, manufactured by General Motors. This was considered the first mechanical heart. Dr. Forest Dewey Dodrill (the surgeon), successfully repaired the patient's mitral valve, and Mr. Opitek lived until 1981.
>
> Dr. Christiaan Barnard (1967), performed the first human heart transplant. The patient, a 53-year-old man, died 18 days later'.

2.2.1 The First Clinical Trial

As described by Bhatt (2010), in his review, in which he quotes from a range of historical studies, the first clinical trial recorded of a new therapy was performed by the surgeon Ambroise Pare in 1537. He was treating a number of wounded soldiers and the casualties were high. As supplies of oil, which were applied to wounds, were not adequate, he had to create a digestive treatment out of yolks of eggs, oil of roses and turpentine. Bhatt (2010) provides an account of that first trial, as described by Ambroise Pare :

> ‘at length my oil lacked and I was constrained to apply in its place a digestive made of yolks of eggs, oil of roses and turpentine. That night I could not sleep at any ease, fearing that by lack of cauterisation I would find the wounded upon which I had not used the said oil dead from the poison. I raised myself early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses’.

Although, Pare had made a significant discovery, it took another 200 years before a planned controlled trial would be organised Bhatt (2010).

2.2.2 The Scurvy Trial

James Lind is recorded as being the first physician to have conducted a controlled clinical trial. The rate of deaths from scurvy, whilst Lind worked on a ship was very high and he decided to plan a comparative trial as described below. Bhatt (2010), provides an account, in his review, in which he quotes from a range of historical studies and as described by James Lind:

> ‘On the 20th of May 1747, I selected twelve patients in the scurvy, on board the Salisbury at sea. Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of the knees. Two were ordered each a quart of cyder a day. Two others took twenty-five drops of elixir vitriol three times a day … Two others took two spoonfuls of vinegar three times a day … Two of the worst patients were put on a course of sea-water … Two others had each two oranges and one lemon given them every day … The two remaining patients, took … an electary recommended by a hospital surgeon … The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of six days fit for duty … The other was the best recovered of any in his condition; and … was appointed to attend the rest of the sick. Next to the oranges, I thought the cyder had the best effects …’ Bhatt (2010).

Although the trial had revealed what diet was best, due to the expense of the fruits, Lind did not recommend using this diet and it took another fifty years before the British Navy made lemon juice, eventually replaced by the cheaper lime juice, a compulsory part of the seaman’s diet Bhatt (2010).

2.2.3 The Placebo

The physician Austin Flint planned the first clinical study comparing a dummy remedy to an active treatment and the concept of the 'placebo' was born . As described by Bhatt (2010), in his review, and in which he quotes Austin Flint:

> 'He treated 13 patients suffering from rheumatism with an herbal extract which was advised instead of an established remedy. In 1886, Flint described the study in his book - A Treatise on the Principles and Practice of Medicine'. "This was given regularly, and became well known in my wards as the 'placeboic remedy' for rheumatism. The favorable progress of the cases was such as to secure for the remedy generally the entire confidence of the patients" Bhatt (2010).

2.2.4 The First Double blind Controlled Trial

A trial to investigate patulin treatment for the common cold was carried out in 1943 by the Medical Research Council (MRC). The study included over a thousand British office and factory works who were suffering from colds as described by Bhatt (2010), in his review:

> 'The study was rigorously controlled by keeping the physician and the patient blinded to the treatment. The treatment allocation was done using an alternation procedure. A nurse allocated the treatment in strict rotation in a separate room. The nurse filed the record counterfoil separately, and detached the code label for the appropriate bottle before asking the patient to visit the doctor. The statisticians considered this an effective random concurrent allocation. However, the outcome of the trial was disappointing as the analysis of trial data did not show any protective effect of patulin' Bhatt (2010).

2.2.5 The First Randomised Curative Trial

The concept of randomisation was first introduced in 1923 and the first randomised trial of streptomycin in pulmonary tuberculosis was performed in 1946 by the MRC, as described below by Bhatt (2010), in his review, in which he quotes from a range of historical studies:

> 'The trial began in 1947. As the amount of streptomycin available from US was limited, it was ethically acceptable for the control subjects to be untreated by the drug—a statistician's dream. This trial was a model of meticulousness in design and implementation, with systematic enrolment criteria and data collection compared with the ad hoc nature of other contemporary research. A key advantage of Dr Hill's randomisation scheme over alternation procedure was "allocation concealment" at the time patients were enrolled in the trial. Another significant feature of the trial was the use of objective measures such as interpretation of x-rays by experts who were blinded to the patient's treatment assignment' Bhatt (2010).

The trial became the model of clinical trial design which has been refined over time but this trial continues to be referred to as ground breaking.

As documented in the above account, clinical trials have progressed significantly since the first accidental discovery by the surgeon Ambroise Pare. Medical research is an important step in discovering new treatments for diseases and providing essential healthcare and benefits to society.

2.3 Human Participant Protection and Welfare

2.3.1 The Nuremberg Code

In the twentieth century, the line between legitimate research on human subjects and criminal assault had been variously drawn, with the demands of the researcher and the voice of the research subject and patient receiving varying recognition. As described below:

> 'With the upswing of clinical research in the early twentieth century and some dramatic breakthroughs in medicine there was a tendency to heroise the researcher in the "fight" against disease. In Nazi Germany, there were strong pressures to conduct research on lives deemed worthless in the hope of producing valuable breakthroughs in medical research to benefit the nation and race. After all, if the mentally ill and racially inferior Jews and Gypsies were going to be killed, their bodies might still serve a useful purpose' Weindling (2015).

Following on from the Nuremberg trials in Germany, where Nazi physicians were tried for crimes related to human experiments on prisoners in concentration camps, the Nuremberg Code was introduced in 1947. Prisoners were taken advantage of by Nazi physicians by being subjected to non-consensual experiments. The Nuremberg trials revealed accounts of pharmaceutical testing, war-injury simulation and other cruelties. The Nuremberg Code, was also known as International Code of Medical Ethics and outlined the first basic elements of research ethics criteria. The original ten essential conditions of experiment requirements demonstrated protection of human participants in clinical trials. It was specifically stated in the document that voluntary consent was essential and that the benefits of research must outweigh the risks. Although the Nuremberg Code provided clear instructions for investigator's responsibilities, the subsequent two decades did not eliminate unethical research. Therefore, although the Nuremberg Code had success in gaining acceptance of ethical research, violations of the code continued Nellhaus and Davies (2017).

An example of unethical research practices was demonstrated in the Tuskegee syphilis study, which took place over forty years and did not adhere to the standards established at Nuremberg. A study was initiated to identify a treatment for syphilis in black males, when there was no known cure and entitled 'Tuskegee Study of Untreated Syphilis in the Negro Male'. However, when penicillin became known to treat the illness in 1947, the researchers did not offer the treatment to the trial participants and this resulted in deaths and infections. The participants were exploited and offered free medical care and health insurance to remain in the trial Nellhaus and Davies (2017).

As stated by Aggarwal and Gurnani (2014), the ten points of The Nuremberg Code are described as follows:

1. ‘Consent of human subjects should be voluntary and informed. Voluntary consent is defined as the willingness of the subject without any means of force, coercion, fraud or deceit. Informed consent means informing the subject on any kind of hazards they may face or any inconvenience they might experience. Any risk to the health of the subject should be disclosed and the subject should be well informed about the nature of the project or experiment and what it constitutes.
2. The experiment results should benefit the society as a whole. The results should not be obtainable by any other methods or means of research.
3. Experimentation of animals should precede the experiment, and results of animal experimentation should form the basis of the design of the experiment.
4. Any kind of physical or mental suffering to the subject should be avoided.
5. If there is reason to believe that the experiment will cause a disabling injury or death to the subject, the experiment should not be performed.
6. The risks should never exceed the benefits.
7. Preparations and facilities should be adequate and proper so as to avoid even the remote possibility of harm, injury, or death to the subject.
8. Only scientifically qualified persons must perform the experiment. The highest degree of skill and the utmost care should be taken throughout every stage of the experiment.
9. The subject may withdraw from the experiment at any point or stage due to physical or mental exhaustion or not being able to continue any further.
10. The investigators must be prepared to terminate the experiment at any point or stage, if they believe the experiment will cause harm, injury, disability or death to the subject’.

As an immediate after-effect of the Nuremberg trials, the World Medical Association (WMA) was formed in 1947.

The Nuremberg code was an important step in ensuring that medical research never compromises the health and safety of the human participants involved in clinical trials. Risks should be weighed carefully and should never exceed the benefits. As such, the benefits of the research should be for society as a whole and not for commercial or other interests of those involved in conducting trials. In addition, only scientifically qualified persons should perform any experimental surgeries or treatments.

2.3.2 The Declaration of Geneva and Helsinki

The WMA took the place of l'Association Professionnelle Internationale des Médecins—an international medical association that had been effectively disbanded during World War II. Physicians from the WMA were appalled at the atrocities revealed at the Nuremberg Trial and, in 1949, as stated below:

> ‘issued a code of medical ethics to condemn what Nazi doctors had done. This code came to be known as the Declaration of Geneva for the city in which it was officially adopted. In it, the WMA laid out general principles to which physicians should hold themselves. For example, “the health of my patients will be my first consideration’ Fischer (2005).

Although the Declaration of Geneva’s goal was noble, inaccurate interpretations became apparent. In order to address this weakness, the WMA evaluated the issue in 1953. Discussions ensued for several years and finally the document, *Ethical Principles for Medical Research Involving Human Subjects*, was approved in 1964. This became known as the Declaration of Helsinki Fischer (2005).

The current version of the document contains three sections in 32 separate paragraphs, each on a specific topic:

1. ‘Section A sets the stage of what human research is and why it is necessary and stresses the obligation of the physician to prioritise participant health.
2. Section B discusses basic principles for medical research and reaffirms points of the Nuremberg Code,
3. Section C discusses research combined with medical care and states that research can only be combined with clinical care if it has the potential to prophylax, diagnose, or treat’ Fischer (2005).

The Declaration of Helsinki provides strict guidelines, as outlined above, to ensure that physicians involved in medical research put the health and welfare of their patients above all else. It is the duty of the physician to protect human participants involved in medical research and to ensure that the research has appropriate value to those involved. As such, the guidance provided in the Declaration of Helsinki has been incorporated in both medical device and medicinal clinical trial regulation.

Regulation 536/2014 for clinical trials for medicine is in line with the Declaration of Helsinki and is defined therein as follows :

> ‘This Regulation is in line with the major international guidance documents on clinical trials, such as the 2008 version of the World Medical Association's Declaration of Helsinki and good clinical practice, which has its origins in the Declaration of Helsinki’ European Medicines Agency (2018a).

The MDR also addresses alignment with the Declaration of Helsinki as follows:

> ‘the rules should be in line with the most recent version of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects’ European Commission (2018a).

2.3.3 The Ethical Considerations of Clinical Trials

According to the MDR, ethics committee ‘means an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients' organisations’ European Commission (2018a). Additionally, the MDR states that clinical investigations shall be subject to scientific and ethical review:

> ‘The ethical review shall be performed by an ethics committee in accordance with national law. Member States shall ensure that the procedures for review by ethics committees are compatible with the procedures set out in this Regulation for the assessment of the application for authorisation of a clinical investigation. At least one lay person shall participate in the ethical review’ European Commission (2018a).

As stated by the Council of Europe in their Guide for Research Ethics Committee Members, Research Ethics Committees (RECs) are multidisciplinary, independent groups of individuals appointed to review biomedical research protocols involving human beings, as the guide states, to help ensure in particular, that:

> ‘the dignity, fundamental rights, safety, and well-being of research participants are duly respected and protected. RECs may be established at local, regional or national level. They may be appointed by institutions or by regional or national authorities and are increasingly provided for by law. Their scope as a local, regional or national REC is defined by the appointing authorities. To fulfil their responsibilities, RECs should possess collective expertise in the fields or disciplines deemed necessary for their work. The appointment mechanism should ensure that potential REC members provide an appropriate balance of scientific expertise, philosophical, legal or ethical backgrounds, and lay views’ Council of Europe (2012).

There should be equality among all REC members. This could pose difficulities in societies with a tradition of high respect for authority and social hierarchy. It is generally accepted that professional members of RECs include scientists, health care professionals, lawyers, and persons with specific expertise in ethics. Other useful disciplines include epidemiology, clinical pharmacology, pharmacy, psychology, sociology, and biostatistics Council of Europe (2012).

As stated in the Council of Europe guide:

> 'Lay members of RECs are usually defined as having no specific qualification with respect to biomedical research, medicine, or health care. They are expected in particular to reflect the views of the public as well as those of patients. REC members should be able to strike an appropriate balance between achieving the greater common good that can be brought about by biomedical research and recognising and protecting the human dignity, rights, health and wellbeing, and interests of research participants. Above all, they must ensure that, where there is a conflict, the interests and welfare of the people participating in research prevail over the sole interest of society or science' Council of Europe (2012).

To summarise, Figure 8 below shows the roles of RECs in the research process

	Before research starts		After research has started	
Research phase	Planning, preparation of the project	Review	Conduct	End of the research
Roles	Providing information to researchers*, as needed	Ethics review of the research proposal	Follow up of the research project, in particular ethical aspects; possible re-review	Review reports from the researchers*

Figure 8: Roles of RECs in the Research Process (Council of Europe 2012)

Only since World War II have principles such as Beauchamp and Childress's four principles such as beneficence (balance benefit with risk), non maleficence (avoidance of intentional harm), autonomy (human rights including the right to make choices, express opinion and take actions based on personal values and beliefs) been taken into consideration when conducting clinical research Kirsteen and Jones (2017).

Informed consent was the main issue addressed in the Nuremburg Code and still is a major consideration in clinical trials today. It is key that the human participant is informed and protected as part of any clinical trial involving human participation. This allows the

participant to make a decision based on facts and known data and many safeguards have been put in place to ensure that clinical trials are run with the health and privacy of the participants at the forefront.

As stated by Raul, *et al.*,(2017), ‘medical ethics and ethical principles have been practiced and debated for centuries in the Hippocratic tradition, but ethical human research standards, protection principles, laws, regulations, and guidelines were gradually introduced and slowly adopted or updated only in the last few decades, primarily as a result of historical events and atrocities committed in the name of research’. Furthermore, as described by Raul, *et al* (2017):

> ‘In recent years, the focus of contemporary medical research ethics has shifted to the protection of the individual patient or volunteer when enrolling as a research subject. Patients are now better informed and aware of their rights and options, especially their right of refusal. The informed consent process has evolved with an emphasis on the subject's autonomy and choice and the adoption of protective procedures for patients who are less than fully autonomous, including the unborn fetus’.

Regulation related to clinical trials is relatively young. However, despite this, it has seen significant evolution in the protection of human participants. Key milestones include the Nuremberg Code and the Declaration of Helsinki. These key developments were designed to apply ethical policies to protect human participants involved in clinical trials. Scientific and biotechnological advances should never outweigh the need to protect those involved in clinical trials Lorenzetti (2015).

2.3.4 Vulnerable Participants

Special protection must be provided for vulnerable clinical trial participants because they are at a higher risk of harm. In that regard, though, sometimes the involvement of vulnerable participants is necessary to develop safe treatments suitable for these groups Éloïse, Genneta and Elgerda (2015).

Special considerations to be met for vulnerable incapacitated participants has been precisely defined in the MDR, which aims to protect vulnerable clinical trial participants, as follows:

> ‘(a)the informed consent of their legally designated representative has been obtained; (b) the incapacitated subjects have received the information referred to in Article 63(2) in a way that is adequate in view of their capacity to understand it; (c) the explicit wish of an incapacitated subject who is capable of forming an opinion and assessing the information referred to in Article 63(2) to refuse participation in, or to withdraw from, the clinical investigation at any time, is respected by the investigator; (d) no incentives or financial inducements are given to subjects or their legally designated representatives, except for compensation for expenses and loss of earnings directly related to the participation in the clinical investigation; (e) the clinical investigation is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical investigations on persons able to give informed consent, or by other research methods;(f) the clinical investigation relates directly to a medical condition from which the subject suffers; (g) there are scientific grounds for expecting that participation in the clinical investigation will produce a direct benefit to the incapacitated subject outweighing the risks and burdens involved. The subject shall as far as possible take part in the informed consent procedure’ European Commission (2018a).

In relation to minors, specific requirements are outlined in the MDR as follows:

> ‘the informed consent of their legally designated representative has been obtained;(b) the minors have received the information referred to in Article 63(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;(c) the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 63(2) to refuse participation in, or to withdraw from, the clinical investigation at any time, is respected by the investigator; (d) no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical investigation; (e) the clinical investigation is intended to investigate treatments for a medical condition that only occurs in minors or the clinical investigation is essential with respect to minors to validate data obtained in clinical investigations on persons able to give informed consent or by other research methods; (f) the clinical investigation either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors; (g) there are scientific grounds for expecting that participation in the clinical investigation will produce a direct benefit to the minor subject outweighing the risks and burdens involved; (h) the minor shall

> take part in the informed consent procedure in a way adapted to his or her age and mental maturity; (i) if during a clinical investigation the minor reaches the age of legal competence to give informed consent as defined in national law, his or her express informed consent shall be obtained before that subject can continue to participate in the clinical investigation' European Commission (2018a).

Protection is outlined for pregnant or breastfeeding women in the MDR as described below:

> '(a) the clinical investigation has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, outweighing the risks and burdens involved; (b) where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child; (c) no incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings directly related to the participation in the clinical investigation' European Commission (2018a).

Additionally the MDR includes requirements for other categories too as follows:

> 'Member States may maintain additional measures regarding persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical investigations, or persons in residential care institutions' European Commission (2018a).

In relation to damage caused by a participant's involvement in a clinical trial, the MDR states:

> 'Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical investigation conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk' European Commission (2018a).

2.4 Case Study

2.4.1 The Paolo Macchiarini Case

The following is a case study of clinical research performed on patients to transplant diseased and non-functioning tracheas with artificial ones. The surgeries were performed by Professor Paolo Macchiarini and this case study is a classic example of the risk to human life when a clinical study fails to follow and comply with regulations. From the review of this case study, as described below, weaknesses are revealed in the way that the trials were conducted such as physician qualifications, lack of notification to the Competent Authority in Sweden called the Medical Products Agency (MPA), lack of informed consent from the participants, ethical approval, ignoring of regulations and falsification of surgical results. This case demonstrates a sober reminder of the high risk to human participants in clinical research when the drive for scientific advancement outweighs regard for human life.

In Autumn 2010, Paolo Macchiarini was recruited by the Karolinska Institutet and Karolinska University Hospital as a visiting professor conducting basic research in the field of regenerative medicine/stem cell biology. At the same time, he was employed on a part-time contract as a consultant and surgeon at Karolinska University Hospital. From 2011–2012, artificial tracheas were surgically implanted in three patients. According to the hospital the operations were care interventions on the basis of a so-called vital indication (i.e. as an attempt to save the patient's lives). However, between 2011 and 2014, all three patients died Karolinska (2018a).

In total, there were seventeen surgeries performed, but for the purpose of this study,the surgeries that will be discussed were performed at the Karolinska University Hospital, Sweden (Patients numbered 10, 11, and 14 below). Brief details of the other fourteen patients are also included. Outlined below is the regulation and standard that should have been followed in this case study. The failures to follow such regulation in this section will also be discussed.

2.4.2 Product Classification

Per the MDD, the Rule 13 covers combination products and applies to the product used in this case study:

> 'All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, as defined in Article 1 of Directive ►M5 2001/83/EC ◄, and which is liable to act on the human body with action ancillary to that of the devices, are in Class III' European Commission (2018d).

The MPA was not notified of the surgeries and therefore no consultation took place to confirm classification or indeed the regulation to be followed. For the purpose of this research, the MDD will be referred to as the regulation applicable, as this is a combination product with the plastic trachea's intended purpose to maintain the airway passage to allow the patient to be ventilated.

2.4.3 Applicable Regulation

At the time that the surgeries were performed between 2010 and 2014, the MDD, MEDDEVs and ISO 14155 was the regulation that should have been followed for clinical trials in Sweden. The details of the required regulation are presented. The specific national requirements by the MPA, for the performance of clinical investigations in Sweden, is presented also.

2.4.4 Surgeries Performed

The following is the full list of patients involved in Macchiarini's experimental surgeries:

1. 'Claudia Castillo, born 1977, suffered from tuberculosis-damaged airways. Operated on 12.06.2008 at Hospital Clinic Barcelona, Spain. The organ was prepared without the knowledge of authorities in the veterinary lab of Martin Birchall at the University of Bristol. **Current State: Alive**.
2. D.D., female, born 1953. Diagnosis unknown (but likely no cancer). She was operated by Macchiarini on her airways twice before she was transplanted in October 2009 at Institut Dexeus in Barcelona. **Current State: Unknown.**
3. Ciaran Lynch, born 2000 without functional trachea, received a homograft from Martin Elliott which functioned for 10 years. The boy received on 15.03.2010 from Macchiarini a trachea transplant (prepared in a lab at Royal Free Hospital, London. **Current State: Alive.**

4. M.K., female, born 1979, from Czech Republic, at the time mother of a 7 month old baby. She had mucoepidermoid carcinoma, was delegated to Macchiarini by her Czech doctor, the thorax surgeon Václav Jedlička. Operated at Careggi Hospital, Florence on 06.07.2010. **Current State: Deceased one year after the surgery.**
5. Keziah Shorten, born 1991, from UK. She had adenoid cystic carcinoma and was operated on 13.07.2010 at Careggi, Florence. **Current State: Deceased two years after surgery**.
6. G.M, female, born 1987, diagnosed with left-side bronchomalacia (softness of bronchi). She was operated on 28.09.2010 at Careggi. **Current State: Unknown.**
7. M.M, female, born 1945, suffered from tracheo-oesophageal fistula, which happened postoperatively after larynx cancer treatment. She was operated on 04.10.2010 at Careggi, Florence with a cadaveric trachea. **Current State: Deceased one year after surgery.**
8. Zhadyra Iglikova, born 1984. Russian patient who suffered tracheostomy after a car accident. She was operated by Macchiarini on 07.12.2010 at National Research Center of Surgery in Moscow. **Current State: Unknown**.
9. Zhadyra Iglikova, born 1984. Russian patient who suffered tracheostomy after a car accident. She was operated by Macchiarini on 07.12.2010 at National Research Center of Surgery in Moscow. **Current State: Deceased one month after surgery.**
10. Andemariam Beyene, born 1973. Diagnosed in Iceland with mucoepidermoid carcinoma, operated on 09.06.2011 at Karolinska University Hospital, Stockholm. He received a plastic trachea made at UCL and bioreactor regenerated at Karolinska Institutet (KI). **Current State: Deceased in 2014.**
11. Christopher Lyles, born 1981, US American, diagnosed with adenoid cystic carcinoma. Operated on 17.11.2011 at Karolinska University Hospital, Stockholm. He received a plastic trachea. **Current State: Deceased in 2012.**
12. Yulia Tuulik, born 1979, Russian, suffered from tracheostomy after a after car accident. Operated on 19.06.2012 at Kuban Medical University, Krasnodar. She received a plastic trachea. **Current State: Deceased in 2014.**
13. Alexandr Zozulya, born 1984, suffered from tracheostomy after car accident. This patient was an alcoholic and smoker, nevertheless operated on 21.06.2012 at Kuban Medical University, Krasnodar with a plastic trachea. **Current State: Deceased in 2014**.

14. Yesim Cetir, born 1990, Turkish, suffered from tracheostomy after botched operation to fix hand sweating. Operated at Karolinska University Hospital, Stockholm, on 24.07.2012, where her right lung was removed, so a plastic trachea could be inserted on 7.08.2012. **Current State: Deceased in 2017.**
15. Hannah Warren, born 2010 born without functional trachea. The little girl was operated on 09.04.2013 at Children's Hospital of Illinois with a plastic trachea. Important fact here is that the FDA repeatedly refused approval for the plastic trachea. Macchiarini eventually convinced the FDA, based on his previous surgery 'successes' and the FDA conceded and granted approval. **Current State: Deceased in 2013.**
16. Sadiq Kanaan, Jordanian. Born 1971, doctor by profession. Suffered from trachea stenosis due to complications from a 20 year-old trauma from car accident. Operated on 9.08.2013 Kuban Medical University, Krasnodar plastic trachea. **Current State: Deceased but time of death is unknown**.
17. Dmitri Onogda, born 1987, Ukrainian citizen of annexed Crimea. Suffered from tracheostomy after a car accident. Operated on 4.06.2014 at Kuban Medical University, Krasnodar, with a plastic trachea. Six months after surgery, the trachea had to be removed as it collapsed. **Current State: Alive but with tracheostomy'** Schneider (2017a).

The following is described in an article in The Guardian by Rasko and Power (2017):

> 'Macchiarini had plastic scaffolds made to order. The first person to receive one of these was Andemariam Beyene, an Eritrean doctoral student in geology at the University of Iceland. His recovery put Macchiarini on the front page of the New York Times. Macchiarini was turning the dream of regenerative medicine into a reality. This is how NBC's Meredith Vieira put it in her documentary about Macchiarini, appropriately called A Leap of Faith: "Just imagine a world where any injured or diseased organ or body part you have is simply replaced by a new artificial one, literally manmade'. Last year, however, the dream soured, exposing an ugly reality' Rasko and Power (2017).

2.5 'The Experiments' - Documentary by Bosse Lindquist

This documentary titled 'The Experiments' was shown on BBC Four in October 2016. The documentary was directed by Bosse Lindquist. Bosse Lindquist, a Swedish journalist, followed the surgeon around for months for Swedish public broadcaster, SVT. Bosse Lindquist presents facts in the documentary that question the truth about the post-operative status of the patients, lack of regulation and approval, and inconsistencies in published articles. This documentary was the inspiration for this research study, in order to establish how the regulation pertaining to clinical research allowed these surgeries to proceed and put the lives of the patients involved at risk and caused death and serious injury The Experiments (2016).

The documentary highlighted the issues surrounding these surgeries and the need for an investigation of the Macchiarini case by Karolinska. As stated by the Karolinska Institutet (2016a):

> 'In January 2016, Swedish Television broadcast a three-part documentary, Experimenten (The Experiments), exposing several examples of misconduct concerning transplantations performed by Paolo Macchiarini, a visiting professor at Karolinska Institutet (KI). The KI University Board decided on the 4th of February 2016 to launch an external inquiry into KI's handling of matters relating to Macchiarini' Karolinska Institutet (2016a).

Furthermore, after that, Karolinska stated:

> 'The Karolinska Institutet University Board (Konsistoriet) has today announced its decision to arrange an external investigation into the "Macchiarini case". The process will cover events taking place at Karolinska Institutet (KI) since the recruitment of surgeon Paolo Macchiarini as visiting professor in 2010 until the present day, when he has been notified by the Vice Chancellor that his contract will not be extended. The University Board deems such an inquiry to be an important part of restoring the confidence of the public, the scientific community, staff and students in the university' KI News (2016b).

Figure 9: Bronchoscopy footage of a normal airway and Andemariam Beyene's 12 months after his operation (Kremer, 2016).

An example of some of what was revealed included the fact that Lindquist uncovered footage of Andemariam Beyene undergoing bronchoscopies, as described by Kremer (2016):

> 'The footage from the surgical camera seemed to conflict with the descriptions of the patient in Macchiarini's published articles. However, instead of an "almost normal airway", the footage showed that a build-up of scar tissue was impeding the passage of air to the right lung. The clips also showed a fistula - a hole into the rest of the body - at the end of the trachea. Dr Pierre Delaere, a professor of respiratory surgery at KU Leuven in Belgium, stated that it was impossible for surgeons to establish a new blood supply to a trachea - donated or synthetic and has called Macchiarini's method 'one of the biggest lies in medical history, because you are doing something that is impossible from a theoretical point of view'' Kremer (2016).

As described by Elliott (2018): ' It has been decades since a work of investigative reporting on a medical research scandal has produced such dramatic consequences. Lindquist repeatedly exposes his subject's lies simply by showing the visual evidence:

> 'video footage from bronchoscopies, first-hand testimony from the whistleblowers, conversations filmed as they occurred in clinics and hospital rooms. When the family members of the victims speak to Lindquist, the pain in their voices is raw' Elliott (2018).

Four researchers who had worked with Macchiarini filed a formal complaint to the President of Karolinska on 18th August 2014, with regard to the surgeries performed. An excerpt from the letter reads:

> 'Dear Prof Hamsten, We would like to hereby make a request for a formal investigation of Prof Paolo Macchiarini, CLINTEC, Karolinska Institutet, on the grounds of scientific misconduct. Having been involved in the treatment and care of three patients who have undergone implantation of synthetic tracheal grafts, and subsequently acquainted with the clinical outcome of these procedures, it has become apparent that the results published by Prof Macchiarini do not correlate with the patients' actual clinical outcome. We have conducted an analysis of the medical records of the patients transplanted with synthetic tracheae and compared them to the outcomes published by Prof Macchiarini. Inquiries to the Swedish Medical Products Agency (Läkemedelsverket) have not yielded any evidence that the synthetic trachea has been approved for clinical implantation' Retractionwatch (2018).

Karolinska agreed to perform an independent investigation, with the investigator agreeing with the claims of the four whistleblowers. However, Hamsten refuted the claims, stating that Macchiarini had acted 'without due care'. As a result, the whistleblowers were severely punished for speaking out:

> 'For their efforts, the whistleblowers were punished. When Macchiarini accused one of them, Karl-Henrik Grinnemo, of stealing his work in a grant application, Hamsten found him guilty. As Grinnemo recalls, it nearly destroyed his career: "I didn't receive any new grants. No one wanted to collaborate with me. We were doing good research, but it didn't matter … I thought I was going to lose my lab, my staff – everything". This went on for three years until, just recently, Grinnemo was cleared of all wrongdoing' Rasko and Power (2017).

Contact was made with Bosse Lindquist by email and an interview requested with him regarding this documentary and the case of Paolo Macchiarini, which he duly accepted.

2.6 Inspire Clinical Trial, UK

The information about this trial is included because Macchiarini and Birchall collaborated to develop the technology surrounding the trachea transplants. INSPIRE is a phase 1 clinical trial in UK, suspended since December 2016, which was about to recruit 4 patients for trachea transplants using the technology of cadaveric tracheas, which Birchall developed, together with his former partner, Macchiarini. ‘ Even the official sponsor of both INSPIRE and TETRA, Cell & Gene Therapy Catapult, sulkily announced to change the status of the former trial from “active, not recruiting” to “suspended”’ Schneider (2018).

See Figure 10 below, accessed on clinicaltrial.gov website, which confirms that the trial is now suspended.

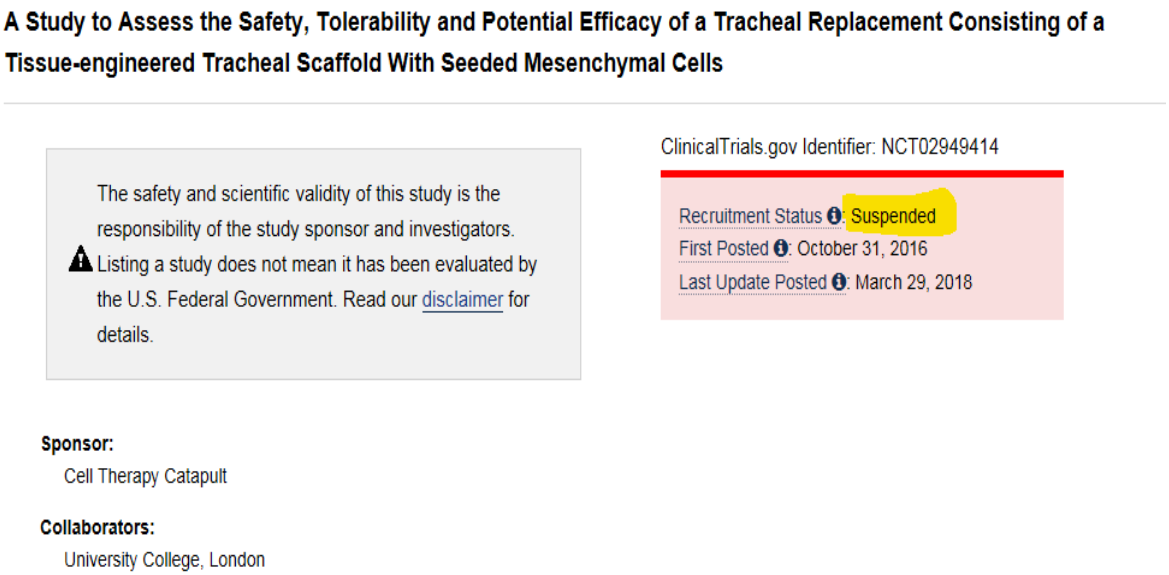

Figure 10: Clinical Trials (Source: [www.clinicaltrials.gov)](http://www.clinicaltrials.gov)

2.7 Guidelines on Conducting Clinical Research in Sweden

According to the MPA, a clinical trial investigation should be performed according to the harmonised standard SS-EN ISO 14155:2011 which provides an assumption of conformance with the MDD. Should the sponsor or manufacturer conducting the trial choose not to follow this standard, they must provide a rationale how an equivalent or higher level of quality will meet the requirements MPA (2015).

As described above, the MPA carries out it's assessment and monitoring of a clinical trial based on the harmonised standard EN ISO 14155:2011 which assures conformance with the medical device directives. The MPA outlines below the definitions of the key stakeholders involved in clinical trials in Sweden.

> *'Principal investigator* - Qualified person responsible for conducting the clinical investigation at an investigation site.
>
> If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team.
>
> *Investigator* - Individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical investigation-related procedures or to make important clinical investigation-related decisions.
>
> *Coordinating investigator* - Investigator who is appointed by the sponsor to coordinate work in a multicentre clinical investigation' MPA (2015).

A clinical trial should not commence without notification to and approval from the MPA. In this regard, the regulation states:

> *'Notification of clinical investigations* - A notification of a clinical investigation should be sent to the MPA in electronic format. The notification may also be submitted either as an attachment to an e-mail. The e-mail address for the MPA is registrator@mpa.se' MPA (2015).

Outlined below are the required documents to be submitted to the MPA:

‘•Clinical investigation plan, Clinical investigator's brochure

•copy of insurance coverage/information on insurance protection for the test subject

•patient information, form for the test subject's consent to participate in the investigation as well as forms for the test subject's consent for the disclosure of medical record data (all parts in Swedish)

•copy of the Ethical Review Board's statement and details of the aspects covered, if they are available when the notification is submitted. Otherwise, a copy of the application to the Ethical Review Board is submitted.

•list of the Swedish investigation site(s) and principal investigator(s), if not specified in the investigation plan

•evidence of competence of the coordinating investigator and the principal investigator for each investigation site

•declaration of conformity with essential requirements’MPA (2015).

The MPA may also request the following documents:

‘•intended labelling of the investigation device

•user manual for staff (Swedish/English text) and/or as required for test subjects (Swedish)

•a copy of the application to the Ethical Review Board

Documents where applicable or that the MPA may request:

•results of the risk assessment or assessments (usually included in the investigator's brochure) or specific risk assessment or assessments with associated reading instructions/code keys including documentation of the risk management

•list of standards applied in full, and a description of deviations from the standard where the standard is a harmonised EN standard (usually included in the investigator's brochure)

•design drawings, and diagrams of components, sub-assemblies, wiring diagrams and intended methods of manufacture, in particular in respect to sterilisation

•documentation in accordance with the Commission Regulation (EU) No 722/2012 if the investigated device is manufactured of tissues from animals

•documentation if the investigated device contains substances derived from human blood

> •documentation if the investigation device contains, as an integral part, a substance which, if used separately, can be considered as a medicinal product (copy of scientific opinion that the notified body has received from a competent authority for the substance in question)
>
> •documentation of the medical devices/medicinal products/substances which the investigational medical device will be used together with or compared to in the clinical investigation (usually included in the investigation plan)
>
> •form for recording data (Case Report Form)
>
> •evaluation form to be completed by the test subject or staff (in Swedish)' MPA (2015).

The MPA processes the application by conducting a review of the documentation provided. A validation is performed within three working days to ensure that all relevant document has been provided. If any documents have been omitted, justification must be provided to the MPA. The application will be processed by the MPA within a maximum of 60 days from the date the application is deemed to be valid. Any errors or omissions are notified to the sponsor by the MPA MPA (2015).

The MPA acknowledges receipt with a letter containing a reference number and when the processing time begins. The invoice is sent from the Department of Finance and Budget at the MPA. If issues arise during the processing of the application, the following applies:

> 'During the processing time, any discrepancies in the notification are identified. The MPA gives the sponsor one opportunity of submitting a supplementation to correct the discrepancies. This supplementation must be with the MPA within ten days. If the sponsor requires more than ten calendar days, there is the option of withdrawing the notification in order to submit a new notification later.
>
> In the renewed notification (resubmission), the MPA's requirements for additions and amendments must be met and complete documentation must be resubmitted. A new processing time of 60 days begins, the investigation notification gets a new reference number but no new notification fee is charged' MPA (2015).

Once the MPA has completed the assessment and provided approval, the clinical trial can begin as outlined below:

> 'The investigation may start when the MPA has notified that there are no objections to the investigation beginning, and that the Ethics Review Board has approved the investigation' MPA (2015).

2.8 Analysis of Failure to Comply with Regulation in this Case Study

Having completed the review of regulations and guidelines pertaining to clinical trials in Europe and Sweden, it can be stated that significant failures were identified in the case study review as outlined below.

2.8.1 Notification to the Competent Authority

There are no records of the MPA being notified about the surgeries. Paolo Macchiarini was the sponsor and, per the regulation, it is the responsibility of the sponsor to submit an application to the Competent Authority, in the country where the clinical investigation will take place, so that the validity of the research can assessed prior to the commencement of a clinical trial. In an interview on Swedish Television, Macchiarini stated that he did not know that he was the person responsible and that there were others appointed to look after such matters. The full details of that interview are available online TV 4 (2017). By not notifying the MPA, assessment and approval could not be performed as the MPA had no visibility or information that these clinical trials were being carried out.

2.8.2 Animal Studies

There is no evidence to support positive results in animal trials.

> 'Today's statement by CEPN's expert group for misconduct in research—which investigates misconduct allegations at the request of Swedish universities—is about a 2014 paper in which Macchiarini and his colleagues gave rats an oesophagus implant made from a donor oesophagus that had been stripped of its cells and "seeded" with stem cells. (Macchiarini tried the same technique on some of his human trachea patients.). The panel asked the authors to hand over the data to back up their conclusions, but despite "repeated and clearly defined requests," it received "incomplete and sporadically incorrect data." Not providing complete data to support a paper—or being unable to provide it—constitutes misconduct in itself, the panel says. But the paper also presents misleading and incorrect data and conclusions. Although the paper concludes that the implants were successful, the data the panel recovered told a different story, the expert group writes. They found that "the rats lost so much weight and deteriorated so much in condition that the experiment should have been stopped'Schneider (2017b).

2.8.3 Qualification of the Sponsor

Paolo Macchiarini's CV contained false information about his qualifications and experience and in this regard,

> 'According to Dr Mattias Corbascio, it is uncertain whether all the degrees and titles listed in Macchiarini's CV were actually authentic, and a comparison of his CVs from different time periods and sources makes it difficult to ascertain where he actually was when he obtained the titles he claimed to have. This served as one of the formal reasons for his dismissal from KI' Teixeira Da Silva (2017, p65).

Karolinska Institutet added that:

> 'It can be concluded that certain statements about positions, job titles, assignments in PM's CV do not correspond with the information provided by his previous employers. According to KI's assessment, these differences are of such a nature that they cannot solely be explained by carelessness or attributed to differences in organisations, language or academic titles. Several of the differences are substantial and cannot be considered negligible. It can thus be concluded that prior to his official employment as a visiting professor in 2010, PM intentionally provided false or misleading information in his CV' Karolinska Institutet (2016c).

2.8.4 Approval of the Ethics Committee

No approval for the surgeries was ever submitted to the Swedish Research Council:

> 'On Jan 1, 2004, a law came into force in Sweden concerning the ethical review of research conducted in human beings. This law covers research conducted in living human beings, on human cadavers, and on biological material from human beings, and the handling of sensitive personal information. The Swedish Research Council considers Paolo Macchiarini's activities to be research conducted in human beings. When research is conducted in human beings, the principal investigator (defined as the state agency or the physical or legal entity under whose organisation the research will be conducted) is obligated by Swedish law to apply for an ethical review. The application must be submitted to one of six regional ethical review boards. These review boards are individual public authorities. Neither Macchiarini, nor the Karolinska Institutet, submitted such an application' Hornlund (2016).

Macchiarini by-passed the ethical laws in place to protect human participants in clinical trials and put the lives of his patients at great risk as an ethical review for participant protection was not performed.

2.8.5 Informed Consent

As stated in ISO 14155:

> 'ISO 14155 requires all study participants to give their informed consent in writing prior to their involvement in the clinical investigation. The written consent must include an information form and a signature form. In some cases, informed consent can be provided by a legally authorised representative' UL Life and Health Science (2017).

Karolinska stated below with regard to informed consent and ethical considerations:

> 'Justification is lacking for treatment of the patients on the grounds of so-called vital indication (when a given treatment is the last resort for survival), and one misses reference to relevant animal experiments which must precede human studies that involve unproven methods. Furthermore, ethical approvals are lacking, as are appropriate informed consents'Karolinska Institutet (2016b).

2.8.6 Reporting of Adverse Events

As stated in the MDD, all serious adverse events occurring during the clinical investigation must be reported:

> 'All serious adverse events must be fully recorded and immediately notified to all competent authorities of the Member States in which the clinical investigation is being performed' European Commission (2018d).

As the MPA were not notified of the trial or of any patient outcomes, there was no visibility or traceability of the surgeries or the deaths and serious injuries that occurred with the three patients who had their surgeries performed at Karolinska Hospital.

From the above account of this case study, evidence exists that key regulation and guidelines in conducting clinical research were not adhered to and, in some cases, ignored completely. This resulted in loss of life and serious injury to the three patients who were in the care of this physician and his team in Karolinska Hospital. The other fourteen patients in other jurisdictions also had similar death and serious injury outcomes.

2.9 Other Factors that affect the protection of Clinical Trial Human Participants

2.9.1 The Role of Medical Journals in Clinical Trials

According to Smith (2006), the way medical journals publish the results of clinical trials has become a serious threat to public health. Furthermore, the publication of a clinical trial:

> 'marks the birth of new medical knowledge, and medical editors are the midwives. Although most editors would like to meet expectant researchers shortly after a clinical trial's conception (or even before), to find out who the parents are and to ensure that the trial receives high quality antenatal care, more often than not labouring researchers arrive at their offices heavily pregnant with results that require immediate, fast-track delivery. Some trials are deposited on the editor's doorstep, so that it is hard to tell who the parents are. Unfortunately, many trialists have become eugenicists, highly adept in the selective breeding of favourable results' Smith (2006).

In relation to the above quote, there is a real danger that medical editors could be selective about publishing successful results providing false or misleading information to society which is a threat to public safety. A practice of only publishing favourable results of clinical trials is misleading and questions the integrity of those clinical trials.

As stated by Teixeira da Silva and Dobránszki (2017), in their review, which includes quotes from other authors:

> 'sometimes retracted papers continue to be cited, even years after their actual retraction. As conservation biologists Cosentino and Veríssimo state,the continued citation of retracted papers is a major issue because it spreads misinformation throughout the scientific literature, providing a false premise for future research and thus seriously impacting the advancement of science. One example includes misinforming the public about the effect of a vaccine on human health, as cited by Wakefield et al., who claimed that a side-effect of the MMR vaccination was behavioural disorders, including autism (in nine out of twelve children studied), because behavioural symptoms occurred in healthy children being vaccinated. The false research paper generated more than a thousand citations, even six years after its 2010 retraction, and spurred a movement against vaccinations, thereby exposing unvaccinated children to health dangers' Teixeira da Silva and Dobránszki (2017).

From the above account, once results and information about clinical studies are cited, despite being retracted, it can take years for those papers to cease being cited. This means that having this misinformation in the public domain results in risks to society and future research.

In relation to the Macchiarini published results of his surgeries:

> ‘Six published papers authored by thoracic surgeon Paolo Macchiarini, a visiting professor at the Karolinska Institute in Stockholm, had misrepresented data from recipients of the artificial windpipes, or tracheas, reports Bengt Gerdin, a general surgeon and professor emeritus at Uppsala University in Sweden. The papers made the operation sound more successful than it was, says Gerdin, who was commissioned by the prestigious Karolinska Institute to examine Macchiarini’s clinical procedures. Gerdin also found that two of the papers described operations that had not received the necessary ethical approval, and that a seventh paper authored by Macchiarini, reporting transplants of artificial oesophagi into rats, had misrepresented results’ Check (2015).

As the evaluation of the case study of Paolo Macchiniari in this thesis demonstrates, death and serious injury were the results of a number of failures to comply with regulation and guidelines but also the publication of false data was a significant factor. By publishing distorted or biased results of clinical trials in medical journals, the integrity of future trials is questionable. More importantly this practice puts the lives of human participants in clinical trials and society as a whole at risk.

2.9.2 Conflict of Interest in Clinical Trial Research

As stated by Sengupta and Honavar (2017), conflicts of interest, also called as competing interests, are defined as

> ‘financial, personal, social or other interests that directly or indirectly influence the conduct of the author with respect to the particular manuscript. Having competing interests in a product or device under consideration is not considered unethical, however, failure to disclose such hidden interests severely jeopardise the outcomes reported in the paper’ Sengupta and Honavar (2017).

Furthermore, as stated by Schaller-Demers (2015):

> ‘It is probably human nature to both cling to and rebel against rules and regulations. On one hand we hate being told what to do and yet it is comforting to know that there is a set of rules, regulations, procedures and/or guidelines to help us navigate the system. Research administrators need to be “expert” in policy – whether it is on a departmental, institutional or sponsorship level. One cannot begin to be compliant, unless one is well versed in policy and procedure. This is no easy task. Sometimes it feels like the rules are changing on a weekly basis. However, in order to practice proper stewardship and to be able to guide researchers appropriately, administrators must rely on the prevailing and relevant rules to be successful’ Schaller-Demers (2015).

Conflicts of interest in relation to medical research can cause decisions to be made that adversely affect the health and welfare of human participants in clinical trials and the public at large. According to Dunn *et al*. (2016):

> ‘For researchers, conflicts of interest describe situations where the impartiality of research may be compromised because the researcher stands to profit in some way from the conclusions they draw. The clearest and most often discussed example of a conflict of interest in biomedical research involves doing research on a specific intervention while receiving research funding or personal remuneration from the company producing that intervention. While there are many other forms of financial and non-financial conflicts of interests, this is the type that is most often measured and discussed. In practice, every researcher holds a set of interests—financial, personal, ideological, or otherwise—which may lead to bias in the context of specific research’ Dunn *et al*. (2016).

Chapter 3: Research Methodology

3.1 Introduction

This section outlines the different options available for conducting research, along with methodologies chosen for this research. Research is categorised as either quantitative or qualitative. Quantitative research uses numbers and accuracy, while qualitative research focuses on human experience and perception. The choice of a study design is very important in any research;

> 'However, to make an appropriate choice of research design, the researcher must take into consideration firstly the concepts he/she is investigating and, secondly, their dimensions and indicators, because the design should ensure the systematic collection and analysis of data appropriate for those dimensions and indicators of the concepts studied' Onen (2016).

As stated by Barnham (2015), the 'distinctions between quantitative and qualitative market research are well rehearsed. The former measures phenomena such as brand awareness, brand penetration, product preferences and elicits numbers and percentages that, at least within the constraints of a given sample, have the status of 'facts'. Qualitative market research, in contrast, is used when more 'in depth' understanding of consumer attitudes, behaviour and motivations is required. The quantitative search for 'facts' can be usefully thought of as a series of 'what?' questions (e.g. what number or percentage of people prefer product 'A' to product 'B', or what number of people in a given population have drunk beer in the past week)'. In that regard:

> 'qualitative research is almost universally associated with 'why?' questions that reference its emergence in motivational research and the suggestion that we can get to 'deeper' levels through such interrogative strategies' Barnham (2015).

3.2 Quantitative Research

Quantitative research is concerned with a structured approach that allows control of variables and outputs. As stated by Rutberg (2018),

> 'in quantitative studies, the researcher uses standardised questionnaires or experiments to collect numeric data. Quantitative research is conducted in a more structured environment that often allows the researcher to have control over study variables, environment, and research questions. As such, quantitative research 'may be used to determine relationships between variables and outcomes. Quantitative research involves the development of a hypothesis – a description of the anticipated result, relationship, or expected outcome from the question being researched' Rutberg (2018).

3.3 Qualitative Research

Qualitative research applies a semi-structured approach and therefore allows more exploration of the research question. According to Choy (2014), 'qualitative studies address the social aspect of research. The researcher uses open-ended questions and interviews subjects in a semi-structured fashion. Interviews often take place in the participant's natural setting or a quiet environment, like a conference room'.

Figure 11 displays the characteristics of qualitative and quantitative research methods.

The Basic Characteristics of Qualitative and Quantitative

Quantitative	Qualitative
Objective	Subjective
Researcher is independent of research	Researcher interacts with research
Value free and unbiased	Value laden and biased
Impersonal voice	Personal voice
Deductive process	Inductive process
Structured	Unstructured
Accurate and reliable through reliability and validity testing	Accurate and reliable through verification
Test a theory	Develop a theory

Figure 11: The Basic Characteristics of Qualitative and Quantitative (Park 2016)

Figure 12 displays the main differences between the two methods.

The Comparison of Qualitative and Quantitative Methods

	Qualitative	Quantitative
Objective / purpose	To gain an understanding of underlying reasons and motivations; to provide insights into the setting of a problem, generating ideas and/or hypotheses for later quantitative research; to uncover prevalent trends in thought and opinion	To quantify data and generalize results from a sample to the population of interest; to measure the incidence of various views and opinions in a chosen sample; sometimes followed by qualitative research, which is used to explore some findings further
Sample	Usually a small number of non-representative cases Respondents selected to fulfill a given quota	Usually a large number of cases* representing the population of interest; randomly selected respondents
Data collection	Unstructured or semi-structured techniques, e.g., individual depth interviews or group discussions	Structured techniques* such as on-street or telephone interviews
Data analysis	Non-statistical	Statistical;* data is usually in the form of tabulations; findings are conclusive and usually descriptive* in nature.
Outcome	Exploratory and/or investigative; findings are not conclusive and cannot be used to make generalizations about the population of interest; develop an initial understanding and sound base for further decision making	Used to recommend a final course of action

Figure 12: The Comparison of Qualitative and Quantitative Methods (Park 2016).

Both qualitative and quantitative research aim to produce results that are reliable and valid. As stated below:

> 'Both quantitative and qualitative research designs seek reliable and valid results. For example, quantitative reliability is dependent on data that are consistent or stable, as indicated by the researcher's ability to replicate the findings. The qualitative method's validity of findings is paramount so that data are representative of a true and full picture of the constructs under investigation. It is a non-trivial matter to infer the behaviour of the whole from the behaviour of its parts' Park (2016).

Quantitative research designs strive to identify and isolate specific variables within the context (seeking correlation, relationships, and causality) of the study. However, qualitative design focuses on a holistic view of the topic being studied (via documents, case histories, observations, and interviews). The two methods adopt different data collection methods, as stated by Park (2016):

> 'Quantitative methods emphasize numerical data and measurable variables. Data is collected under controlled conditions in order to rule out the possibility that variables other than the ones under study can account for the relationships identified. Qualitative methods emphasize observation and interpretation. Data are collected within the context of their natural situations' Park (2016).

3.4 Mixed Methods

The evolution of the mixed methods approach allows for greater flexibility when approaching a research question. As stated by Lund (2012), in his review, which includes quotes from other authors: 'the mixed methods movement represents a blending of quantitative and qualitative methods in research, and it can be said to have been evolved historically from the notion of "triangulating" information from different data sources (Campbell & Fiske 1959; Denzin 1978; Morse 1991; Patton 1990). Mixed methods have been used in both basic and applied research, especially in the applied field of evaluation research' Lund (2012).

Figure 13 below provides a graphical overview of the key differences between quantitative and qualitative research methods.

Figure 13: Quantitative vs. Qualitative Research: What's the Difference? (Market Research Man, 2017)

Figure 14 provides an overview of interaction between both quantitative and qualitative methods.

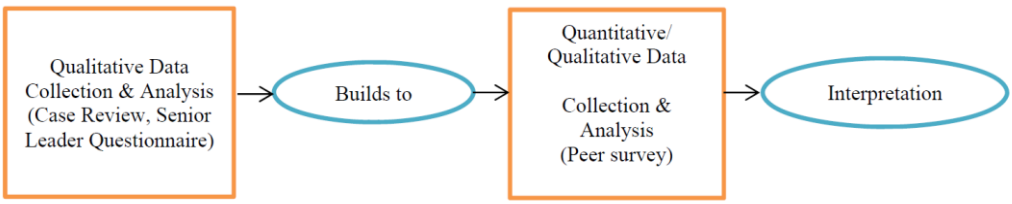

Figure 14: Exploratory Sequential Mixed Methods (Creswell, 2014)

3.5 Research Questions

This study's research questions include:

1. Evaluation of clinical trial history to determine the evolution and lessons learned from the past.
2. Evaluation of European medical device regulation to determine if it protects the welfare of human participants in clinical trials.
3. Evaluation and review of a case study to identify if weaknesses exist in the medical device clinical trial regulation and process which puts human participants at risk.
4. Identify what other factors affect the protection of human participants in medical device clinical trials.

3.6 Research Strategy

The research methodology that was chosen to address the research questions was primarily qualitative research, with some quantitative research, therefore, it is a mixed method approach, as outlined below.

3.6.1 Case Study

A case study was performed to investigate and analyse a real-life example of a process involving human participants in a clinical trial. This case study exemplifies the importance of adherence to regulation in relation to the performance of clinical research and the protection of human participants. Disregard for regulation and guidelines, in this case, resulted in loss of life and serious injury to patients involved in experimental surgeries. This case study provides a real-life example of the consequences to patients involved in clinical research that has not followed and complied with the regulation and standards that exist for protection of human life. As stated by Ridder (2017), in his review, which includes quotes from other authors:

> 'case study research scientifically investigates a real-life phenomenon in-depth and within its environmental context. Such a case can be an individual, a group, an organisation, an event, a problem, or an anomaly (Burawoy 2009; Stake 2005; Yin 2014). Unlike in experiments, the contextual conditions are not delineated and/or controlled, but part of the investigation. Typical for case study research is non-random sampling. Contrary to quantitative logic, the case is chosen because the case is of interest (Stake 2005), or it is chosen for theoretical reasons (Eisenhardt and Graebner 2007). For within-case and across-case analyses, the emphasis in data collection is on interviews, archives, and (participant) observation (Flick 2009: 257; Mason 2002: 84).

Case study researchers usually triangulate data as part of their data collection strategy, resulting in a detailed case description (Burns 2000; Dooley 2002; Eisenhardt 1989; Ridder 2016; Stake 2005: 454)' Ridder (2017).

Design tests	Case study tactics	Research phase of the tactic
Construct validity	Multiple source of evidence	Data collection
	Establish chain of evidence	Data collection
	Key informants review draft case study report	Composition
Internal validity	Pattern matching	Data analysis
	Explanation building	Data analysis
	Rival explanations	Data analysis
	Logic models	Data analysis
External validity	Theory in single case studies	Research design
	Replication logic in multiple case studies	Research design
Reliability	Case study protocol	Data collection
	Case study database	Data collection

Figure 15: Case Study Tactics for Design Tests (Tumele 2015)

3.6.2 Individual Interviews

Individual interviews from a cross section of organisations were identified: Competent Authorities, Notified Bodies, Investigative journalists, clinical professionals, and industry leaders. The interviewees were selected based on the following criteria:

1) Knowledge and expertise of clinical trial regulation – experience and knowledge of this area is limited to a small number of organisations and functions.
2) Accessibility – access to industry and regulator contacts was already established through my work.
3) Regulator Vs Industry experience – comparisons between industry and regulator perspective
4) Clinician expertise – to understand the clinical perspective of clinical trial regulation.

Interviews are usually used as a means of obtaining data and information for scientific studies Azevedo *et al.* (2017). Interviews provide the opportunity to collect qualitative data in which the researcher can use in a meaningful way Frels and Onwuegbuzie (2013).

A structured interview is organised with a set of pre-determined questions which require mostly yes or no responses. As such, the interviewer would have little flexibility. You could say that this type of interview is more of a quantitative nature. Alternatively, there is an

unstructured open-ended interview in which more meaningful information can be obtained. In conducting an unstructured interview, greater flexibility exists between interviewer and interviewee. The semi-structured interview is more flexible than the structured interview in that it allows the interviewer to probe questions to gain more depth of response Alshenqeeti (2014).

For this research, the semi-structured approach was utilised, as this allowed the flexibility to probe and extract additional relevant information, as needed. For the purpose of this research, phone interviews were chosen due to the geographical location of the participants and in the interest of time and efficiency.

3.6.3 Sampling

3.6.3.1 Case Study

Regarding the selection of cases, the case study research is not described as a sampling research. By choosing one case study, it allows the researcher to gain an in-depth understanding of that particular case. It is important that the appropriate case study is chosen to ensure that it addresses the research question Stake (1995).

In choosing one case study for the research, an in-depth understanding was obtained of the weaknesses and complexities involved in that clinical trial. The advantages of a single case study include the opportunity to gain a deep understanding of the phenomenon, identify patterns and relationships which can test the theory Ridder (2017).

The case study of Paolo Macchiarini was used as an example of how, despite regulation and guidelines being in place, human participants can suffer abuse, injury, and death when those regulations and guidelines are ignored.

3.6.3.2 Individual Telephone Interviews

Ten interviewees were purposely selected and invited to participate in a telephone interview. Interviewees came from a cross section of sources. Each interviewee was chosen for their functional and subject matter expertise, experience, and knowledge of the clinical trial process and regulation. With the exception of Bosse Lindquist and Professor Delaere, each interviewee was provided with the interview questions, prior to the interview, in order to prepare for the interview.

3.6.4 Interview Questions

Below is the interview question template, which was prepared and used when conducting the interviews. Prior to completion of the questionnaire, a pilot was conducted with a member of the Regulatory Affairs team in order to ascertain if the questions were legible and well understood. With the feedback received, some questions were revised, with more verbiage added for clarification.

Interview Questions for Qualitative Research on the Dissertation titled:

European Clinical Trial Medical Device Regulation and the Protection of Human Participants

Name:
Job Title
Organization:

Note: All information received is confidential and your name will not be reported in the dissertation.

Question 1

In addition to the MDD/MDR, what national regulations are followed for Clinical Trials in your region? Are there any specific or significant differences between the National and European requirements?

Response:

Question 2

Who initiates the need for a Clinical Trial? Who monitors the overall process?

Response:

Question 3

How are human participants recruited normally for the trials?

Response:

Question 4

Are Consent forms completed and documented for every human participant in Clinical trials? Who reviews and approves the suitability?

Response:

Question 5

How are the risks versus benefits explained to the clinical trial participant?

Response:

Question 6

How are participants privacy protected?

Response:

Question 7

Who are the main stakeholders involved in reviewing and approving a clinical trial?

Response:

Question 8

What process is in place to monitor the progress and results of the clinical trial performed?

Response:

Question 9

How are adverse events reported and monitored? Who is responsible for monitoring and reporting?

Response:

Question 10

What triggers a suspension or cessation of a clinical trial? Who is responsible to take the final decision?

Response:

Question 11

What is the process if death or injury occurs to a participant? Who is responsible to review and escalate?

Response:

Question 12

Are clinical trials conducted at (Please tick what applies) :

- One centre
- Multi centres within one region
- Multi centres and regions

Additional Comments:

Question 13

In multi-regional trials, how are the global regulations controlled and complied with? Who oversees all the centres for regulation compliance?

Response:

Question 14

How is information on adverse events and progress of the study between multi centre/regional trials shared?

Response:

Question 15

Are results of clinical trials available publicly and by which means?

Response:

Question 16

Are successful and unsuccessful cases publicly available via Medical Journals? If not, by what other means?

Response:

Question 17

If medical journals are used, how are results validated? Who is responsible for managing the articles written?

Response:

Question 18

What involvement has your Competent Authority and Notified Body in the clinical trial process, once the Clinical Trial is approved?

Response:

Question 19

Who appoints the Ethics Board for the Clinical Trial?

Response:

Question 20

Who approves the healthcare professionals qualifications for clinical trial participation?

Response:

Question 21

What training is provided to key stakeholders and healthcare professionals in the clinical trial process?

Response:

Question 22

Who is involved in sponsorship for the clinical trials?

- Industry
- Healthcare Facilities
- Other, please state

Response:

Question 23

Do you think that when compared with the Medical Device Directives that the Medical Device Regulation will provide more protection for human participants in clinical trials.

Question 24

Please provide your rationale for your answer to question 23.

Response:

Thank you for participating in my interview.

3.6.5 Interview with Bosse Lindquist

Further to the email request to Bosse Lindquist, a phone call was arranged for 24th March 2018. We discussed the Paolo Macchiarini case in some detail and an explanation was provided of the interest in the case based on the research. Bosse stated that a lot of the scientific articles had been retracted that Macchiarini had published about his surgical experiments. He said that Macchiarini had been acquitted of charges on the basis that the courts could not determine if his patients would not have died despite the surgical procedures performed. The case will be re-opened this Summer 2018 amid growing concerns about the actions and detrimental outcomes for the patients involved. He also referred me to the clinical trial – ASPIRE – and stated that it had since been suspended based on the findings presented in relation to the Macchiarini case. He said that none of the experiments had been approved by the MPA. He also referred me to Leonid Schneider at 'For Better Science', as he was closely following and documenting the case also. He advised me to use the links available on Leon's website for further information also. Bosse is also writing a book on this case, which will be published in September 2018.

3.6.6 Professor Pierre Delaere

Pierre Delaere is a professor for respiratory surgery at KU Leuven, Belgium, and one of the earliest and fiercest critics of Paolo Macchiarini. As cited:

> 'The engineered trachea was represented as a regenerated trachea after applying bone marrow cells to a de-cellularised or synthetic scaffold. There is no scientific foundation whatsoever to assume why stem cells would support airway tissue regeneration in this setting. In addition, even if a trachea-like organ would be generated, it would irrefutably fail after implantation if adequate blood supply had not been restored. As expected, the implantation of de-cellularised and synthetic scaffolds resulted in extremely high morbidity and mortality rates. At this point in time, this form of airway regeneration should be regarded as hypothetical and scientifically unfounded' Delaere and Raemdonck (2016).

Professor Delaere wrote to the KI Ethics Council with his concerns about Macchiarini's conduct, but his claims were dismissed by KI's professor of Healthcare Ethics, Niels Lynöe. Delaere advised: "one of the biggest lies in medical history, because you are doing something that is impossible from a theoretical point of view and not grounded in medical trials. You do new things to people which are destined to fail, so for me this is a criminal act. This is medical torture" Schneider (2016).

Pierre Delaere commented: ‘If I had the option of a synthetic trachea or a firing squad, I’d choose the last option because it would be the least painful form of execution’ The Experiments (2016).

Professor Delaere was contacted by email and asked if he would be willing to conduct an interview. He responded in a timely manner but declined and referred to Bosse Lindquist who he stated was closely following the case. Professor Delaere’s rationale for not providing information was stated as lack of time to provide such information and that a lot of the information needed is already available on the internet.

3.6.7 Data Analysis

Data analysis is concerned with the task of examining data to address the hypotheses and research question Creswell (2014). The approach in quantitative data analysis is that the researcher tests one or more hypotheses. The goal is to identify if any relationship is observed between variables and if there are any statistical significance. Data analysis in qualitative research involves a process of creating explanations which are meaningful and consistent from the results obtained in the study Gelo, *et al,* (2008).

Some criticisms have arisen in relation to case study research in that the subjectivity of the researcher can have a strong influence on the result obtained. There is a danger because of this that the study could be biased Tumele (2015).

Chapter 4: Analysis and Discussion

This section presents the results from the literature review and the individual interviews, and then reviews the elements of the case study in relation to the research questions asked. The aim of the research was to investigate the following questions:

1. Evaluation of clinical trial history to determine the evolution and lessons learned from the past.
2. Evaluation of European medical device regulation to determine if it protects the welfare of human participants in clinical trials.
3. Evaluation and review of a case study to identify if weaknesses exist in the medical device clinical trial regulation and process which puts human participants at risk.
4. Identify what other factors affect the protection of human participants in medical device clinical trials.

4.1 Summary of Results

4.1.1 Research Question One - Evaluation of Clinical Trial history to determine the evolution and lessons learned from the past.

As explored in the literature research, clinical research has advanced significantly and has brought benefits to patients and society as a whole. New technologies and therapies that combat disease and prolong life have been the driving force, for the most part, in clinical research. Human participation has been of key importance in the advancement of new technologies and in combating disease and prolonging life.

The first accounts of clinical trials revealed the evolution of clinical trials as related to drug therapies. Medical device innovations, evolved, for the most part, from a need to invent a solution to, or address a medical emergency or disease. An example of this is the invention of the stethoscope New York Times (2012). This would indicate that the evolution of clinical trials is more related to experiments for drug therapies. Clinical trials for medical devices have evolved and mirrored those drug trials.

Drug trial evolution is accountable to pioneering physicians, such as Ambroise Pare, James Lind and Austin Flint, who paved the way for the advancement of scientific knowledge and clinical trials that have saved lives and helped to advance treatments to combat and treat diseases that we have today Bhatt (2010)

The first clinical trial, as conducted by the surgeon Ambroise Pare, came about by chance and necessity rather than a planned approach. While treating wounded soldiers, the supplies of oil became depleted, and he had to create a digestive treatment as an experiment to address the shortage. He applied the digestive treatment to some soldiers and oil to the others as an experiment. Pare discovered that his digestive treatment revealed better results that the original oil treatment. This was a significant discovery Bhatt (2010). Following on from that first trial, and another 200 years on, James Lind was the first physician to conduct a controlled clinical trial. To combat the rate of deaths from scurvy, whilst working on a ship, Lind planned a comparative trial in which he treated some patients with cider, elixir, vinegar, sea water compared with provision of oranges and lemons. The patients who took the oranges and lemons were able to return to duty within six days. Despite this important discovery, due to the expense of the fruits, the diet was not recommended for another fifty years by the British Navy Bhatt (2010). Austin Flint invented the concept of the placebo which involves comparing an active treatment to a dummy treatment to establish results. This was another significant discovery in advancing the clinical trial process Bhatt (2010). Advancing further, the introduction of the first double blind control trial in 1943 and the first randomised curative trial 1946 by the Medical Research Council set the model of clinical trial design which we see today Bhatt (2010).

Medical research has a dark history too and, as evident during World War II, the Nazis inflicted unnecessary suffering and death on the Jewish race in the name of medical research Weindling (2015). The lives of those who were forced to participate in this research, without consent, were deemed worthless and unnecessary death and suffering was inflicted on the participants in these trials. This was demonstrated again in relation to the Tuskegee syphilis study on black males, which continued for forty years, despite the introduction of the Nuremburg code during that timeframe. Researchers withheld treatment from the participants when, in 1947, penicillin became the standard treatment for syphilis Nellhaus and Davies (2017). The Tuskegee study exemplifies the necessity of providing protections for research subjects and is a reminder of the fact that human dignity and welfare must never be compromised for science. The cruel and unnecessary experimentation on concentration

camp prisoners were publicised during the Nuremberg Trials in Germany in the aftermath of World War II. The Nuremberg Code and the Declaration of Helsinki formed a basis for establishing the principles of free and informed consent in order to avoid exploitation in scientific experiments involving human participants. The Declaration of Helsinki has been recognised as one of the most authoritative statements on ethical standards for human research in the world Nellhaus and Davies (2017).

We have come a long way since those first experiments and many milestones in the history of medical research has achieved significant benefits for the society. However, we must never forget the past in order to ensure that clinical research continues to have value, maintain respect for human dignity, follow principles of informed consent, and be compliant with regulation, which protects, not only the lives of human participants, but also society as a whole.

4.1.2 Research Question Two - Evaluation of European Medical Device Regulation to determine if it protects the welfare of human participants in Clinical Trials.

4.1.2.1 Literature Review

The regulation of medical devices in Europe is the task of the European Commission. Legislation covers implantable, non-implantable, and in vitro diagnostics medical devices. The MDD has been replaced by the MDR which was approved in April 2017. The MDR have very clear and defined rules which are binding across all European member states European Commission (2018c). In relation to rules on clinical evidence, the MDR has strengthened the significance of clinical evidence and approval of clinical trials European Commission (2018c). Changes from the directives to regulation came about due to weaknesses in the regulatory system, which resulted in serious adverse events occurring with medical devices manufactured by, for example, the Poly Implant Prothèse and the De Puy metal implant Van Norman (2016) and Cohen (2011).

Compared with drugs, a clinical trial is not required for all medical devices. Clinical trials for medical devices are performed in relation to risk classification but for drugs a clinical trial is always required. The MDR requires that all class IIb and III devices have a clinical investigation performed, unless there is sufficient justification for not doing so European Commission (2018a). The national competent authority in which the trial will be performed must be notified prior to initiating a trial. A clinical trial should not commence without the approval of the competent authority and the ethics committee. The competent authority

requires detailed documentation, including informed consent forms, to be submitted for review prior to clinical trial initiation. The MDD and MDR requires the clinical trial to be conducted per the harmonised standard EN ISO 14155:2011 which provides detailed requirements for the protection of human participants Cenelec (2017).

The European Commission provides a range of guidance documents, known as MEDDEV's which promote a common approach to performing clinical trials European Commission (2018e). The importance of informed consent is embedded into the MDR as a requirement European Commission (2018a).

The literature review of European regulation provides evidence of significant regulation and guidance for performing clinical trials for medical devices, as provided in the MDD, MDR, MEDDEV's, and EN ISO 14155:2011. The regulation determines requirements prior to the product being legally placed on the market. All devices must adhere to stringent regulations depending on the degree of risk. Compared to the MDD, the MDR has put significantly more focus on clinical evaluation and investigation both prior to release to market and post-market. Strict provisions in relation to clinical investigations involving human participants have been put into the new regulation, which establishes laws in relation to areas such as clinical benefit, rights and safety of human participants, informed consent, qualifications of professionals, care of vulnerable participants, and the medical care requirements during any clinical investigation.

European regulation has evolved and the research demonstrates that the health and well being of human participants in clinical trials are protected through compliance with the European directives and regulation, MEDDEV guidelines, and EN ISO 14155. However, regulation cannot cover every conceivable scenario, and challenges still exist with ensuring that the regulations are adhered to and followed. Regulations, if by-passed and ignored, result in loss of life and serious injuries to the participants involved in clinical trials.

4.1.2.2. Results of Individual Interviews

Sample Size and Type

A sample size of 10 interviewees were chosen from the following sectors:

- Competent Authorities: 3
- Notified Bodies: 2
- Industry Professionals: 3 (Clinicians and clinical managers)
- Investigative Journalist: 1
- Clinical Physician: 1

All interviewees remained anonymous, except for Bosse Lindquist and Professor Delaere.

Figure 16 below provides a breakdown of interview type and sample size.

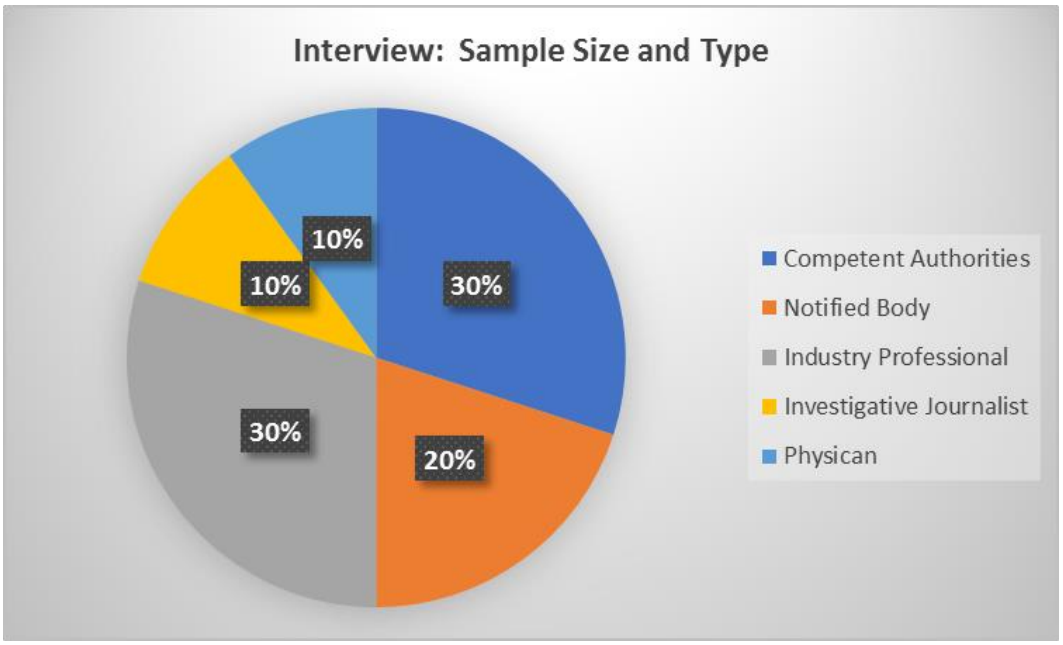

Figure 16: Interview Sample Size and Type

Response Rate

Out of 10 requested interviews, 2 interviews were declined by the notified bodies. One interview was declined by Professor Delaere (clinical physician). The rationale provided by the Notified Bodies was that they are not allowed to engage in such interviews, as it constitutes a conflict of interest and would be seen as consultancy, which is forbidden in their protocol. The rationale provided by Professor Delaere was that he currently did not

have sufficient time to engage in such an interview, and he thus referred me to Bosse Lindquist (investigative journalist). Professor Delaere also stated that a lot of the information, which documents his comments and opinions, regarding the Macchiarini case is well documented on the internet.

Figure 17 provides an overview of the interview response rate achieved.

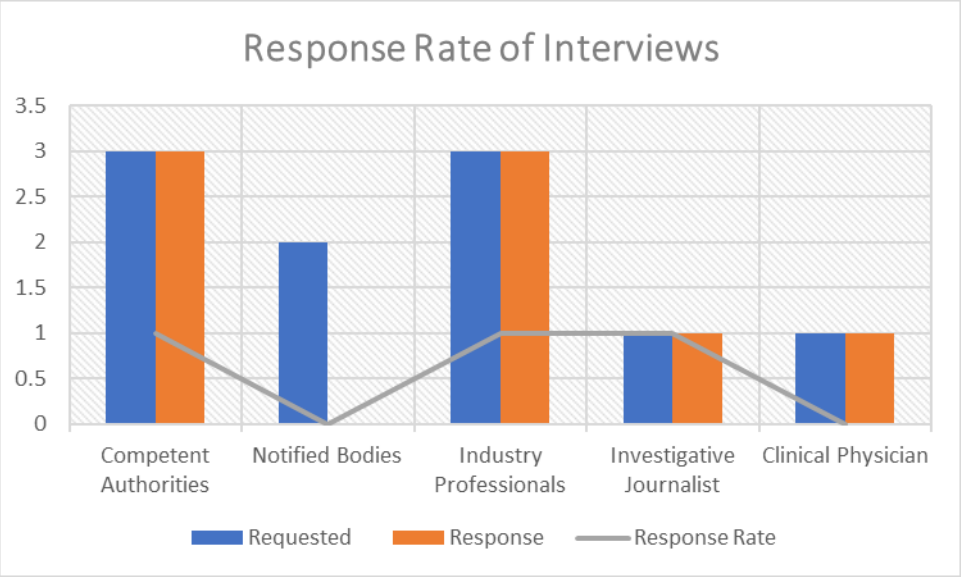

Figure 17: Response Rate of Interviews

Format and Length of Interviews

Six interviewees were furnished with the list of questions prior to the interview. The interview with Bosse Lindquist was unstructured and therefore no list of questions was submitted in advance. Professor Delaere declined to participate and therefore questions were not forwarded to him.

Each interview was approximately one hour in length.

Recording Method

Six interviews were conducted via Webex/Dial-in, which allowed the interviewee to view the responses being documented as the interview was being conducted. The interview with Bosse Lindquist was conducted by phone.

4.2 Results of Interviews

In order to condense the results of the 24 questions addressed in the interviews, I have grouped together the results of the interviews into key themes. A snapshot of quotes from the interviews is also included in the results below. Full transcripts of all interviews are contained in Appendix 2.

4.2.1 Theme 1: European Regulation

A high level of consistency of response was evident across all interviews, as outlined below. Consistency and adherence to the regulations can provide a highly effective and robust regulatory framework. The MDR has brought significant improvements that aim to give greater protection, healthcare and access to compliant and safe products that are placed on the market. The requirements for clinical trials of medical devices are significantly enhanced and include many specific requirements to ensure that participants involved in clinical studies are appropriately protected. The regulation question was addressed in Question 1: (In addition to the MDD/MDR, what national regulations are followed for Clinical Trials in your region? Are there any specific or significant differences between the National and European requirements?).

> HPRA, Ireland responded: *'Apart from our internal procedures, HPRA do not follow any specific guidelines in addition to the MDD/MDR and the transposition into Irish law'.*
>
> The MPA, Sweden, responded: *'The Swedish Medical Products Agency (Läkemedelsverket) regulates medical devices by three different regulations: Läkemedelsverkets föreskrifter (LVFS 2003:11) om medicintekniska produkter (medical devices), Läkemedelsverkets föreskrifter (LVFS 2001:5) om aktiva medicintekniska produkter för implantation (active implantable medical devices), and Läkemedelsverkets föreskrifter (LVFS 2001:7) om medicintekniska produkter för in vitro diagnostik (in vitro diagnostic devices). In-house medical devices are regulated by The National Board of Health and Welfare (Socialstyrelsen)'*.
>
> Industry Professional (1) responded: *'There are no other regulations. ISO14155 standard is applicable'*.
>
> Industry Professional (3) responded: *'EN ISO 14155 is the applicable standard for clinical trial good clinical practice. The MDD/MDR is the European regulation to be followed in addition to national laws per European country'*
>
> MHRA, UK responded: *'The medical device regulation 2002'*.

The degree of consistency among the interviewees was very high, as each quoted compliance with MDD/MDR, ISO EN 14155 and national laws. Figure 18 demonstrates that all

interviewees comply with the MDD/MDR, ISO EN 14155 and additionally the UK and Sweden have national laws specific to their countries which meet the MDD/MDR requirements. Consistency in regulation protects public health, thus, welfare and laws and guidelines, if adhered to, are key in ensuring safe and quality products are used in/on humans and placed on the market.

Figure 18 below provides results of responses to Question 1.

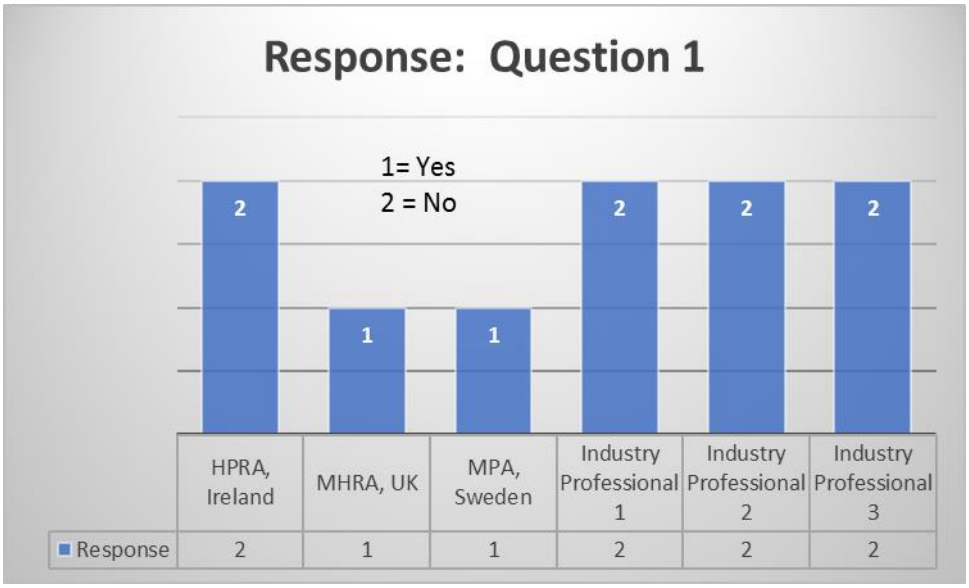

Figure 18: Response Question 1

4.2.2 Theme 2: Informed Consent

All respondents stated that, for all clinical trials, an informed consent document must be obtained and retained by the physician and the risks/benefits must be explained to the participants by the physician. The industry respondents stated that regular visits are conducted to ensure that the clinical trial protocol, including the retention of consent forms are checked. The subject was addressed in Question 4: (Are Consent forms completed and documented for every human participant in Clinical trials? Who reviews and approves the suitability?)

> HPRA, Ireland responded: *'Yes all patients recruited into a study must be consented in line with ISO 14155, in addition to the requirements of the Declaration of Helsinki. The consents forms and patient information leaflets are reviewed and approved by the ethics committee and the HPRA'.*

MPA, Sweden responded: *'Yes. For medical devices, the MPA assesses the consent forms and decides whether they are appropriate. The Ethics committee may likewise be involved in questions concerning the consent'.*

Industry Professional (1) responded*: 'Yes, consent forms are completed for every human participant (by the legal representative or guardian if the patient is unable to or too young. However, for retrospective anonymised data, the ethics committee may grant a waiver, e.g. Historical video data that is anonymised by the hospital prior to providing the information to the Sponsor. Ethics has to approve the waiver. Review and Suitability: Pre-market study – Competent Authority review, Ethics Committee review and would have to approve. Post market study Ethics Committee reviews and approves'.*

Industrial Professional (3) responded: *'Yes, all participants have to complete a Consent Form. The risks and benefits have to be explained to the participant prior to the form being completed and signed. The physician is responsible, normally, for completing this task. The Ethics Committee have to review and approve the consent forms'.*

The informed consent of human participants is of vital importance in protecting the rights and welfare of human participants in clinical trials. The physician has the key role of explaining the risks, benefits, and options related to inclusion in the clinical trial in lay person's terms, in order that the participant can make an informed decision and provide consent to participate in the trial. As demonstrated by Figure 19, this question had 100% consistency.

Figure 19 provides the results of response to Question 4.

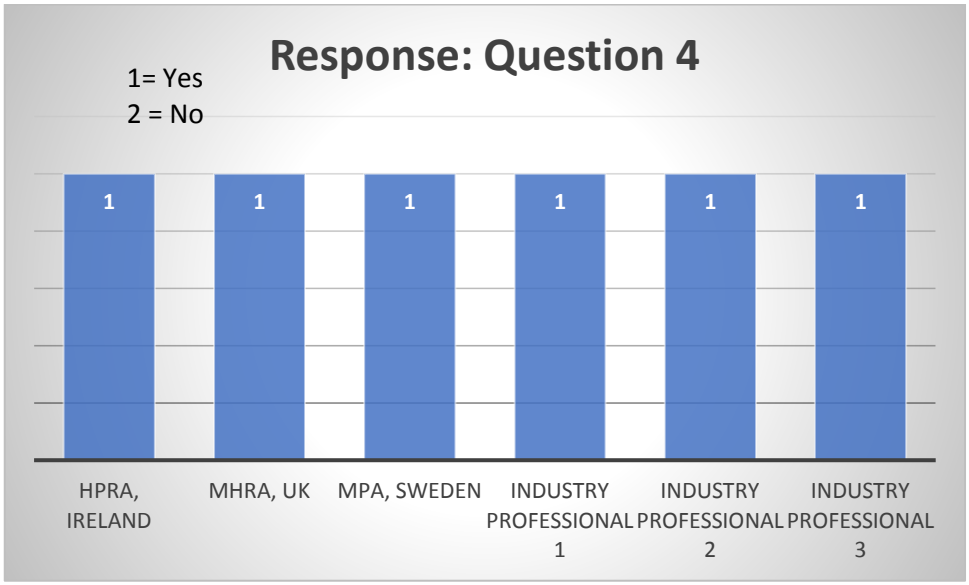

Figure 19: Response Question 4

4.2.3 Theme 3: Public Visibility of Clinical Trials

The response to this question was variable. The subject was addressed in Question 15: (Are results of clinical trials available publicly and by which means?)

> HPRA, Ireland responded: *'All clinical investigations must be conducted in accordance with the Declaration of Helsinki which provides for the research registration and publication and dissemination of results'.*
>
> MPA, Sweden responded: *'Under MDD and individual national regulations there is no requirement for sponsors to make results public: however, a study report has to be produced. Under the MDR, it will be mandatory to publish this in Eudamed, which will be available for the general public. In case a sponsor decides to publish the results of a completed trial, this is at the time generally made public by way of a scientific paper'.*
>
> Industrial Professional (2) responded: *'Yes, on clinicaltrails.gov website – the clinical trial has to be announced and the results posted'.*
>
> Industrial Professional (3) responded: *'On clinicaltrials.gov website'.*
>
> MHRA, UK responded: *'This is at the discretion of the manufacturer/academic body'*

The responses to this question suggest variances in approach by country, with national transposition of the MDD allowing for variation in how the results of trials are reviewed and monitored for the public. With the MDR, there will be no further variation, as all clinical trial results will have to be published on the EU portal – Eudamed. Figure 20 demonstrates the variances which were noted in the U.K. and Sweden.

Figure 20 provides the results of the response to question 15.

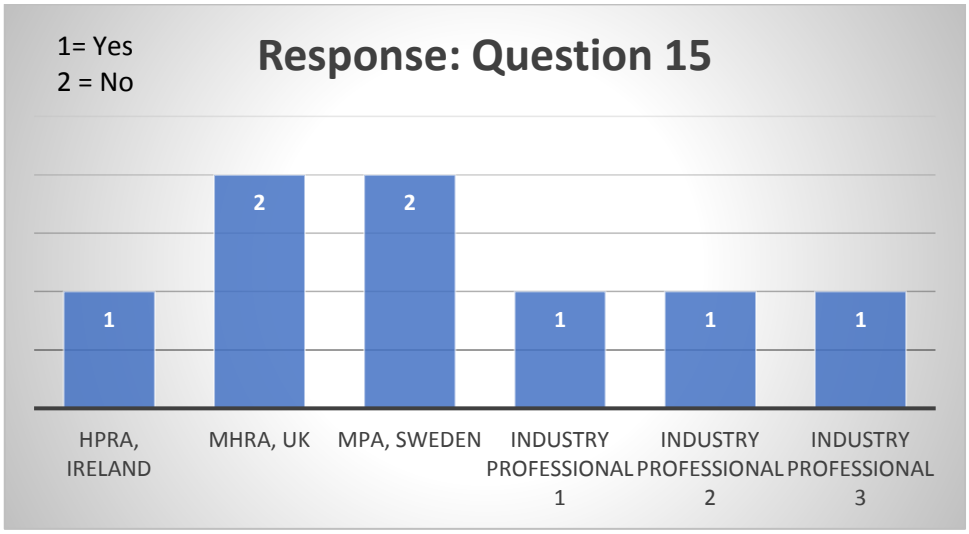

Figure 20: Response Question 15

4.2.4 Theme 4: Responsibility for Initiating a Clinical Trial

The final decision to initiate a clinical trial is with the sponsor. The Competent Authority reviews and, if satisfied, based on the MDD/MDR , EN ISO 14155, and national laws, will approve the initiation of the clinical trial. The sponsor monitors the progress of the trial and the physician chooses the specific patients that meet the requirements of the clinical trial protocol. The subject was addressed in Question 2: (Who initiates the need for a Clinical Trial? Who monitors the overall process?)

> HPRA, Ireland responded: *'In general, the sponsor of a clinical study is responsible for deciding if a CI is needed and for the subsequent monitoring. As detailed in EN ISO 14155, there are a range of stakeholders, such as Competent Authorities, Research and Ethics Committees, Principal Investigators who each have monitoring roles'.*
>
> MPA, Sweden responded: *'The sponsor initiates the clinical trials. The sponsor is responsible for his clinical trial, including it's monitoring'.*
>
> Industrial Professional (2) responded: *'The sponsor identified the need for clinical evidence in liaison with the Notified Body. The final decision to initiate the clinical trial is with the sponsor'.*
>
> Industrial Professional (3) responded: *'The sponsor'.*
>
> MHRA, UK responded: *'The initiation of a trial is lead by manufacturers of medical devices, clinicians/academics mainly. MHRA assesses applications and any amendments, MHRA also monitors adverse incidents and reviews the final report'*

Consistency was revealed across all interviewees. The sponsor has the overall responsibility for the entire clinical trial and must comply with the regulation and liaise with the regulators, ethics committees, and key stakeholders to ensure the health and safety of the human participants. Figure 21 demonstrates the consistency of the compliance to regulation and guidelines.

Figure 21 provides results of response to Question 2.

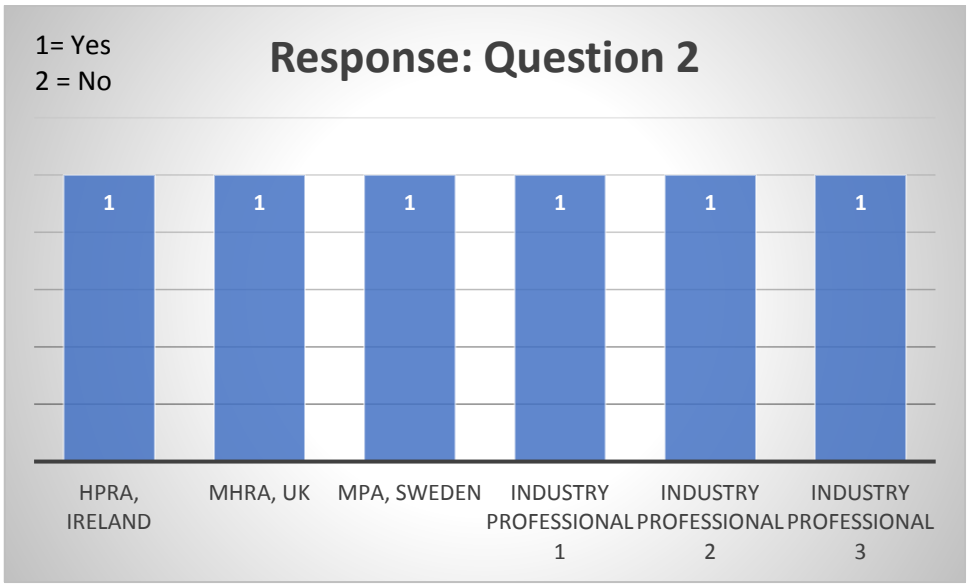

Figure 21: Response Question 2

4.2.5 Theme 5: Medical Journals

Industry professionals stated that articles are normally written by physicians/clinical professionals, but it would be the industry standard to have a clause in the protocol which states that articles / results of trials must be reviewed and validated by the sponsor, prior to publication. The Competent Authorities interviewed returned varying responses, with some not commenting on this subject at all. The was addressed in Questions 16 and 17: (16) Are successful and unsuccessful cases publicly available via Medical Journals? If not, by what other means? (17) If medical journals are used, how are results validated? Who is responsible for managing the articles written?)

> HPRA, Ireland responded: *'The HPRA cannot comment on the representativeness of published journals (response to question 16). 'The HPRA cannot comment on the validity of published journals' (response to question 17).*
>
> MPA, Sweden responded: *'In case the sponsor decides to make the results of a trial public, the usual means are by e.g. publication in a scientific journal, or as a presentation or poster presented at a scientific medical meeting'(response to question 16). 'The MPA cannot categorically answer this question. Papers in medical journals are as a rule peer reviewed by a number of expert reviewers; if a paper is published in that manner, then it will have been validated by the reviewers, and accepted for publication after scientific scrutiny. The quality of this scrutiny itself is dependent on decisions by the publisher. Obviously, if a paper is published without a peer review, then the results presented constitute the interpretation of the sponsor. In this case, it*

will be up to the reader to decide what attitude to take concerning it' (response to question 17)

Industrial Professional (1) responded: *'All clinical studies have a report at the conclusion and if accepted by a journal, publication. If industry sponsored, the MDT review and approve the report. If physician study, Medtronic will review for intellectual property only' (response to question 16). 'Whoever is the sponsor of the study validates the results. The sponsor would be the author (medical writer)' (response to question 17).*

Industrial Professional (3) responded: *'Physicians are usually the authors of medical journal articles. For Medtronic, they are not allowed to publish unless the article is reviewed by Medtronic'.*

MHRA, UK responded: *'This is at the discretion of the manufacturer/academic body'.*

As demonstrated in Figure 22, none of the Competent authorities could provide comment to this question. The industry professionals all agreed that the sponsor is responsible for reporting results of a clinical trial. If industry sponsored, they will review and approve. If the sponsor is a physician, industry may review for intellectual property only.

Figure 22 provides results to response to Questions 16 and 17.

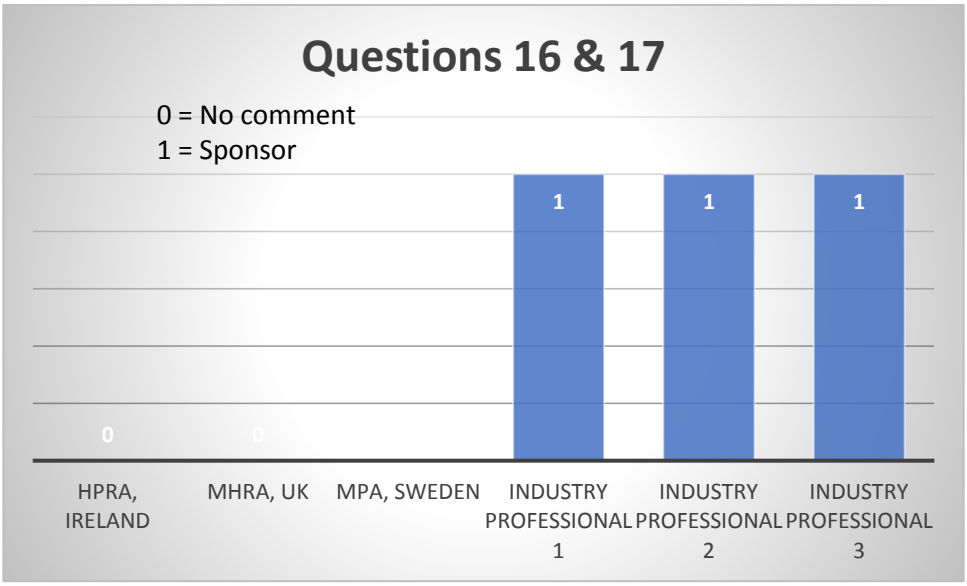

Figure 22: Response Questions 16 & 17

4.2.6 Theme 6: Qualifications of the Healthcare Professional in Clinical Trials

The healthcare professional/physician should be appropriately qualified, as per EN ISO 14155, to ensure that they are able to perform the tasks involved in conducting the clinical trial. This was addressed in Question 20: (Who approves the healthcare professional qualifications for clinical trial participation?)

HPRA, Ireland responded: *'ISO 14155 states that all parties participating in the conduct of the clinical investigation shall be appropriately qualified by education and/or experience to perform their tasks and this shall be documented appropriately'.*

MPA, Sweden responded: *'Based on the CV and other relevant information the MPA does this as far as Sweden is concerned. The qualifications are regulated in Läkemedelsverkets föreskrifter, bilaga 10, 2.3.6'.*

Industrial Professional (2) responded: *'The sponsor is responsible and the criteria is based on the Clinical Trial protocol, type of profession, cases performed. Per EN ISO 14155, the sponsor will perform a site qualification visit to ensure that the hospital is qualified to perform the clinical trial'.*

MHRA, UK responded: *'MHRA review CVs of any principle investigator'.*

As Figure 23 demonstrates, all interviewees responded by stating that the sponsor is responsible except for the MPA which state that they are responsible to review and approve.

Figure 23 provides results to the response to Question 20.

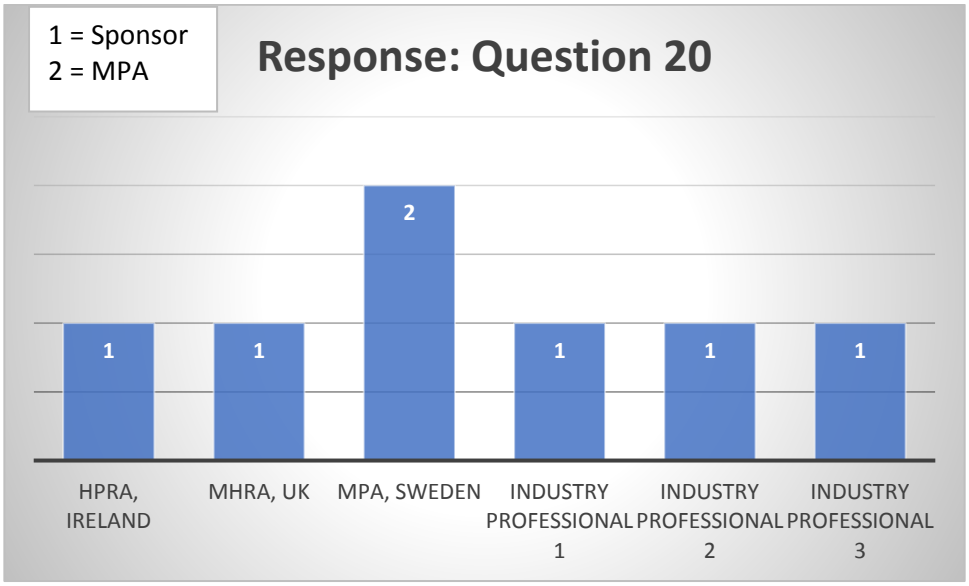

Figure 23: Response Question 20

4.2.7 Theme 7: Clinical Trial Sponsorship

Industry are the main sponsors of clinical trials. In some cases, physicians may be requested by their governments to initiate a clinical trial and, in these cases, the government will fund the trial. This is addressed in Question 22: (Who is involved in sponsorship for the clinical trials? Industry, Healthcare Facilities, Other, please state)

HPRA, Ireland responded: *'For 'clinical investigations', these can be carried out by all of the above and also by healthcare practitioners'.*

MPA, Sweden responded : *'Any of the three mentioned above. A sponsor must have the necessary qualifications to conduct a trial in accordance with the regulatory requirements'.*

Industry Professional (1) responded: *'Industry, Advocacy Groups, Institution Trusts or physicians'.*

Industrial Professional (3) responded: *'Mostly industry and some physicians'.*

MHRA, UK responded: *'Various'*

Figure 24 demonstrates 100% consistency in response to this question.

Figure 24 provides results to response to question 22.

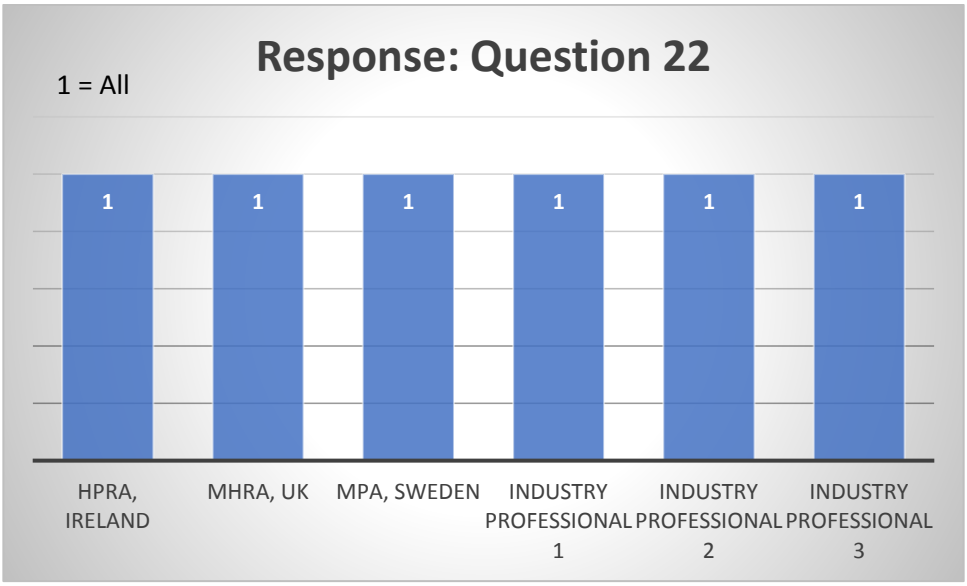

Figure 24: Response Question 22

4.3 Research Question Three - Evaluation and review of a case study to identify if weaknesses exist in the Medical Device Clinical Trial regulation and process which puts human participants at risk

The case study of surgical experiments conducted by Paolo Macchiarini are documented. A review of his profile revealed certain fraudulent information in relation to his medical and professional qualifications. Three patients had surgeries performed at the prestigious Karolinska Hospital in Sweden, where Macchiarini was a visiting professor from 2010 to 2013, before he continued a research contract, until February 2016.

The accounts of the total of seventeen patients who underwent the trachea surgeries are documented in Section 5.2. What follows are the key areas in this case study where the regulations were not complied with:

4.3.1 Key Area 1: Professional Qualifications of Physician

As stated in the MDD, which was the directive in place at the time of this case study:

> 'The investigations must be performed under the responsibility of a medical practitioner or another authorised qualified person in an appropriate environment. The medical practitioner or other authorised person must have access to the technical and clinical data regarding the device' European Commission (2018a).

When compared with the MDR:

> 'The investigator shall be a person exercising a profession which is recognised in the Member State concerned as qualifying for the role of investigator on account of having the necessary scientific knowledge and experience in patient care. Other personnel involved in conducting a clinical investigation shall be suitably qualified, by education, training or experience in the relevant medical field and in clinical research methodology, to perform their tasks' European Commission (2018a).

From the account of Macchiarini's profile, it was suggested that he falsified some of his academic credentials on resumes. The documentary by Bosse Lindquist revealed also that Harriet Wallbert, who was the vice-chancellor of the Karolinska Institute, pushed through his appointment, despite the fact that he had very negative references and dubious claims on his resume. The qualifications of the physician must be appropriate for the clinical trial being conducted. As such, qualifications and resumes should always be scrutinized and verified by the investigation site as part of the overall clinical trial plan. Failure to do so, as demonstrated in the case study, can result in loss of life and serious injury to participants involved in clinical research.

4.3.2 Key Area 2: Approval of the Ethics Board

As stated in the MDD:

> ‘Member States may however authorise manufacturers to commence the relevant clinical investigations before the expiry of the period of 60 days, insofar as the relevant ethics committee has issued a favourable opinion on the programme of investigation in question, including its review of the clinical investigation plan’ European Commission (2018a).

When compared to the MDR:

> ‘an ethics committee, set up in accordance with national law, has not issued a negative opinion in relation to the clinical investigation, which is valid for that entire Member State under its national law’ European Commission (2018a).

As revealed in the documentary by Bosse Lindquist, there was no approval sought or given by Stockholm’s ethical review board, which was based at Karolinska. The transplant surgery constituted clinical research and therefore compliance with EU regulation and national policies should have been followed which would have prevented the negative patient outcomes.

Assessing the risk-benefit to participants is the main responsibility of an ethics committee, who give final approval for implementation of any clinical trial proposal. The safety and well-being of the human participant in clinical trials, and as stipulated by European law, must be a key consideration before a clinical trial can commence.

4.3.3 Key Area 3: Approval by the Competent Authority in Sweden – MPA

As stated in the EN ISO 14155 documented in Appendix 3:

> ‘Clinical investigations conducted under ISO 14155 cannot commence until written approval has been provided by the investigation’s ethics committee and, if required, the relevant regulatory authorities where the clinical investigation is being conducted’. When compared with MDR Article 62, Section 4(a): ‘the clinical investigation is the subject of an authorisation by the Member State(s) in which the clinical investigation is to be conducted, in accordance with this Regulation, unless otherwise stated’ UL Life and Health Sciences (2017).

As revealed in the case study, the MPA were not notified and, therefore, did not approve the trial. Additionally, adverse events which occurred with the patients were not notified to the MPA. In order for the Competent Authority to establish if the clinical trial complies with all European and national laws, they must be notified, in order to review and decide on approval.

4.3.4 Key Area 4: Informed Consent

As stated in the regulation EN ISO 14155 documented in Appendix 3:

> 'ISO 14155 requires all study participants to give their informed consent in writing prior to their involvement in the clinical investigation. The written consent must include an information form and a signature form. In some cases, informed consent can be provided by a legally authorised representative. The principles of informed consent are embedded in the Nuremburg Code and the Declaration of Helsinki and forms the basis for the assurance of the health and well-being of all human participants in clinical trials. The aim of informed consent is to provide sufficient information to a potential human participant, in a way which is easily understood a voluntary decision can be made on whether or not to participate in the research study' UL Life and Health Sciences (2017).

As revealed in the case study, the surgeries were being performed under the title of compassionate use and Macchiarini claimed that he wasn't really doing clinical research but just caring for his patients which over-rode the basic principles of patient safety and informed consent. The responsibility of conducting clinical trials ethically are with the people involved in the clinical trial. All stakeholders involved must understand their obligations and should not abuse their power for personal benefit. The rights, safety, and well-being of clinical trial participants should always override the interest of science and society, to avoid any possible abuse in the name of social cause.

4.3.5 Key Area 5: Clinical Device Safety

As stated by the MDD:

> 'All the appropriate features, including those involving the safety and performances of the device, and its effect on patients must be examined' European Commission (2018a).

When compared to the MDR:

> 'to establish and verify the clinical safety of the device and to determine any undesirable side-effects, under normal conditions of use of the device, and assess whether they constitute acceptable risks when weighed against the benefits to be achieved by the device' European Commission (2018a).

Furthermore, it states:

> 'the investigational device(s) in question conform(s) to the applicable general safety and performance requirements set out in Annex I apart from the aspects covered by the clinical investigation and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the subjects. This includes, where appropriate, technical and biological safety testing and pre-clinical evaluation, as well as provisions in the field of occupational safety and accident prevention, taking into consideration the state of the art' European Commission (2018a).

There were no documented accounts that any pre-testing was performed to identify clinical safety or a risk assessment of the clinical benefits of the technology in the case study in this research. Medical devices technology continues to grow, offering technological advances in the combat and treating of diseases. However, these advances may also carry predictable, as well as unforeseen, risks, which, in some circumstances, may lead to immediate life-threatening consequences. Pre-testing is one of the key requirements in order to establish the safety and efficacy of the medical device before it is placed on the market.

4.3.6 Key Area 6: Reporting of Adverse Events and Deaths

As per EN ISO 14155, documented in Appendix 3:

> 'All adverse events and deficiencies related to the medical device under investigation must be documented as they occur and in a timely manner. They then need to be reported, as per the requirements' UL Life and Health Sciences (2017).

The MPA were not informed of any adverse events or deaths related to these surgeries and, therefore, had no visibility into the risk to the participants involved. The MPA were not notified about the clinical trial and, therefore, as they were not informed, no review, assessment, or action could be taken by the regulatory body.

4.3.7 Key Area 7: Patient Care

As stated in the MDD:

> 'to determine any undesirable side-effects, under normal conditions of use, and assess whether they constitute risks when weighed against the intended performance of the device' European Commission (2018a).

When compared to the MDR:

> 'the clinical investigation has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects, and both the risk threshold

> and the degree of distress are specifically defined in the clinical investigation plan and constantly monitored' European Commission (2018a).

In this case, the pain, suffering, and deaths of the participants was unnecessary. It was revealed in the case study that none of the patients had life-threatening conditions when the surgeries were performed and, therefore, these unapproved surgeries were deemed to be unnecessary and caused the death and sufferings of those involved. According to Delaere, Macchiarini's experiments were bound to end badly. As he stated in the Experiments programme by Bosse Lindquist:

> 'If I had the option of a synthetic trachea or a firing squad, I'd choose the last option because it would be the least painful form of execution' The Experiments (2016).

4.4 Research Question Four - Identify what other factors affect the protection of human participants in Medical Device Clinical Trials

4.4.1 The Role of Medical Journals

The manner in which medical journals publish clinical trial results has become a serious threat to public health because it marks the birth of medical knowledge. There is a tendency to fast-track selective positive results in order to promote researchers work Smith (2006). The practice of publishing only favourable results of clinical trials is misleading and questions the integrity of those clinical trials.

Even when published results are retracted, it can take years for those results to cease being cited Teixeira da Silva and Dobranszki (2017). Public safety is at risk when false results of clinical trials are cited in medical journals. When misinformation is spread in this way throughout the scientific community, it provides a false perception for future research and more importantly, can have devastating results for society.

Medical journals give credibility to pioneers of new research and can sensationalize the benefits over the risks. It is stated in the case study that Paolo Macchiarini published six papers that misrepresented the real facts and results of his experiments Check (2015).

Based on the research, it can be stated that publishing false or unsubstantiated results of clinical trials, put the lives of participants in future trials and society as a whole at risk.

4.4.2 Conflict of Interest

Conflicts of interest describe situations where the impartiality of research may be compromised because the researcher stands to profit in some way from the conclusions they draw. It can take the form of financial, social, or personal gain and adversely affect decisions and conclusions that are drawn from medical research Sengupta and Honavar (2017).

There are different forms of conflicts of interest including financial, personal and ideological which can lead to in bias in the medical research. If impartiality is compromised by conflict of interest and the researcher stands to profit in some way, it can affect the conclusions that are drawn Dunn *et al* (2016).

In the case study of Paolo Macchiarini, it is clearly documented that Macchiarini was driven by a need to gain recognition as a ground breaking physician in regenerative technologies,

which blinded him to the regulations and the safety and care of the human participants in his experiments. As recounted in the case study, those in charge at Karolinska ignored warnings of his misconduct because they wanted to gain notoriety as pioneers in the scientific field of regenerative medicine.

Chapter 5: Conclusions and Recommendations

The aim of this research was to investigate the following key areas:

1. Evaluation of clinical trial history to determine the evolution and lessons learned from the past.
2. Evaluation of European medical device regulation to determine if it protects the welfare of human participants in clinical trials.
3. Evaluation and review of a case study to identify if weaknesses exist in the medical device clinical trial regulation and process which puts human participants at risk.
4. Identify what other factors affect the protection of human participants in medical device clinical trials.

In order to address the above objectives of this study, a review of the following major categories of literature with respect to Clinical Trials was performed:

- History of Clinical Trials
- European Clinical Trial Regulations for Medical Devices
- Clinical Trial Ethics
- Clinical Trials with Vulnerable Participants
- Real Life Case Study
- The Role of Medical Journals in Clinical Trials
- Conflicts of Interest

A detailed literature review was conducted to evaluate and understand the evolution of clinical trials and lessons learned from past history. A review of European medical device regulation was also completed to determine if legislation exists to protect the health and safety of human participants in clinical trials. A real-life case study was then reviewed to identify what happens when legislation is by-passed and patient lives are put at risk while conducting clinical experiments. A review of what other factors might affect the health and safety of human participants in clinical trials, which included a review of medical journals and conflict of interest, was then detailed. A summary of the conclusions, along with recommendations, will now be outlined.

5.1 Research Question 1: Evaluation of Clinical Trial history to determine the evolution and lessons learned from the past

The following themes were revealed in performing the literature review:

5.1.1 Conclusion 1 – The Evolution of the Clinical Trial Process

The literature review revealed that clinical research has evolved significantly over the centuries. The first accounts of clinical trials were primarily related to drug therapies. Medical device innovations were created, for the most part, from a need to invent a solution to address a medical emergency or disease. Literature searches yielded very little information on the evolution of clinical trials for medical devices and this indicated that the advancement of clinical trials was born from experiments for drug therapies. This was demonstrated from the record of the first clinical trial, as conducted by the surgeon Ambroise Pare, which was created by chance and necessity rather than a planned approach, to the arrival of the first double blind control trial in 1943 and the first randomised curative trial 1946 by the Medical Research Council which set the model of clinical trial design which we see today.

Ethical principles and regulation evolved through significant historical milestones, from the unethical behaviour displayed with the Tuskedee and World War II crimes, to the present day regulation and standards that provide essential protection for clinical trial participants and society as a whole. Respect for human dignity and informed consent must never be ignored over the need for scientific and medical advancement.

Despite the evolution of clinical trial regulation that aim to protect the safety and well-being of participants, as is seen from the case study in this research, it cannot cover every conceivable situation. If regulation is ignored and not adhered to, it can and has had detrimental results for the human participants.

5.1.1.1 Recommendations for the future

As medical device and drug trials have separate European regulations, a recommendation could be that both regulations for clinical trials be merged into one. Both already follow the principles of EN ISO 14155 so it would be a further step in ensuring that all clinical trials are performed and regulated in a standardised way. This would ensure greater visibility, transparency and protection for clinical trial participants and society as a whole.

The MDR is a significant development of the regulation regarding clinical investigations and will bring a high level of protection for clinical trial participants through the introduction of the centralised database, and increased requirements on clinical investigations for high risk products, class IIb and III. A significant increased amount of clinical data on medical devices will be made available to the public and to healthcare professionals via the Eudamed portal, which will increase transparency and traceability also.

5.1.2 Conclusion 2 – Lessons Learned from the History of Clinical Trials

Medical research has had a negative impact on human clinical trial participant safety, as evident during World War II, when the Nazis inflicted cruel experiments causing suffering and death on the Jewish race in the name of medical research. These participants had no say in their involvement in these trials and were forced to participate in this research, without consent, because their lives were deemed worthless. This was demonstrated again in relation to the Tuskegee syphilis study on black males. The Tuskegee study exemplifies the necessity of providing protections for research subjects and is a reminder of the fact that human dignity and welfare must never be compromised for science. The Nuremberg Code and the Declaration of Helsinki formed a basis for establishing the principles of free and informed consent in order to avoid exploitation in scientific experiments involving human participants.

5.1.2.1 – Recommendations for the Future

Informed consent is provided to clinical trial participants by the physician and the risks and benefits must be explained to each participant in a language that is understandable. A recommendation could be that, in addition to the presence of the physician, representatives from the ethics committee, clinical experts and the competent authority also be present during this procedure, to ensure that no bias or undue force is exercised to any participant. Medical research should never compromise the health and safety of the human participants involved in clinical trials.

5.2 Research Question 2: Evaluation of European Medical Device Regulation to determine if it protects the welfare of human participants in Clinical Trials

5.2.1 Conclusion 1 – MDD and MDR Evaluation

A detailed literature review was conducted to determine if European regulation exists to protect the welfare of human participants in clinical trials. The first step in regulatory compliance in Europe is determining the classification that applies to the applicable product. Under the MDD and the MDR, classification is determined using a risk-based approach. Unless safety and conformance can be demonstrated by other means, a specifically designed clinical investigation will likely be required. Clinical investigations are required for Class IIb and III devices unless there is sufficient clinical data justification available. In order to gain approval of a clinical trial, the manufacturer/sponsor must notify the national competent authority and the ethics committee in which the clinical trial will take place. The competent authority reviews the submission and makes a decision on whether the trial can proceed. A lengthy list of documents are required for review by the competent authority which must comply with the MDD/MDR, EN ISO 14155 and the MEDDEV guidelines, for example; confirmation that appropriate safety measures have been taken for the study participants, copy of the ethics committee opinion, informed consent forms and confirmation that the device conforms to the essential requirements. Based on the outcome of the review of the documentation provided to the competent authority, the clinical investigation may be approved or rejected. Clinical trials can also be suspended or terminated if the competent authority is notified of any adverse events or deaths which pose risk to the participants involved in that clinical trial.

Compared with the MDD, the MDR has provided more detailed requirements for the performance of clinical investigations and this has increased the protection and welfare of human participants. The MDDs have been replaced by the MDR, which were approved on 5th April 2017. The difference between a directive and a regulation is important; directives have been ratified by the EU Parliament and transposed into national law by each member state, whereas Regulations have very clear and defined rules that are binding across all member states. This means that there can be no interpretation of the requirements and each member state must implement the regulation in exactly the same way. The introduction of the new centralised database called Eudamed will mean that there will visibility to all member states when a clinical trial is registered.

5.2.1.1 Recommendations for the Future

The MDD came into law in 1992 and the change to the MDR came into effect in 2017. This was a gap of 25 years. During that timeframe, significant changes to technology/software involved in medical devices were introduced and these advances were not addressed in the MDD. A recommendation could be that the MDR be reviewed and updated every three years as we live in a fast-changing world and as new technologies and therapies develop, it is important that we include regulation that protects the health and safety of clinical trial participants and society as a whole.

5.2.2 Conclusion 2 – EN ISO 14155 and MEDDEV Guidelines

The essential ethical requirements of ISO 14155 are intended to protect the rights, safety and well-being of the human subjects that are part of a clinical investigation. This is a harmonised standard which means that compliance with this standard implies a presumption of conformity with the MDD and MDR. The clauses in the standard aim specifically at the protection of human participants involved in clinical trials and provide precise requirements which outweigh any commercial or scientific concern. Each clause addresses specific topics, for example; ethical considerations, clinical investigation planning, clinical investigation conduct, privacy and confidentiality and adverse events and device deficiencies. Originally published in 1996, it has been extensively revised and the current revision is EN ISO 14155:2011. This means that the standard effectively addresses the advancements in medical device technology.

The European Commission provides a range of guidance documents to assist stakeholders in implementing directives and regulation related to medical devices. The MEDDEVs promote a common approach to be followed by manufacturers and Notified Bodies that are involved in conformity assessment procedures. The MEDDEVs are drafted by authorities charged with safeguarding public health in conjunction with all stakeholders; industry associations, health professionals associations, Notified Bodies and European Standardisation Organisations. The MEDDEVs promote consistency and detailed steps in conducting clinical evaluations and investigations.

5.2.2.1 Recommendations for the Future

As the medical device technology advances at a fast rate, it is important that all standards and guidance documents are aligned. A recommendation could be that EN ISO 14155 and the MEDDEVs be updated at the same time as the MDR to ensure consistency and protection of human participants in clinical trials. It is important that the path to clinical evidence is clear and concise to ensure that regulation is understood and followed correctly.

5.3 Research Question 3: Evaluation and review of a case study to identify if weaknesses exist in the Medical Device Clinical Trial regulation and process which puts human participants at risk

5.3.1 Conclusion

An in-depth review of the real-life case study of Paolo Macchiarini revealed that weaknesses exist at healthcare facility level when regulation is ignored by clinicians/physicians and hospital ethics boards involved in clinical research. By by-passing regulation, patients suffered injury and death and were subject to gruelling post-operative complications. The drive for power and recognition blinded those involved to the safety and well-being of their patients. Issues were not reported and those who did raise concerns were dismissed and reprimanded. No reporting of adverse events were notified to the national competent authority and results of the trials that were published in medical journals were subsequently deemed to be fraudulent and did not document the post-operative events that occurred with the patients involved. The MHRA approved a trial in the UK, which was linked to the Paolo Macchiarini experiments, but they had no data on the surgeries that were performed in other geographies, so they did not have the information needed to make proper judgements. That UK trial has since been suspended when the real facts of the Macchiarini case came to light. Because the clinical trial was not processed per the regulation, multiple failures occurred and resulted in serious injury and death to the participants involved. It can be concluded that, although robust regulation and guidelines are in place to protect the health and well-being of clinical trial participants, as demonstrated in the analysis of this case study, weaknesses exist that allow clinicians and surgeons to by-pass those regulations which results in serious adverse outcomes for the human participants.

5.3.1.1 Recommendation for the Future

In this case study, although regulation and guidelines existed which would have protected the lives and well-being of the human participants in the clinical trials, the fact that the sponsor or the hospital did not inform the competent authority or the ethics committee meant that the MPA or the ethics committee had no knowledge of the trial. Therefore, without this essential review, key failures existed such as lack of qualifications of the physician, no informed consent from the participants, no knowledge of the clinical safety of the device used, no reporting of adverse events and deaths and lack of patient care. A recommendation could be that regulation be introduced that addresses clinical trials which

are initiated by physicians and hospitals, such as a mandatory quarterly audit by the ethics committee and the competent authority of all hospitals involved in clinical trials to establish if all trials have followed regulation and guidelines and have been notified to the authorities for review and consideration. This could ensure that serious injury and loss of life, which were demonstrated in the case study in this research, could be avoided for the future.

5.4 Research Question 4: Identify what other factors affect the protection of human participants in Medical Device Clinical Trials

5.4.1 Conclusion

A literature review was conducted on two other factors that could affect the lives of human participants in clinical trials: medical journal articles, and conflict of interest. Medical journals are widely regarded by the scientific community and can give credibility to medical research. However, when fraudulent claims are documented in these articles, it puts future research and the lives of human participants in clinicals trials at risk, as seen from the approval of the UK trial by the MHRA. It was also evident in the case study where Paolo Macchiarini published six papers which misrepresented the results of the clinical trials. Sensationalising medical breakthroughs without factual evidence to support such claims puts human participants and society as a whole at risk.

Conflict of interest can include financial, personal, or social gain, which, if exists, will adversely affect decisions made in relation to results and, ultimately, patient health and well-being. The case study in this research demonstrated that personal gain and the need for scientific recognition resulted in serious injury and loss of life to the human participants in the clinical trials performed. Conflict of interest creates a risk that can affect professional judgement or action, which is driven not by the primary action of medical research and patient care, but by a secondary competing interest which puts the lives of human participants in clinical trials at risk.

5.4.1.1 Future Recommendations

In relation to medical journal publications of clinical trial results, a recommendation could be that a legally binding contract between the sponsor, the ethics committee and the competent authority specify exact requirements prior to publication. It is important that any claims made be verified clinically and ethically to ensure that false information is not put in the public domain which results in risk to the lives of human participants in clinical trials and society as a whole.

In relation to conflict of interest in clinical trials, as this can influence judgement and decisions, a recommendation could be that any conflict of interest by any key stakeholder such as the sponsor, investigator or study co-ordinator, be revealed and included in the

submission to the competent authority and ethics committee, for consideration and review prior to approval and registration of the clinical trial.

5.5 Overall Conclusion

The evolution of clinical trials, which involves human participants has shown, for the most part, that research has led to significant discoveries, development of new therapies and benefits, which has enhanced the health and well-being of society. Ethical principles and regulation evolved through significant historical milestones, from the unethical behaviour displayed with the Tuskedee and World War II crimes, to the present day regulation and standards that provide essential protection for clinical trial participants and society as a whole. Respect for human dignity and informed consent must never be ignored over the need for scientific and medical advancement. Compared with the MDD, the MDR has provided more detailed requirements for the performance of clinical investigations and this has increased the protection and welfare of human participants. Regulations have very clear and defined rules that are binding across all member states. This means that there can be no interpretation of the requirements and each member state must implement the regulation in exactly the same way. The introduction of the new centralised database called Eudamed will mean that there will visibility to all member states when a clinical trial is registered.

Although robust regulation and guidelines have evolved and are in place to protect the health and well-being of clinical trial participants, as demonstrated in the analysis of this case study, weaknesses exist that allow clinicians and surgeons to by-pass those regulations which results in serious adverse outcomes for the human participants.

Medical journals are widely regarded by the scientific community and can give credibility to medical research. However, when fraudulent claims are documented in these articles, it puts future research and the lives of human participants in clinicals trials at risk. Sensationalising medical breakthroughs without factual evidence to support such claims puts human participants and society as a whole at risk. Conflict of interest creates a risk that can affect professional judgement or action, which is driven not by the primary action of medical research and patient care, but by a secondary competing interest which puts the lives of human participants in clinical trials at risk.

As demonstrated by the literature review and case study analysis, the clinical trial process and regulation has evolved significantly, but we must continue to ensure that lessons are

learned from events as they occur and regulation and guidelines are continuously updated to address any weaknesses or failures that are identified in order to protect the lives and well-being of human participants in clinical trials and society as a whole.

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Appendices

Appendix 1 - Glossary of Terms and Acronyms

‘Clinical Data:

The safety and/or performance information that is generated from the use of a device. Clinical data are sourced from:

— clinical investigation(s) of the device concerned; or

— clinical investigation(s) or other studies reported in the

scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or

— published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be

demonstrated.

Clinical Evaluation:

The assessment and analysis of clinical data pertaining to a medical

device to verify the clinical safety and performance of the device

when used as intended by the manufacturer.

Clinical Evidence:

The clinical data and the clinical evaluation report pertaining to a

medical device.

Clinical Investigation:

Any systematic investigation or study in or on one or more human subjects, undertaken to assess the safety and/or performance of a medical device.

Clinical Investigation Plan:

Document that states the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation.

Clinical Performance:

The ability of a medical device to achieve its intended purpose as claimed by the manufacturer.

Clinical Safety:

The absence of unacceptable clinical risks, when using the device according to the manufacturer's Instructions for Use.

Device intended for Clinical Investigation:

any device intended for use by a duly qualified medical practitioner when conducting investigations as referred to in Sections 2.1 of Annex 7 of directive 90/385/EEC and section 2.1 of Annex X of directive 93/42/EEC in an adequate human clinical environment.

Endpoint: Indicators measured or determined to assess the objectives of a clinical investigation, prospectively specified in the clinical investigation plan. (EN ISO 14155_2:2009, modified).

Residual Risk: Risk remaining after risk control measures has been taken (EN ISO 14971:2009).

Risk Management:

The systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk (EN ISO 14971:2009)'.

Per Regulation (EU) 2017/745, the following definitions apply:

''investigational device' means a device that is assessed in a clinical investigation;

‘clinical investigation plan’ means a document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation;

‘clinical data’ means information concerning safety or performance that is generated from the use of a device and is sourced from the following: — clinical investigation(s) of the device concerned, — clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated, — reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated, — clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up;’

Appendix 2 - Transcripts from Interviews

Interview with the UK Competent Authority: MHRA, UK

Interview Questions for Qualitative Research on the Dissertation titled:

European Clinical Trial Medical Device Regulation and the Protection of Human Participants

Name:

Job Title

Organization: MHRA

Question 1

In addition to the MDD/MDR, what national regulations are followed for Clinical Trials in your region? Are there any specific or significant differences between the National and European requirements?

Response: The medical device regulations 2002.

Question 2

Who initiates the need for a Clinical Trial? Who monitors the overall process?

Response: the initiation of a trial is lead by manufacturers of medical devices, clinicians/academics mainly. MHRA assesses applications and any amendments, MHRA also monitors adverse incidents and reviews the final report.

Question 3

How are human participants recruited normally for the trials?

Response: various methods – advertising/clinics/known to the clinician/through hospital admissions

Question 4

Are Consent forms completed and documented for every human participant in Clinical trials? Who reviews and approves the suitability?

Response: this is best answered by HRA. MHRA review the proposed consent forms and patient information sheets. The investigators in the trial are expected to ensure informed consent is obtained and documented for each participant

Question 5

How are the risks versus benefits explained to the clinical trial participant?

Response: MHRA does not have oversight of this.

Question 6

How are participants privacy protected?

Response: Not for MHRA to answer

Question 7

Who are the main stakeholders involved in reviewing and approving a clinical trial?

Response: Regulatory, technical, statistical and clinical assessors within MHRA. Where required external experts are also sought. HRA and the RECs also conduct their own assessment.

Question 8

What process is in place to monitor the progress and results of the clinical trial performed?

Response: Any serious adverse events are to be reported to MHRA at the earliest opportunity. MHRA also can request reports at various timepoints of the trial. MHRA review the final reports.

Question 9

How are adverse events reported and monitored? Who is responsible for monitoring and reporting?

Response: Reported to MHRA. These are reviewed by the regulatory and clinical team.

Question 10

What triggers a suspension or cessation of a clinical trial? Who is responsible to take the final decision?

Response: a serious concern regarding the safety or performance of a device. The sponsor of the trial may decide to stop the study early. MHRAs clinical investigations team are responsible for reviewing ongoing safety and may also make this decision if

the sponsor has not already done so. It is important to note, often the manufacturer has already suspended the study to investigation.

Question 11

What is the process if death or injury occurs to a participant? Who is responsible to review and escalate?

Response: this is to be reported to MHRA and will be reviewed with the clinical team.

Question 12

Are clinical trials conducted at (Please tick what applies) :

- One centre
- Multi centres within one region
- Multi centres and regions

Additional Comments: All of the above.

Question 13

In multi regional trials, how are the global regulations controlled and complied with? Who oversees all the centres for regulation compliance?

Response: the trial team should ensure compliance – each region is monitored by their own regulatory body.

Question 14

How is information on adverse events and progress of the study between multi centre/regional trials shared?

Response: An EU portal allows member states to share decisions. if concerns are raised the decision can be taken to discuss with other regions where the trial is being conducted.

Question 15

Are results of clinical trials available publicly and by which means?

Response: this is at the discretion of the manufacturer/academic body.

Question 16

Are successful and unsuccessful cases publicly available via Medical Journals? If not, by what other means?

Response: as above

Question 17

If medical journals are used, how are results validated? Who is responsible for managing the articles written?

Response: Not MHRA remit.

Question 18

What involvement has your Competent Authority and Notified Body in the clinical trial process, once the Clinical Trial is approved?

Response: monitoring of incidents and review of final report.

Question 19

Who appoints the Ethics Board for the Clinical Trial?

Response: Not for MHRA to answer. Refer to HRA

Question 20

Who approves the healthcare professionals qualifications for clinical trial participation?

Response: MHRA review CVs of any principle investigators.

Question 21

What training is provided to key stakeholders and healthcare professionals in the clinical trial process?

Response: not for MHRA

Question 22

Who is involved in sponsorship for the clinical trials?

- Industry
- Healthcare Facilities
- Other, please state

Response: various

Question 23

Do you think that when compared with the Medical Device Directives that the Medical Device Regulation will provide more protection for human participants in clinical trials.

Yes

Question 24

Please provide your rationale for your answer to question 20.

Response:

Thank you for participating in my interview.

Interview with the Irish Competent Authority, HPRA

Interview Questions for Qualitative Research on the Dissertation titled:

European Clinical Trial Medical Device Regulation and the Protection of Human Participants

Name:

Job Title: Medical Officer

Organization: Health Products Regulatory Authority (HPRA)

Question 1

In addition to the MDD/MDR, what national regulations are followed for Clinical Trials in your region?

Response: Apart from our internal procedures, HPRA do not follow any specific guidelines in addition to the MDD/MDR and the transposition into Irish law.

Are there any specific or significant differences between the National and European requirements?

Response: The HPRA is not in a position to comment on requirements in other Member States.

Question 2

Who initiates the need for a Clinical Trial? Who monitors the overall process?

Response: In general, the sponsor of a clinical study is responsible for deciding if a CI is needed and for subsequent monitoring. As detailed in EN ISO 14155, there are a range of stakeholders, such as Competent Authorities, Research and Ethics Committees, Principal Investigators who each have monitoring roles.

Question 3

How are human participants recruited normally for the trials?

Response: The sponsor usually identified a patient population who it would like to enrol, recruitment can then be offered in different ways on a case by case basis – for example on an ITT basis.

Question 4

Are Consent forms completed and documented for every human participant in Clinical trials? Who reviews and approves the suitability?

Response: Yes all patients recruited into a study must be consented in line with ISO 14155, in addition to the requirements of the Declaration of Helsinki.

The consents forms and patient information leaflets are reviewed and approved by the ethics committee and the HPRA.

Question 5

How are the risks versus benefits explained to the clinical trial participant?

Response: This takes place during the informed consent process and should be conducted in accordance with a patient information and informed consent document which may provide further detail and occasionally specific requirements, i.e. the need for a 'cooling off period'.

Question 6

How are participants privacy protected?

Response: Section 5.8 in ISO14155 discuss patient privacy and confidentiality of data. Other requirements, for example the GDPR and national requirements may also apply.

Question 7

Who are the main stakeholders involved in reviewing and approving a clinical trial?

Response: The HPRA and the local ethics committee

Question 8

What process is in place to monitor the progress and results of the clinical trial performed?

Response: The process is different for the sponsor, investigator, Competent Authority. For Competent Authorities, progress is monitored in a number of ways. This may include requiring interim reports, the submission of serious adverse events. In Ireland, clinical investigations are also required to have a final clinical investigation report submitted following the close out of the study. In the MDR on-site audits will also be required for investigations in Europe.

Question 9

How are adverse events reported and monitored? Who is responsible for monitoring and reporting?

Response: Reportable events have to be reported by the sponsor of the clinical investigation, which could be the manufacturer, the authorized representative or another person or entity in accordance with European Commission guidance MEDDEV 2.7/3. Reportable events must be reported in line with Meddev 2.7/3 which outlines reporting timelines and causality assessment. The European Commission website has a link to the reporting form template for the summary SAE tabulation which sponsors are advised to use. The table gives a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to participating NCAs each time a new reportable event or a new finding to an already reported event is to be reported. More detailed information has to be provided on request of an NCA, if so requested by using the individual reporting form.

Question 10

What triggers a suspension or cessation of a clinical trial? Who is responsible to take the final decision?

Response: If an unacceptable risk to subjects develops in the investigation, or when so instructed by the ethics committee or regulatory authorities, the sponsor shall terminate or suspend the clinical investigation. The sponsor shall consider terminating a particular site's or investigator's participation in the clinical investigation if monitoring and/or auditing identifies serious and/or persistent non-compliance on the part of an investigator.

The terminating party shall justify its decision and promptly inform the other parties with whom they are in direct communication; these secondary parties shall promptly inform the parties with whom they are in direct communication. If the sponsor terminates or suspends an individual site for any reason, they shall inform the responsible regulatory authority and assure the ethics committee is notified, either by the investigator or personally. If the reason for termination or suspension is safety, the sponsor shall inform all other investigators. The Sponsor remains responsible for provisions to follow-up any patients already enrolled in the clinical investigation.

Question 11

What is the process if death or injury occurs to a participant? Who is responsible to review and escalate?

Response: A serious adverse events includes AE that led to a death, injury or permanent impairment to a body structure or a body function and must be reported in accordance with Annex 7, section 2.3.5 of Directive 90/385/EEC and Annex X, section 2.3.5 of Directive 93/42/EEC. Death or injury must be reported immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event. The competent authority is responsible for reviewing the SAE and taking appropriate action if need.

Question 12

Are clinical trials conducted at (Please tick what applies) :

- ☐ One centre
- ☐ Multi centres within one region
- ☐ Multi centres and regions

Additional Comments: All of the above

Question 13

In multi regional trials, how are the global regulations controlled and complied with? Who oversees all the centres for regulation compliance?

Response:

The HPRA cannot provide information with respect to other Authorities or jurisdictions.

Question 14

How is information on adverse events and progress of the study between multi centre/regional trials shared?

Response:

The HPRA cannot provide information with respect to other Authorities or jurisdictions.

Question 15

Are results of clinical trials available publicly and by which means?

Response: All clinical investigations must be conducted in accordance with the Declaration of Helsinki which provides for the research registration and publication and dissemination of results.

Question 16

Are successful and unsuccessful cases publicly available via Medical Journals? If not, by what other means?

Response: The HPRA cannot comment on the representativeness of published journals.

Question 17

If medical journals are used, how are results validated? Who is responsible for managing the articles written?

Response: The HPRA cannot comment on the validity of published journals.

Question 18

What involvement has your Competent Authority and Notified Body in the clinical trial process, once the Clinical Trial is approved?

Response:

The HPRA approach to post-approval monitoring is reached upon a case by case basis, taking into account many factors such as the novelty of the technology, the degree of risk exposed to patients.

Question 19

Who appoints the Ethics Board for the Clinical Trial?

Response: The HPRA cannot comment on this.

Question 20

Who approves the healthcare professionals qualifications for clinical trial participation?

Response: ISO 14155 states that all parties participating in the conduct of the clinical investigation shall be appropriately qualified by education and/or experience to perform their tasks and this shall be documented appropriately

Question 21

What training is provided to key stakeholders and healthcare professionals in the clinical trial process?

Response: Deciding upon the training requirements is the responsibility of the sponsor. ISO14155 states that an initiation visit for each participating site or alternatively an investigator meeting shall be conducted at the beginning of the investigation to ensure that the investigator and staff have been trained in device use and understand the requirements of the CIP.

Question 22

Who is involved in sponsorship for the clinical trials?

- Industry
- Healthcare Facilities

- Other, please state

Response: For 'clinical investigations' these can be carried out by all of the above and also by healthcare practitioners.

Question 23

Do you think that when compared with the Medical Device Directives that the Medical Device Regulation will provide more protection for human participants in clinical trials.

Yes

Question 24

Please provide your rationale for your answer to question 20.

Response: This question is unclear.

Thank you for participating in my interview.

Interview with the Swedish Competent Authority – MPA

Interview Questions for Qualitative Research on the Dissertation titled:

European Clinical Trial Medical Device Regulation and the Protection of Human Participants

Name:

Job Title Clinical Assessor, M.D., Ph.D.

Organization: Swedish Medical Prodicts Agency

Question 1

In addition to the MDD/MDR, what national regulations are followed for Clinical Trials in your region? Are there any specific or significant differences between the National and European requirements?

Response: the Swedish Medical Products Agency (Läkemedelsverket) regulates medical devices by three differnt regulations: Läkemedelsverkets föreskrifter (LVFS 2003:11) om medicintekniska produkter (medical devices), Läkemedelsverkets föreskrifter (LVFS 2001:5) om aktiva medicintekniska produkter för implantation (active implantable medical devices), and Läkemedelsverkets föreskrifter (LVFS 2001:7) om medicintekniska produkter för in vitro diagnostik (in vitro diagnostic devices). In-house medical devices are regulated by **The National Board of Health and Welfare (Socialstyrelsen).**

There are a number of differences as compared to the MDD, however in most aspects they are quite similar to the MDD. When the MDR will be implied in 2020, the Swedish current regulations will be more or less identical to it; some aspects may however be the subject of national Swedish regulation.

Question 2

Who initiates the need for a Clinical Trial? Who monitors the overall process?

Response: the sponsor initiates clinical trials. The sponsor is responsible for his a clinical trial, including its monitoring.

Question 3

How are human participants recruited normally for the trials?

Response: the MPA has no general answer to this question. In general, participants in one way or other will be asked if they are interested to participate. If so, the trial can be conducted after the participants have signed a patients consent document. Cases also do exist where

trials are conducted involving patients who are unable to sign the informed consent documentation; in these cases other procedures are necessary in order to include them.

Question 4

Are Consent forms completed and documented for every human participant in Clinical trials? Who reviews and approves the suitability?

Response: Yes. For medical devices, the MPA assesses the consent forms and decides whether they are appropriate. The Ethics committee may likewise be involved in questions concerning the consent .

Question 5

How are the risks versus benefits explained to the clinical trial participant?

Response: the sponsor has the responsibility for a trial, including procuring a procedure whereby the participants are informed of risks and benefits. This information must be composed so that it is clear that the participants understand it.

Question 6

How are participants privacy protected?

Response: by Swedish regulation concerning patient data safety, e g Socialstyrelsens föreskrifter och allmänna råd (HSLF-FS 2016:40) om journalföring och behandling av personuppgifter i hälso- och sjukvården

Question 7

Who are the main stakeholders involved in reviewing and approving a clinical trial?

Response: the Swedish Medical Products Agency (MPA) (Läkemedelsverket) and the Ethics Committee

Question 8

What process is in place to monitor the progress and results of the clinical trial performed?

Response: the progress is followed by both the sponsor and the MPA. All adverse events have to be recorded and assessed by the sponsor. Serious Adverse Events are also to be monitored by the sponsor, and also submitted for assessment by the MPA as the trial is progressing. If necessary, a trial must be stopped or interrupted; the MPA may also decide that a study is stopped, during its continuous assessment of the incoming reports. The results of a trial have to be documented in a study report. Under the MDD, sponsors have to submit this to the MPA upon request; under the MDR the study report is to be published in Eudamed.

Question 9

How are adverse events reported and monitored? Who is responsible for monitoring and reporting?

Response: see question 9

Question 10

What triggers a suspension or cessation of a clinical trial? Who is responsible to take the final decision?

Response: circumstances proving that participants are in danger of being injured or killed, or actual incidents where they are, or if the device does not have the performance stated by the manufacturer, as per the nature of an individual trial. For further detailed guidance, see MEDDEV 2.7/3 revision 3, May 2015, Clinical Investigations: Serious Adverse Event Reporting Under Directives 90/385/EEC and 93/42/EEC, and SS-EN ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practice (ISO 14155:2011). The sponsor/manufacturer has the responsibility; however, in Sweden, the MPA may also decide on stopping a trial, if it finds reasons to do so, even in disagreement with the sponsor/manufacturer.

Question 11

What is the process if death or injury occurs to a participant? Who is responsible to review and escalate?

Response: incidents are to be reported in accordance with MEDDEV 2.7/3 revision 3, May 2015 and SS-EN ISO 14155:2011, see question 10.

Question 12

Are clinical trials conducted at (Please tick what applies) :

- ☐ One centre
- ☐ Multi centres within one region
- ☐ Multi centres and regions

Additional Comments: all of the three alternatives above occur.

Question 13

In multi regional trials, how are the global regulations controlled and complied with? Who oversees all the centres for regulation compliance?

Response: for Worldwide trials where EU/EEC is represented, the sponsor must have a legal representative, which will bear the responsibility within the in the EU/EEC. This responsibility also is transferred into each participating member state. Trials must follow the

regulations in each individual member state, as transposed from the MDD. The responsibility for overseeing regulatory compliance for all centres rests with the sponsor.

Question 14

How is information on adverse events and progress of the study between multi centre/regional trials shared?

Response: sponsor is required by the medical device regulations to report adverse events to all participating centers by submitting them on a common report form, covering all centers, to the Competent Authorities (CA) in the member states where the trial is undertaken, in Sweden the MPA. The sponsor may also distribute e g annual reports to the CAs. In Sweden this is not mandatory; some sponsors do, and some don't send such reports to the MPA.

Question 15

Are results of clinical trials available publicly and by which means?

Response: under the MDD and individual national regulations there is no requirement for sponsors to make results public: however, a study report has to be produced. Under the MDR, it will be mandatory to publish this in Eudamed, which will be available for the general public. In case a sponsor decides to publish the results of a completed trial, this is at the time generally made public by way of a scientific paper.

Question 16

Are successful and unsuccessful cases publicly available via Medical Journals? If not, by what other means?

Response: in case the sponsor decides to make the results of a trial public, the usual means are by e g publication in a scientific journal, or as a presentation or poster presented at a scientific medical meeting.

Question 17

If medical journals are used, how are results validated? Who is responsible for managing the articles written?

Response: the MPA cannot categorically answer this question. Papers in medical journals are as a rule peer reviewed by a number of expert reviewers; if a paper is published in that manner, then it will have been validated by the reviewers, and accepted for publication after scientific scrutiny. The quality of this scrutiny itself is dependent on decisions by the publisher. Obviously, if a paper is published without a peer review, then the results presented constitute the interpretation of the sponsor. In this case, it will be up to the reader to decide what attitude to take concerning it.

Question 18

What involvement has your Competent Authority and Notified Body in the clinical trial process, once the Clinical Trial is approved?

Response: the MPA continuously follows the progress of a trial based on the serious adverse event reporting, and sponsor´s progress reports, should such be submitted. Also, in case other information is detected by the MPA, we may take action as found appropriate. The MPA cannot answer for how Notified Bodies involve themselves in trials.

Question 19

Who appoints the Ethics Board for the Clinical Trial?

Response: this is regulated in Förordning (2007:1069) med instruktion för regionala etikprövningsnämnder.

Question 20

Who approves the healthcare professionals qualifications for clinical trial participation?

Response: based on the CV and other relevant information the MPA does this as far as Sweden is concerned. The qualifications are regulated in Läkemedelsverkets föreskrifter, bilaga 10, 2.3.6.

Question 21

What training is provided to key stakeholders and healthcare professionals in the clinical trial process?

Response: the MPA has no information concerning this issue. It does not fall within the scope of MPA regulation.

Question 22

Who is involved in sponsorship for the clinical trials?

- Industry
- Healthcare Facilities
- Other, please state

Response: any of the three mentioned above. A sponsor must have the necessary qualifications to conduct a trial in accordance the with the regulatory requirements.

Question 23

Do you think that when compared with the Medical Device Directives that the Medical Device Regulation will provide more protection for human participants in clinical trials.

Response: this is a question of opinion to which the MPA cannot answer. What can be mentioned, however, is that the requirements for being allowed to conduct a clinical trial under the MDR are both higher and more detailed in comparison to the current MDD/ Läkemedelsverkets föreskrifter.

Question 24

Please provide your rationale for your answer to question 20.

Response: the MPA has no rationale concerning this issue; the issue is regulated as of our answer in question 20

Thank you for participating in my interview.

Interview with Industrial Professional # 1

Interview Questions for Qualitative Research on the Dissertation titled:

European Clinical Trial Medical Device Regulation and the Protection of Human Participants

Name:	
Job Title	Senior Clinical Affairs Manager
Organization:	Medtronic

Note: All information received is confidential and your name will not be reported in my dissertation.

Question 1

In addition to the MDD/MDR, what national regulations are followed for Clinical Trials in your region? Are there any specific or significant differences between the National and European requirements?

Response:

There are no other regulations. ISO14155 standard is applicable.

Question 2

Who initiates the need for a Clinical Trial? Who monitors the overall process?

Response:

Normally from the Sponsor Company for new device or new use of an existing device. Regulator could require it – e.g. part of the license – they request more clinical data in real life as part of the license approval. A consultant (sponsor) in a hospital may have an idea and he will devise a clinical trial. Manufacturer could provide product or funding if applicable. Monitoring: The sponsor is responsible for the monitoring.

Question 3

How are human participants recruited normally for the trials?

Response:

They are invited to partake. Their eligibility is determined per the Protocol - there is exclusion and inclusion criteria for the trial. The physician invites them to partake.

Question 4

Are Consent forms completed and documented for every human participant in Clinical trials? Who reviews and approves the suitability?

Response:

Yes, consent forms are completed for every human participant (by the legal representative or guardian if the patient is unable to or too young. However, for retrospective anonymised data, the ethics committee may grant a waiver. E.G. Historical video data that is anonymised by the hospital prior to providing the information to the Sponsor. Ethics has to approve the waiver. Review and Suitability: Pre-market study – Competent Authority review, Ethics Committee review and would have to approve. Post market study Ethics Committee reviews and approves.

Question 5

How are the risks versus benefits explained to the clinical trial participant?

Response:

Two ways – in the information leaflet which is presented with the Consent Form. The physician explains the risks and benefits to the participant.

Question 6

How are participants privacy protected?

Response:

Privacy protected because none of the human participants personal data is provided to the sponsor. They are identified by the assigned study number only. The participant is fully informed of the data transmission pathway and consents to it.

Question 7

Who are the main stakeholders involved in reviewing and approving a clinical trial?

Response:

Medtronic: Medical Officer, the Global VP (or delegate), Clinical Manager and Program Manager. External: CA, NBs, Ethics Committees.

Question 8

What process is in place to monitor the progress and results of the clinical trial performed?

Response:

The Clinical Affairs Dept monitor (Monitoring plan) and the Programme Manager oversees, Medical Review Board (Internally). Data management and safety committees, depending on the study. Externally: Registered on open website and results published on an open website e.g.: clinicaltrials.gov.

Question 9

How are adverse events reported and monitored? Who is responsible for monitoring and reporting?

Response:

Starts with the patient experiencing the event and reporting or observed, then the physician or co-ordinator reporting to the sponsor and then the sponsor will ensure that the event is reported appropriately to the regulator. The Investigator will also report to the EC as appropriate.

Question 10

What triggers a suspension or cessation of a clinical trial? Who is responsible to take the final decision?

Response:

The sponsor could suspend/cease if there was new information regarding safety or efficacy issues. Other reasons include poor recruitment, dangerous management, as a consequence of an audit finding or the regulatory authority could demand it, following an inspection.

Question 11

What is the process if death or injury occurs to a participant? Who is responsible to review and escalate?

Response:

The sites are trained to report to the sponsor immediately and to the Ethics Committee. The reporting pathway is established before the study is initiated. The sponsor is responsible to review and escalate.

Question 12

Are clinical trials conducted at (Please tick what applies) :

- ☐ One centre
- ☐ Multi centres within one region
- ☐ Multi centres and regions

Additional Comments: Yes, all of above, depending on the CT

Question 13

In multi regional trials, how are the global regulations controlled and complied with? Who oversees all the centres for regulation compliance?

Response:

The sponsor's legal and compliance department and regulatory department define the regulatory parameters. The sponsors policies and SOPs capture applicable regulations so it is mandatory to comply with these. The programme Manager and the monitors ensure site compliance.

Question 14

How is information on adverse events and progress of the study between multi centre/regional trials shared?

Response:

3 ways: Email, newsletter and investigator meetings. Under discussion (email and newsletter) due to GDPR.

Question 15

Are results of clinical trials available publicly and by which means?

Response:

Clinicaltrials.gov website. When MDR is in place, it will be Eudamed.

Question 16

Are successful and unsuccessful cases publicly available via Medical Journals? If not, by what other means?

Response:

All clinical studies have a report at the conclusion and if accepted by a journal, publication. If Medtronic sponsored, then MDT review and approve the report. If physician study, Medtronic will review for intellectual property only.

Question 17

If medical journals are used, how are results validated? Who is responsible for managing the articles written?

Response:

Whoever is the sponsor of the study validates the results. The sponsor would be the author (medical writer).

Question 18

What involvement has your Competent Authority and Notified Body in the clinical trial process, once the Clinical Trial is approved?

Response:

If for CE mark: Annual periodic safety and status update. SAE reporting also. If post market – none.

Question 19

Who appoints the Ethics Board for the Clinical Trial?

Response:

For Medical Device studies, the institution where the study is located.

Question 20

Who approves the healthcare professionals qualifications for clinical trial participation?

Response:

The Sponsor reviews the CV to ensure proper qualifications. Also HCP is checked with the Medical Council website to ensure he/she is licensed in Ireland. Hhowever, not all countries have a medical licence website.

Question 21

What training is provided to key stakeholders and healthcare professionals in the clinical trial process?

Response:

GCP (All have to this qualification), training on safety reporting, on the products and on the CIP (Clinical Investigation Protocol)

Question 22

Who is involved in sponsorship for the clinical trials?

- Industry
- Healthcare Facilities

- Other, please state

Response:

Industry, Advocacy Groups, Institution Trusts or physicians

Question 23

Do you think that when compared with the Medical Device Directives that the Medical Device Regulation will provide more protection for human participants in clinical trials.

Yes, because there is more post market clinical follow up being built into the program plan prior to submission for approval process.

Question 24

Please provide your rationale for your answer to question 23.

Response:

As above

Thank you for participating in my interview.

Interview with Industrial Professional #2

Interview Questions for Qualitative Research on the Dissertation titled:

European Clinical Trial Medical Device Regulation and the Protection of Human Participants

Name:	
Job Title	Senior Director Clinical, Quality and Compliance
Organization:	Medtronic, The Netherlands
Date of Interview:	

Note: All information received is confidential and your name will not be reported in my dissertation.

Question 1

In addition to the MDD/MDR, what national regulations are followed for Clinical Trials in your region? Are there any specific or significant differences between the National and European requirements?

Response:

EN ISO 14155 is the main guidance document for clinical trial good clinical practice. The MDD/MDR is followed for the execution of the clinical trial. Every country has their own national laws to protect their citizens which is in addition to the EU regulation for the approval of clinical trials.

Question 2

Who initiates the need for a Clinical Trial? Who monitors the overall process?

Response:

The sponsor identifies the need for clinical evidence in liaison with the Notified Body. The final decision to initiate the clinical trial is with the sponsor.

Question 3

How are human participants recruited normally for the trials?

Response:

The Sponsor will select hospitals to participate based on well known physicians, Key Opinion Leaders (KOLs) in a particular field. The clinical trial Protocol documents the exclusion criteria to control the type of patients who can participate. The physician chooses the specific patients that are applicable and that meet the requirements of the clinical trial protocol.

Question 4

Are Consent forms completed and documented for every human participant in Clinical trials? Who reviews and approves the suitability?

Response:

YES, all patients have to sign a consent form prior to participation in a clinical trial. The responsibility to have the forms signs is with the physician. Normally the sponsor will prepare the document. The Consent Form is approved by the Ethics Committee and sometimes the content is agreed with the Notified Body. It is the responsibility of the physician to update the sponsor on the status of the consent forms. There are a lot of differences in requirements by country. Data protection is adapted to be compliant with national laws.

Question 5

How are the risks versus benefits explained to the clinical trial participant?

Response:

The risk and benefits are documented in the Consent Form. The risks and benefits are explained to the participant by the physician. The sponsor goes to the hospital to verify that all Consent Forms are properly signed.

Question 6

How are participants privacy protected?

Response:

The sponsor will never have the full name or identity of the participant. The sponsor will only have a patient code.

Question 7

Who are the main stakeholders involved in reviewing and approving a clinical trial?

Response:

Sponsor's internal stakeholders include Regulatory, Quality and Business Units. Externally, there are Ethics Committee, Competent Authorities, Physicians/KOLs. The Sponsor would seek medical input from physicians/KOLs. The Ethics Committee and Competent Authority are involved prior to study.

Question 8

What process is in place to monitor the progress and results of the clinical trial performed?

Response:

The Sponsor monitors the clinical trial by going to the hospital, reviewing files, ensuring that all adverse events are reported. The Sponsor checks for accuracy, patient consent and that the clinical trial is being conducted according to the clinical trial Protocol.

Question 9

How are adverse events reported and monitored? Who is responsible for monitoring and reporting?

Response:

The physician is the first person who should report any adverse event/issue experienced to the Sponsor immediately.

Question 10

What triggers a suspension or cessation of a clinical trial? Who is responsible to take the final decision?

Response:

If there is an unexpected first event, this could initiate a suspension or cessation of the trial. High risk studies have a Data Safety Board (Body of Physicians who review safety events). The Sponsor reports any adverse events to the Competent Authority. The Competent Authority can also request a suspension or cessation of the clinical trial.

Question 11

What is the process if death or injury occurs to a participant? Who is responsible to review and escalate?

Response:

Same response as Question 10.

Question 12

Are clinical trials conducted at (Please tick what applies) :

- ☐ One centre
- ☐ Multi centres within one region
- ☐ Multi centres and regions

Additional Comments: All of the above.

Question 13

In multi regional trials, how are the global regulations controlled and complied with? Who oversees all the centres for regulation compliance?

Response:

The Sponsor is responsible for meeting all global regulatory requirements. The regulators in specific countries can perform inspections to ensure that any clinical trial is meeting the regulatory requirements of that region.

Question 14

How is information on adverse events and progress of the study between multi centre/regional trials shared?

Response:

If there is an adverse event in a clinical trial that occurs in one country, the results are notified to all physicians participating in the trial and the Competent Authorities in all regions are also notified.

Question 15

Are results of clinical trials available publicly and by which means?

Response:

YES, on clinicaltrials.gov website - the clinical trial has to be announced and the results posted.

Question 16

Are successful and unsuccessful cases publicly available via Medical Journals? If not, by what other means?

Response:

Clinical trials are published publicly via ClinicalTrials.gov. A sponsor cannot control duplication in a Medical Journal. Medtronic have an agreement written into the clinical trial protocol that the physician cannot duplicate the clinical trial data in a medical journal. Physicians are mainly the authors of medical journal articles. For Medtronic, they are not allowed to publish unless the article is reviewed by Medtronic.

Question 17

If medical journals are used, how are results validated? Who is responsible for managing the articles written?

Response:

See response to Question 16

Question 18

What involvement has your Competent Authority and Notified Body in the clinical trial process, once the Clinical Trial is approved?

Response:

The Competent Authorities perform inspections and puts focus on the protection of the human participants in the clinical trial. They scrutinize the adverse event reporting and are involved in the execution of the clinical trial. The Notified Body will be involved to review clinical results for CE Mark purposes as proof of clinical evidence.

Question 19

Who appoints the Ethics Board for the Clinical Trial?

Response:

By law, every hospital has to have an Ethics Committee. Some countries have a National Ethics Committee also. In those countries, a clinical trial would be approved firstly by the national Ethics Committee and then by the hospital Ethics Committee.

Question 20

Who approves the healthcare professionals qualifications for clinical trial participation?

Response:

The Sponsor is responsible and the criteria is based on the Clinical Trial protocol, type of profession, cases performed. Per EN ISO 14155, the Sponsor will perform a site qualification visit to ensure that the hospital is qualified to perform the clinical trial.

Question 21

What training is provided to key stakeholders and healthcare professionals in the clinical trial process?

Response:

Training is provided by the Sponsor on the products, procedure, protocol, Good Clinical Practice or any special circumstances.

Question 22

Who is involved in sponsorship for the clinical trials?

- Industry
- Healthcare Facilities
- Other, please state

Response:

Mostly industry. Sometimes also physicians as their government may sponsor them to perform some research.

Question 23

Do you think that when compared with the Medical Device Directives that the Medical Device Regulation will provide more protection for human participants in clinical trials.

Response: Yes

Question 24

Please provide your rationale for your answer to question 23.

Response: Per response to question 20

Thank you for participating in my interview.

Interview with Industrial Professional #3

Interview Questions for Qualitative Research on the Dissertation titled:

European Clinical Trial Medical Device Regulation and the Protection of Human Participants

Name:	
Job Title	Snr Director, Clinical Affairs
Organization:	Medtronic, U.S.
Date of Interview:	

Note: All information received is confidential and your name will not be reported in my dissertation.

Question 1

In addition to the MDD/MDR, what national regulations are followed for Clinical Trials in your region? Are there any specific or significant differences between the National and European requirements?

Response:

EN ISO 14155 is the applicable standard for clinical trial good clinical practice. The MDD/MDR is the European regulation to be followed in addition to national laws per European country.

Question 2

Who initiates the need for a Clinical Trial? Who monitors the overall process?

Response:

The sponsor

Question 3

How are human participants recruited normally for the trials?

Response:

The physician is responsible for choosing the patients based on the requirements in the clinical trial protocol.

Question 4

Are Consent forms completed and documented for every human participant in Clinical trials? Who reviews and approves the suitability?

Response:

Yes, all participants have to complete a Consent Form. The risks and benefits have to be explained to the participant prior to the form being completed and signed. The physician is responsible, normally, for completing this task. The Ethics Committee have to review and approve the consent forms.

Question 5

How are the risks versus benefits explained to the clinical trial participant?

Response:

The risks and benefits are contained within the Consent Form and should be explained by the physician, in understandable language, to the CI participants.

Question 6

How are participants privacy protected?

Response:

Patient coding and the sponsor will not have the patient details, only patient code.

Question 7

Who are the main stakeholders involved in reviewing and approving a clinical trial?

Response:

Ethics Committees, Competent Authorities, Physicians/KOLs.

Question 8

What process is in place to monitor the progress and results of the clinical trial performed?

Response:

The sponsor should monitor progress and check that all requirements in the CI protocol are being met and adhered to.

Question 9

How are adverse events reported and monitored? Who is responsible for monitoring and reporting?

Response:

The physician should report any adverse event/issue to the Sponsor immediately.

Question 10

What triggers a suspension or cessation of a clinical trial? Who is responsible to take the final decision?

Response:

If there is an unanticipated first event which puts the participants at considered risk. All adverse events should be reported by the sponsor to the Competent Authority. Based on the review of reported events, the Competent Authority can request that the trial be stopped or suspended.

Question 11

What is the process if death or injury occurs to a participant? Who is responsible to review and escalate?

Response:

Same response as Question 10.

Question 12

Are clinical trials conducted at (Please tick what applies) :

- ☐ One centre
- ☐ Multi centres within one region
- ☐ Multi centres and regions

Additional Comments: All of the above.

Question 13

In multi regional trials, how are the global regulations controlled and complied with? Who oversees all the centres for regulation compliance?

Response:

It is the responsibility of the Sponsor to meet all regulatory requirements. The regulators in specific countries are tasked with ensuring that all Cis meet the regulatory requirements.

Question 14

How is information on adverse events and progress of the study between multi centre/regional trials shared?

Response:

All adverse events which occur in a one country must be notified to all countries so that they can notify the regulators in their countries.

Question 15

Are results of clinical trials available publicly and by which means?

Response:

On clinicaltrials.gov website.

Question 16

Are successful and unsuccessful cases publicly available via Medical Journals? If not, by what other means?

Response:

Physicians are usually the authors of medical journal articles. For Medtronic, they are not allowed to publish unless the article is reviewed by Medtronic.

Question 17

If medical journals are used, how are results validated? Who is responsible for managing the articles written?

Response:

See response to Question 16

Question 18

What involvement has your Competent Authority and Notified Body in the clinical trial process, once the Clinical Trial is approved?

Response:

The Competent Authorities will perform inspections and focus on the protection of human participants.. They review the adverse event reporting. The Notified Body will be involved to review clinical results for CE Mark purposes as proof of clinical evidence.

Question 19

Who appoints the Ethics Board for the Clinical Trial?

Response:

Every hospital has to have an Ethics Committee. Depending on national law, some countries have a National Ethics Committee also. In those countries, a clinical trial would be approved firstly by the national Ethics Committee and then by the hospital Ethics Committee.

Question 20

Who approves the healthcare professionals qualifications for clinical trial participation?

Response:

Per EN ISO 14155.

Question 21

What training is provided to key stakeholders and healthcare professionals in the clinical trial process?

Response:

Training is provided by the Sponsor

Question 22

Who is involved in sponsorship for the clinical trials?

- Industry
- Healthcare Facilities
- Other, please state

Response:

Mostly industry and some physicians.

Question 23

Do you think that when compared with the Medical Device Directives that the Medical Device Regulation will provide more protection for human participants in clinical trials.

Response: Yes

Question 24

Please provide your rationale for your answer to question 23.

Response: Per response to question 20

Thank you for participating in my interview.

Appendix 3 – ISO 14155 Clauses

Ethical Considerations - (Clause 4)

The essential ethical requirements of ISO 14155 are intended to protect the rights, safety and well-being of the human subjects that are part of a clinical investigation. Adherence to these core principles outweighs any other commercial or scientific concerns such as:

Improper Influence or Inducement - No improper influence or inducement of any parties involved in a clinical investigation should not take place by either the sponsor or the investigator UL Life and Health Sciences (2017).

Compensation for Human Subjects - Compensation is only allowed if it is per national regulations and it cannot be of a nature that would encourage or influence participation in the trial UL Life and Health Sciences (2017).

Oversight Communications - The appointment of an independent ethics committee protects the rights, safety and well-being of the clinical trial participants. This clause outlines detailed requirements in relation to initial and ongoing communication between the sponsors and investigators and the ethics committee UL Life and Health Sciences (2017).

Vulnerable Populations - Using vulnerable participants is not allowed. Such participants should only be considered if the clinical trial cannot be conducted otherwise. When vulnerable participants are used, it is imperative that the clinical trial is designed to address the health issues of those participants and there should be a direct health benefit UL Life and Health Sciences (2017).

Informed Consent -All clinical trial participants must provide their informed consent in writing. The informed consent must be signed and include information related to the trial. For some cases, the informed consent is provided by an legally authorised representative UL Life and Health Sciences (2017).

This clause provides specific and essential guidance to protect the rights, safety and well-being of clinical trial participants.

Clinical Investigation Planning - (Clause 5)

Prior planning for a clinical investigation is a key element of ISO 14155 requirements. The standard requires undertaking the following planning activities in advance of any clinical investigation UL Life and Health Sciences (2017):

Risk Analysis - A risk analysis that meets the requirements of of ISO 14971 must be performed in order to identify any potential risk and/or adverse effects which clinical trial participants may be exposed to UL Life and Health Sciences (2017).

Justification - Based on the evaluation of pre-clinical data and clinical evaluation of the medical device, a justification for the design of the clinical investigation must be prepared UL Life and Health Sciences (2017).

Clinical Investigation Plan - Per Annex A of ISO 14155, A clinical investigation plan (CIP) must be developed UL Life and Health Sciences (2017).

Investigator's Brochure -As detailed in Annex B of ISO 14155, The investigator's brochure provides the investigator(s) with sufficient device safety or performance data to justify human participation during a clinical trial UL Life and Health Sciences (2017).

Case Report Forms - As detailed in Annex C of ISO 14155, Case report forms must be compiled in order to collect and record data for each participant during the clinical trial UL Life and Health Sciences (2017).

Monitoring Plan - The sponsor has to prepare a monitoring plan which is based on an assessment of the appropriate extent and nature of monitoring for the clinical trial UL Life and Health Sciences (2017).

Investigation Site Selection - A rationale for choosing a specific site for a clinical trial must be documented UL Life and Health Sciences (2017).

This clause provides prescriptive detail as to risk assessment, clinical trial planning and protocol.

Clinical Investigation Conduct - (Clause 6)

Clinical investigations conducted under ISO 14155 cannot commence until written approval has been provided by the investigation's ethics committee and, if required, the relevant regulatory authorities where the clinical investigation is being conducted. Subsequent to those approvals, clinical investigation sponsors and investigators must address the following requirements UL Life and Health Sciences (2017):

Investigation Site Initiation - For investigation site, an initiation meeting or visit is required. A document log of meeting attendees, their functions and scope of authority must be created UL Life and Health Sciences (2017).

Investigation Site Monitoring - Investigation monitoring activities should be conducted, per the monitoring plan detailed above UL Life and Health Sciences (2017).

Adverse Events and Device Deficiencies - Reporting and documenting of all adverse events, as they occur and in a timely manner is mandatory. All adverse event should be reported to the relevant Competent Authorities UL Life and Health Sciences (2017).

Other Documents and Documentation - Any amendments or changes to any required forms or documents must be documented with a rationale for the change. A log of subjects enrolled in the clinical trial must be maintained. Significant changes to the investigation plan are subject to Ethic Committee approval UL Life and Health Sciences (2017).

Privacy and Confidentiality - The privacy and confidentiality of all information pertaining to participants must be maintained throughout the investigation. All data must be secured against unauthorized access UL Life and Health Sciences (2017).

Document and Data Control All documents and data created during a clinical trial must be controlled and maintained to ensure traceability UL Life and Health Sciences (2017).

Device Accountability -Access to medical devices involved in the clinical trial must be controlled so that there use is limited to the clinical trial being performed UL Life and Health Sciences (2017).

Subject Accountability - Clinical trial participants enrolled must be documented and accounted for during the course of the trial. Where a participant withdraws from the trial, a rationale for their withdrawal must be documented UL Life and Health Sciences (2017).

Auditing - If deemed necessary or appropriate by the sponsor, an audit of the clinical trial may be performed by the sponsor or an appointed third-party to assess compliance with the CIP UL Life and Health Sciences (2017).

This clause provides the requirements that must be satisfied before a clinical trial can be approved or be initiated.

Close-Out of Clinical Investigation - (Clause 7)

This clause of the standard addresses procedures for closing out a clinical investigation, including instances in which an investigation is suspended or terminated for significant reasons. Specific provisions of this clause include UL Life and Health Sciences (2017):

Suspension or premature Termination clinical trial can be suspended or prematurely terminated by the sponsor, the principal investigator, the ethics committee or a regulatory authority if there is reasons such as unacceptable risks to participants, or serious or repeated deviations by the investigator from the CIP. Whoever terminates the trial must document in writing the rationale for this action and report it as per the requirements UL Life and Health Sciences (2017).

Routine Close-out of investigation - ISO 14155 details a number of reporting and notification actions to be performed when the trial is completed. This is intended to ensure that all records and documents are complete, that all open issues related to the investigation have been resolved, and that any remaining clinical investigation materials have been properly disposed of UL Life and Health Sciences (2017).

Clinical Investigation Report - As detailed in Annex D of ISO 14155, when a clinical trial has been completed or terminated, a final written report must be prepared that identifies the medical device that was evaluated in the investigation, a description of the methodology and the design of the investigation, and an analysis of the data. A copy of the report should be provided to the ethics committee and regulatory authorities UL Life and Health Sciences (2017).

Document Retention - As detailed in Annex E of ISO 14155, copies of the final clinical investigation report and all relevant clinical investigation documents must be retained by the sponsor and principal investigator as required under applicable regulatory requirements (UL Life and Health Sciences,2017).

Appendix 4 – Literature Protocol

Purpose

The purpose of this protocol is to define the criteria which will be utilized to perform a literature search and report for the dissertation titled: 'European Clinical Trial Medical Device Regulation and the Protection of Human Participants'

Scope

The scope of the literature search includes a query of scientific databases Embase and PubMed for a ten year time period. It is expected that this will provide sufficient coverage of any literature that might have arose during the time period.

Search Criteria

- **Date of Research:** 17th June 2018
- **Completed by** Christina Donegan
- **Timeline** Added to databases from 2010 to 2018 *

  **Note: Publications from outside of this timeframe will be accepted if it appropriately supports the rationale.*

- **Literature Sources:**

  Search Databases considered/proposed:

  - Peer reviewed Scientific literature, e.g. PubMed, Google Scholar, Science Direct
  - Clinical Trial Registers – e.g. Clinicaltrials.gov.com

  PubMed is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics. The United States National Library of Medicine (NLM) at the National Institutes of Health maintains the database as part of the Entrez system of information retrieval.

  Google Scholar is a freely accessible web search engine that indexes the full text or metadata of scholarly literature across an array of publishing formats and disciplines. Released in beta in November 2004, the Google Scholar index

includes most peer-reviewed online academic journals and books, conference papers, theses and dissertations, preprints, abstracts, technical reports, and other scholarly literature, including court opinions and patents.

Cochrane Reviews are systematic reviews of primary research in human health care and health policy, and are internationally recognized as the highest standard in evidence-based health care resources. They investigate the effects of interventions for prevention, treatment, and rehabilitation.

Strategy

Development of an appropriate set of Research questions related to the dissertation title.

Methods

Period covered by Search: 10 years

Literature Sources used to identify data:

 Science Direct

 Pubmed

 Google Scholar

 Internal Company and External Presentations

 Conferences

 Google

Keyword Search

Clinical Trial, Medical Devices, Regulation, Europe, History, Ethics, Informed Consent, Medical Journals

The PICO method was used to build search terms. A PICO (patient characteristics, type of intervention, control, and outcome queries) was designed to determine the keyword search terms. Compilation of a list of keywords, their synonyms and corresponding MeSH terms from each aspect of the research question was completed.

- Filter using Boolean logic for retrieval of information.
- Each search set progresses the overall search results from general to specific findings.
- Take screen shot of each search to demonstrate number of articles retrieved and date/time
- Log each result search in a continuous log
- Export abstracts from articles into a format that allows ease of review
- Do a quick review of each article and determine if it is appropriate or not
- Exclude articles not considered appropriate and document rationale for exclusion
- Log each article that is considered appropriate for full review

The search strategy is determined by the Search Criteria (mentioned above) and employed within research database (PUBMED) using Boolean logic for information retrieval. The search Strategy will also be applied to Google Scholar and Science Direct. The search strategy is captured below to illustrate the precise search approach taken to yield search results.

Stage 1 - Identification of Pertinant Data

Database Used: PUBMED

Accessed: 17th June 2018

Timeframe: 2010 - 2018

Search	Query	Items found
1	Search (Clinical Trial) AND Medical Devices	76217
2	Search (Clinical Trial) AND Medical Devices Filters: published in the last 10 years	35364
3	Search ((Clinical Trial) AND Medical Device) AND Regulation Filters: published in the las	515
4	Search (((Clinical Trial) AND Medical Devices) AND Regulation) AND Europe Filters: pub	59
5	Search ((((Clinical Trial) AND Medical Devices) AND Regulation) AND Europe) AND Medi	16
6	Search (Clinical Trial) AND History Filters: published in the last 10 years	12274
7	Search (Human Research) AND History Filters: published in the last 10 years	110176
8	Search (Clinical Trials) AND Evolution Filters: published in the last 10 years	3219
9	Search Bhatt Filters: published in the last 10 years	4059
10	Search (Medical Research) AND Evolution Filters: published in the last 10 years	27728
11	Search (Medical Research) AND History Filters: published in the last 10 years	58730
12	Search (Clinical Research) AND History Filters: published in the last 10 years	45491
13	Search (Clinical Trial) AND Ethics Filters: published in the last 10 years	6557
14	Search (Clinical Trial) AND Informed Consent Filters: published in the last 10 years	4184
15	Search ((Clinical Trial) AND Informed Consent) AND Regulation Filters: published in the	1673
16	Search (((Clinical Trial) AND Informed Consent) AND Regulation) AND Europe Filters: pu	198
17	Search ((((Clinical Trial) AND Informed Consent) AND Regulation) AND Europe) AND Me	3
18	Search (Clinical Trial) AND Medical Journals Filters: published in the last 10 years	1478
19	Search ((Clinical Trial) AND Medical Journals) AND Europe Filters: published in the last 1	165
20	Search Clinical Trials Filters: published in the last 10 years	499636

Database Used: Google Scholar

Accessed: 17th June 2018

Timeframe: 2010 – 2018

Search #	Search Term	Items Found
1	Clinical Trial AND Medical Devices	17,600
2	Clinical Trial AND Medical Devices AND Regulation	17,500
3	Clinical Trial AND Europe AND Medical Devices AND Regulation AND Europe	17,300
4	Clinical Trial AND Europe AND Medical Devices AND Regulation AND Europe AND Medical Device Regulation	31
5	Clinical Trial AND History	170,000
6	Clinical Research AND History	912,000
7	Medical Research AND History	1,620,000
8	Clinical Trial AND Ethics	645,000
9	Clinical Trial AND Informed Consent	162,000
10	Clinical Trial AND Informed Consent AND Regulation	6
11	Clinical Trial AND Informed Consent AND Regulation AND Europe	0
12	Clinical Trial AND Informed Consent AND Regulation AND Europe AND Medical Devices	0
13	Clinical Trial AND Medical Journals	59,700

Database Used: Science Direct

Accessed: 17th June 2018

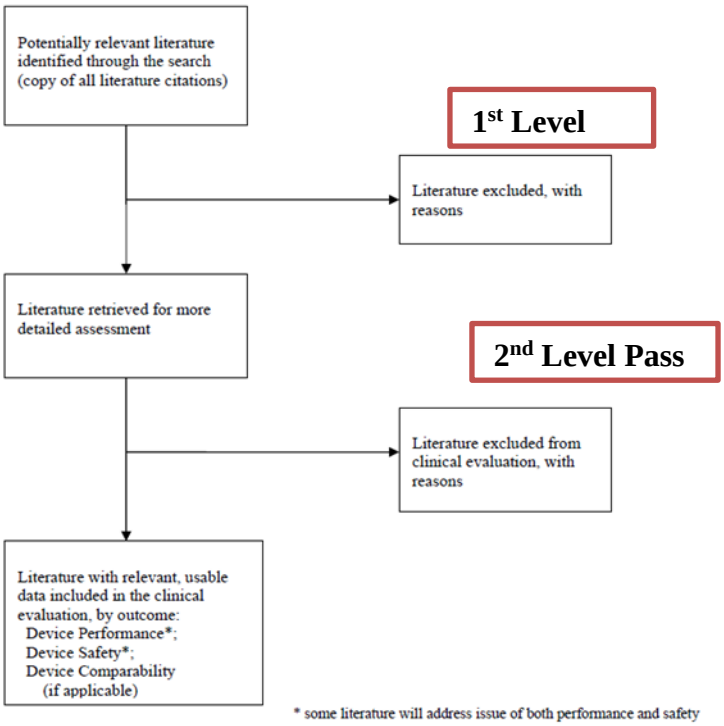
Timeframe: 2010 – 2018

Search #	Search Term	Items Found
1	Clinical Trial AND Medical Devices	75,408
2	Clinical Trial AND Medical Devices AND Regulation	26,527
3	Clinical Trial AND Europe AND Medical Devices AND Regulation AND Eurc	10,738
4	Clinical Trial AND Europe AND Medical Devices AND Regulation AND Eurc	10,721
5	Clinical Trial AND History	191,270
6	Clinical Research AND History	308,497
7	Medical Research AND History	285,446
8	Clinical Trial AND Ethics	82,486
9	Clinical Trial AND Informed Consent	113,398
10	Clinical Trial AND Informed Consent AND Regulation	19,027
11	Clinical Trial AND Informed Consent AND Regulation AND Europe	5,301
12	Clinical Trial AND Informed Consent AND Regulation AND Europe AND M	1,586
13	Clinical Trial AND Medical Journals	141,460

Stage 2 – Appraisal of Pertinent Data

The grading system used to appraise the data was taken from Appendix D of the GHTF SG5 document N2R8:2007 on Clinical Evaluation

(Appendix D: A Possible Method of Appraisal)



Inclusion Criteria

Selection criteria used to choose articles included first read abstracts and if rejected it was considered a 1st level pass. If not clear, full text articles were retrieved and if rejected was considered a 2nd level pass. If the article met selection criteria it was included in the analysis. If not, it was excluded.

Exclusion Criteria

Included and excluded publications were determined by the author and confirmed during the peer review process. The exclusion criteria listed below provides several examples and is not intended as a complete list of exclusion criteria.

- Paper has abstract available only
- Paper related to pharmaceuticals
- Paper not related to Europe
- Paper not related to clinical trial regulation
- Paper related to actual clinical trials performed

Selection criteria used to choose articles included first read abstracts and if rejected it was considered a 1st level pass. If not clear, full text articles were retrieved and if rejected was considered a 2nd level pass. If the article met selection criteria it was included in the analysis. If not, it was excluded.

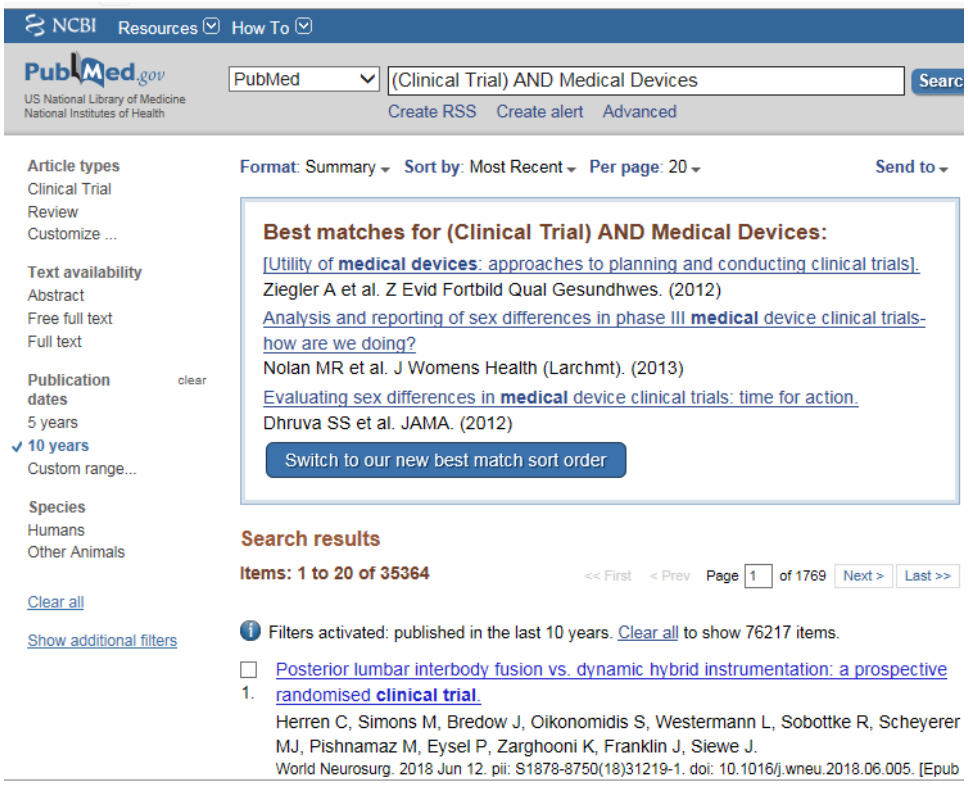
Conclusion

Conclusion

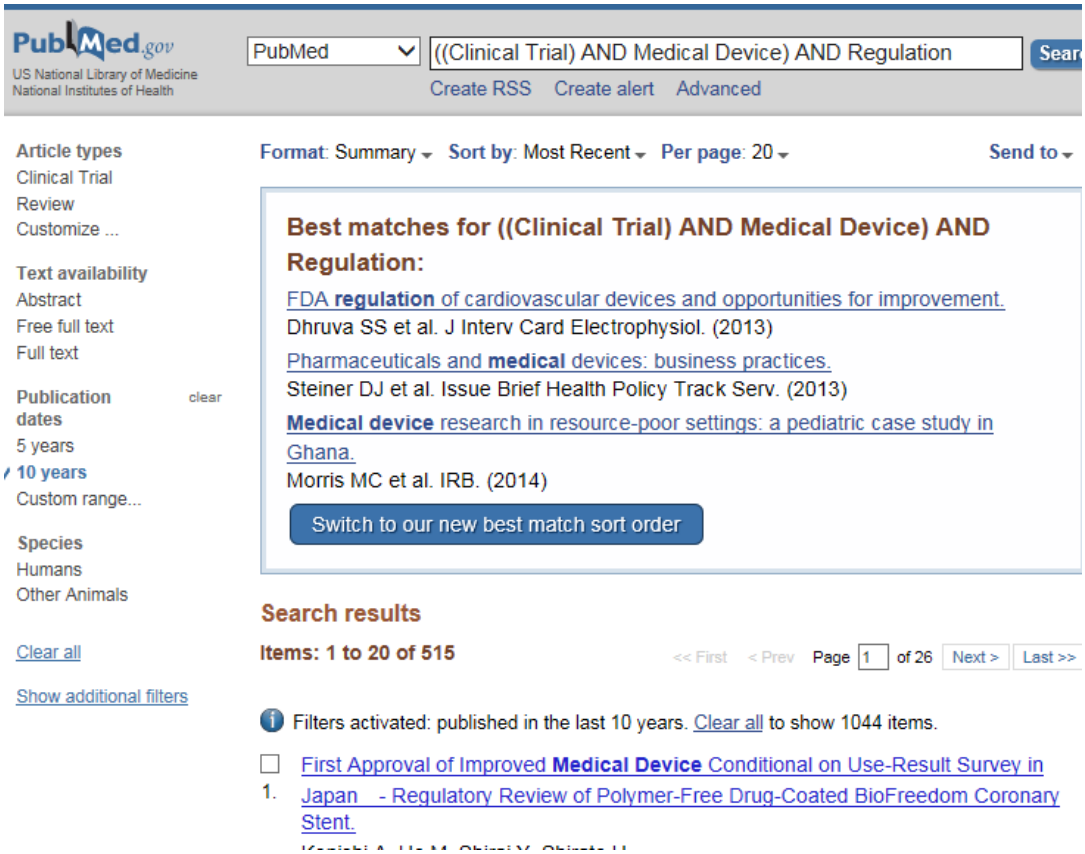
Articles that met the selection criteria are included in the dissertation and are referenced in the dissertation bibliography.

Pubmed Search – 17th June 2018

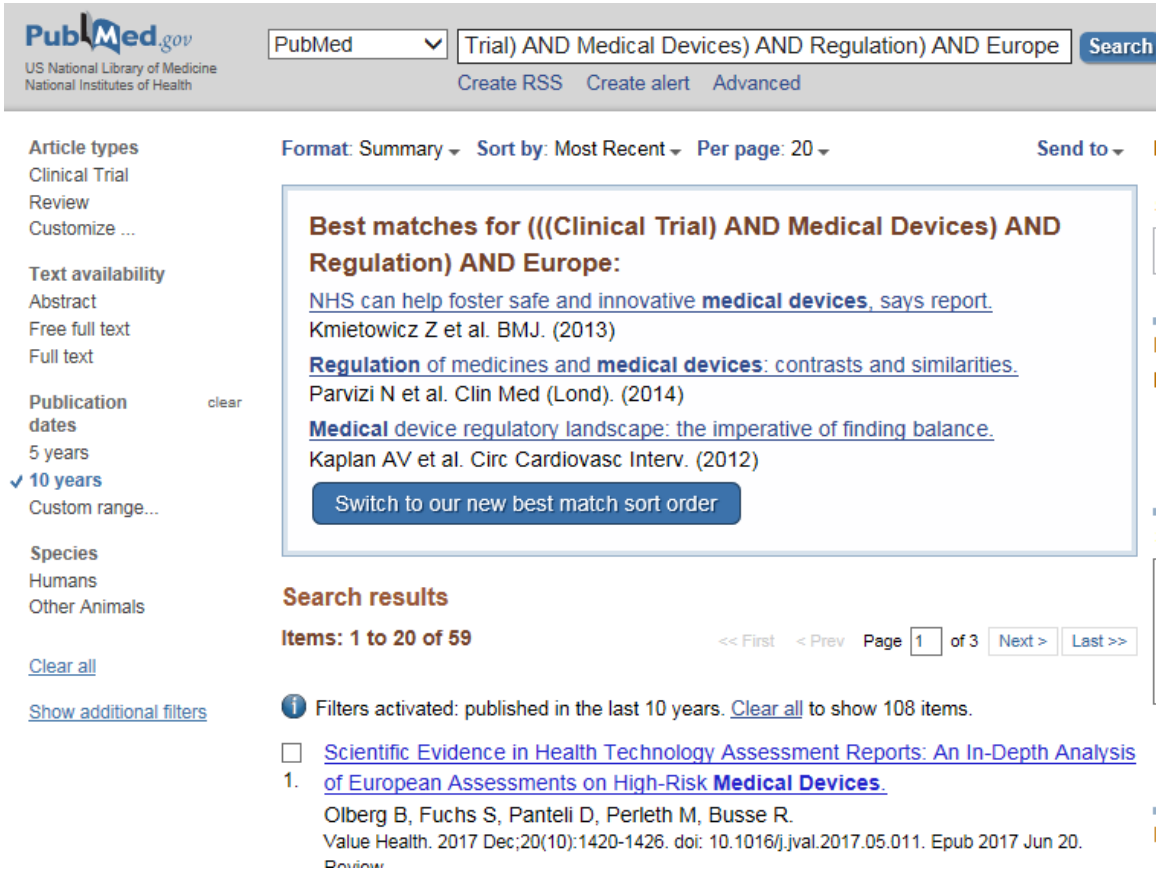
Search Criteria: Clinical Trial AND Medical Devices – 17th June 2018



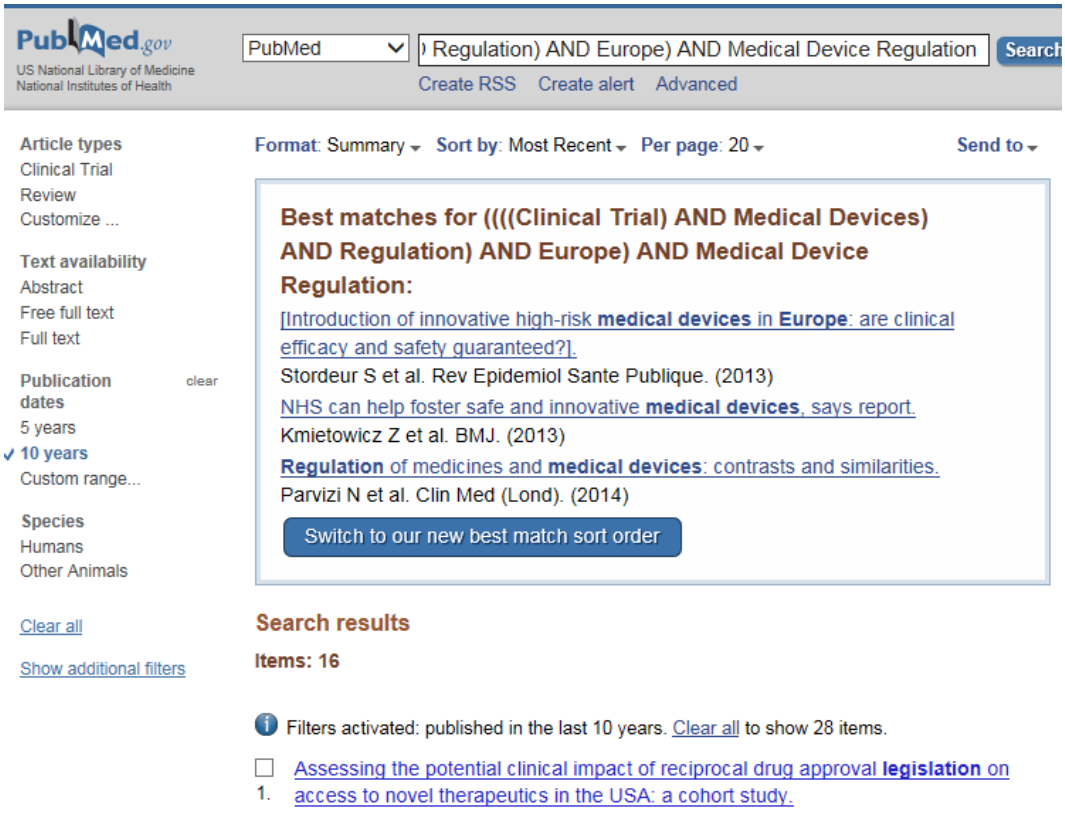
Search Criteria: Clinical Trial AND Medical Devices AND Regulation – 17th June 2018



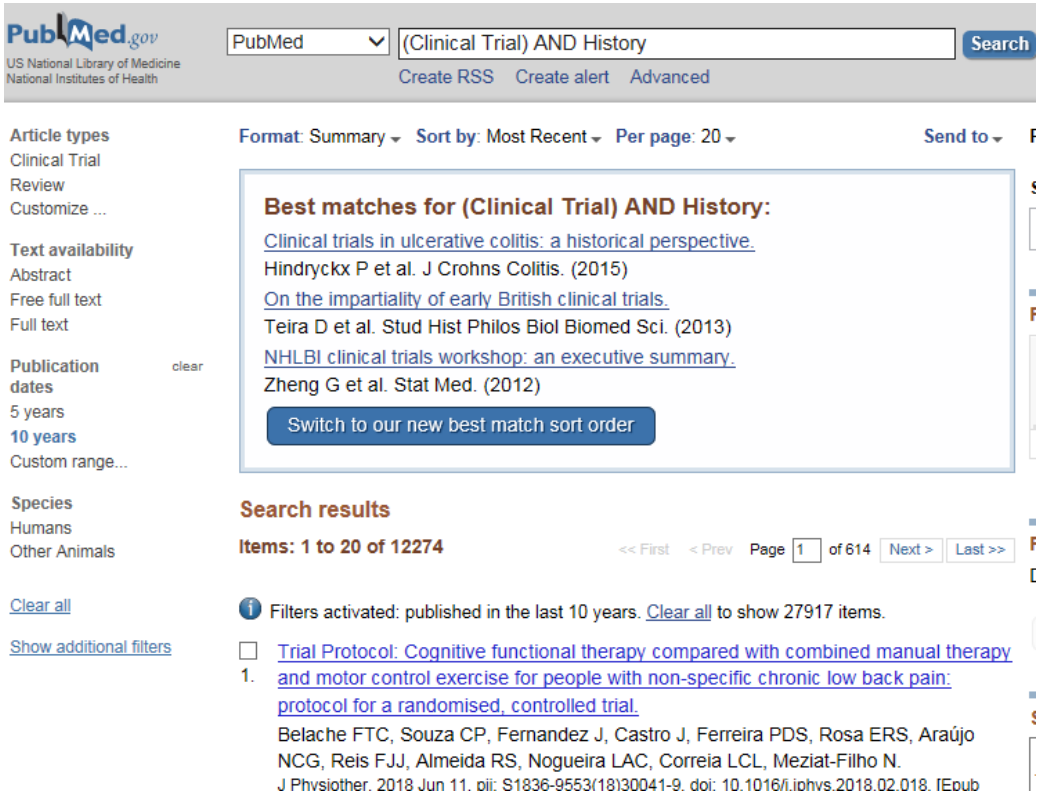
Search Criteria: Clinical Trial AND Medical Devices AND Regulation AND Europe



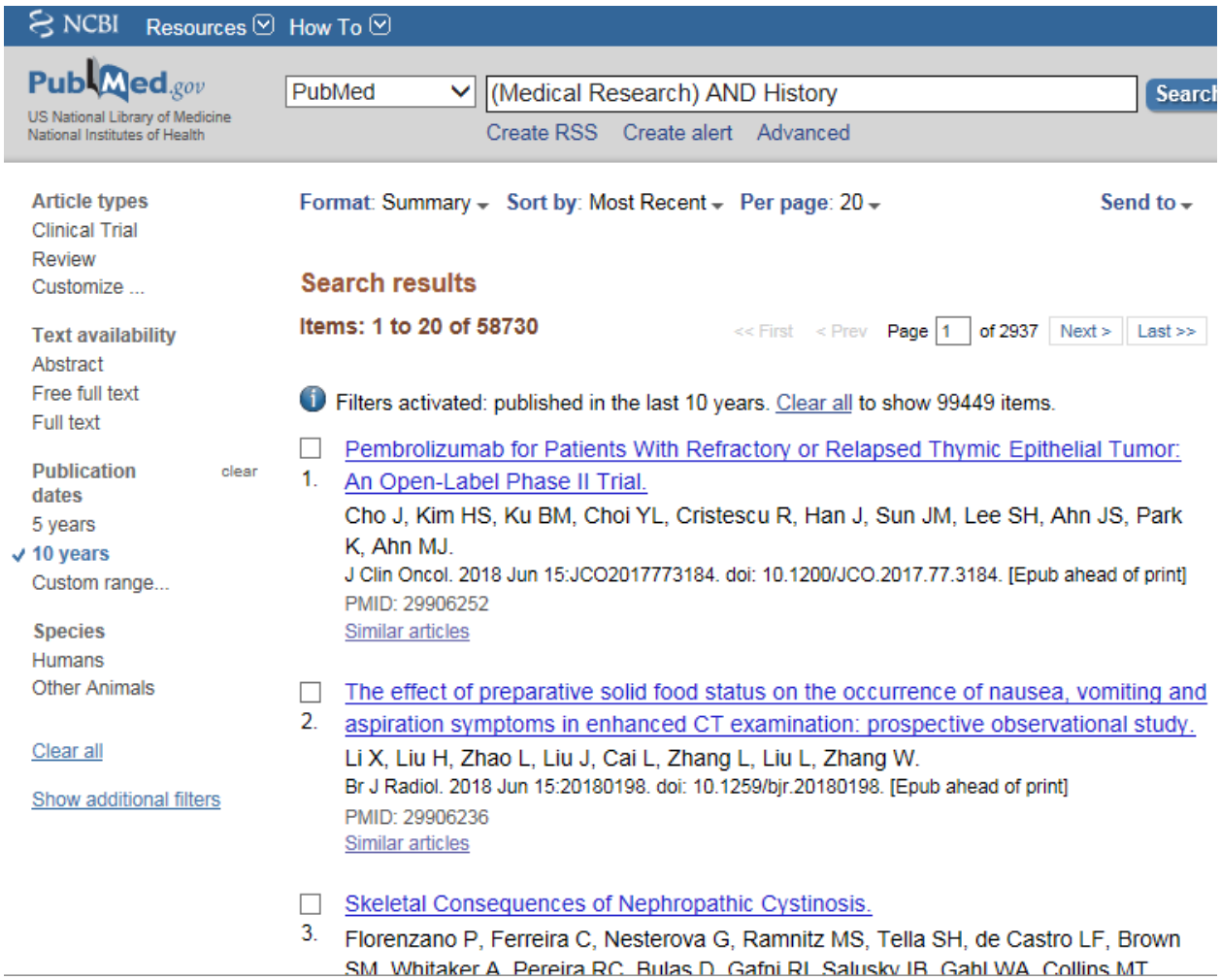
Search Criteria: Clinical Trial AND Medical Devices AND Regulation AND Europe AND Medical Device Regulation



Search Criteria: Clinical Trial AND History



Search Criteria: Medical Research AND History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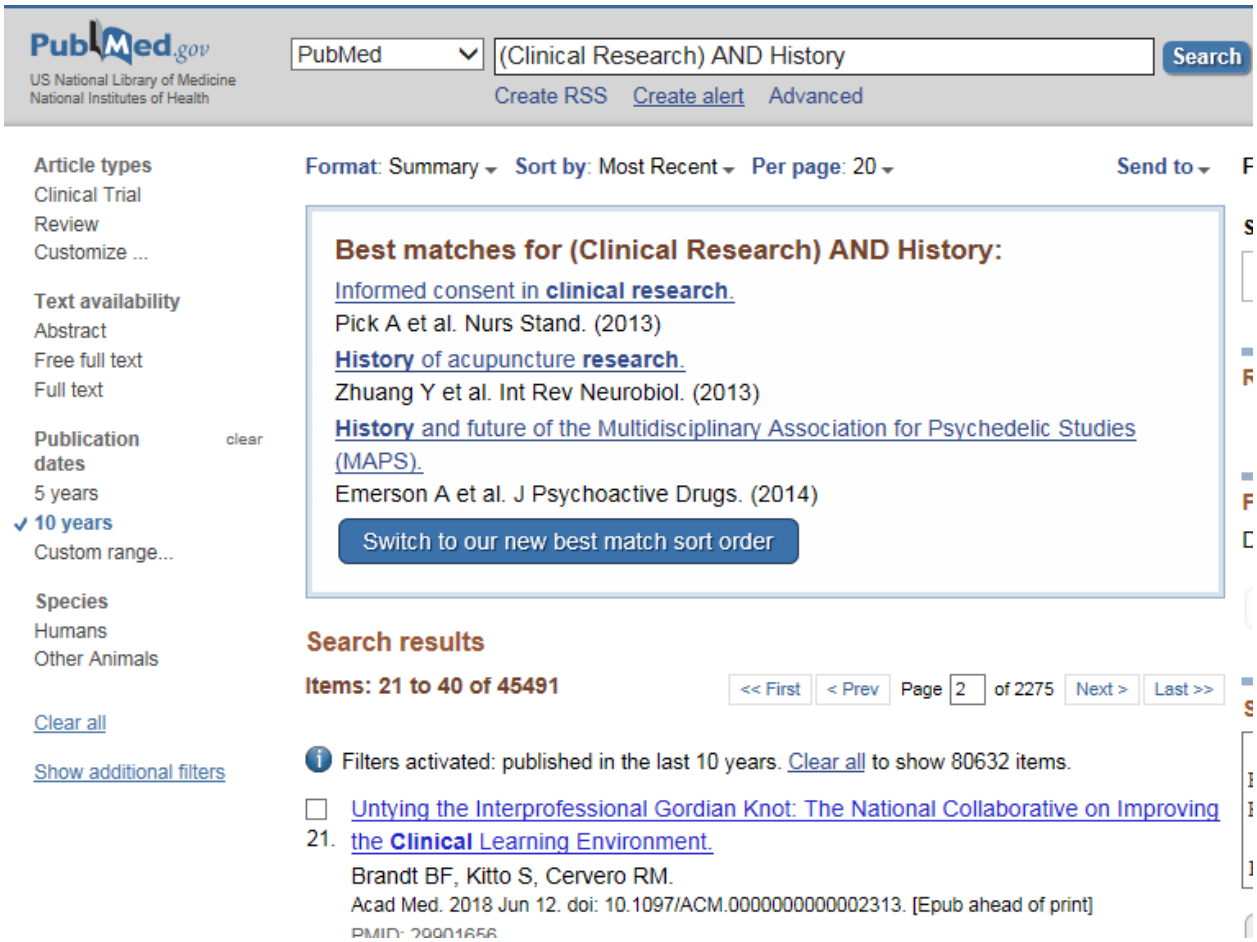

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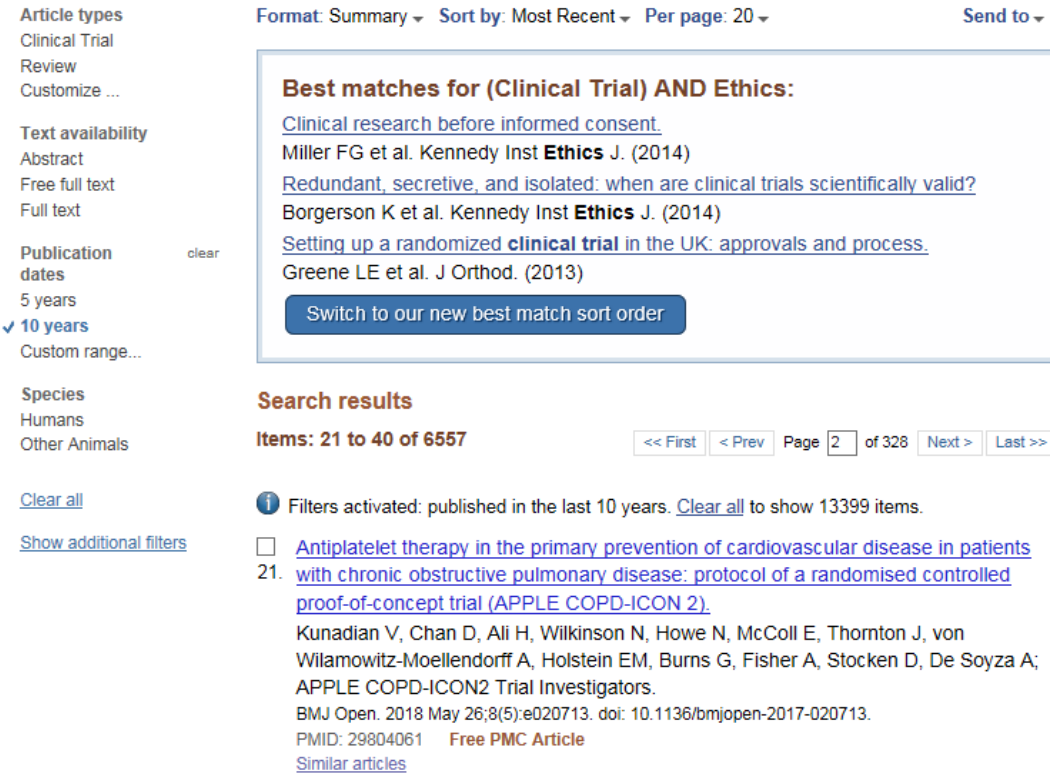

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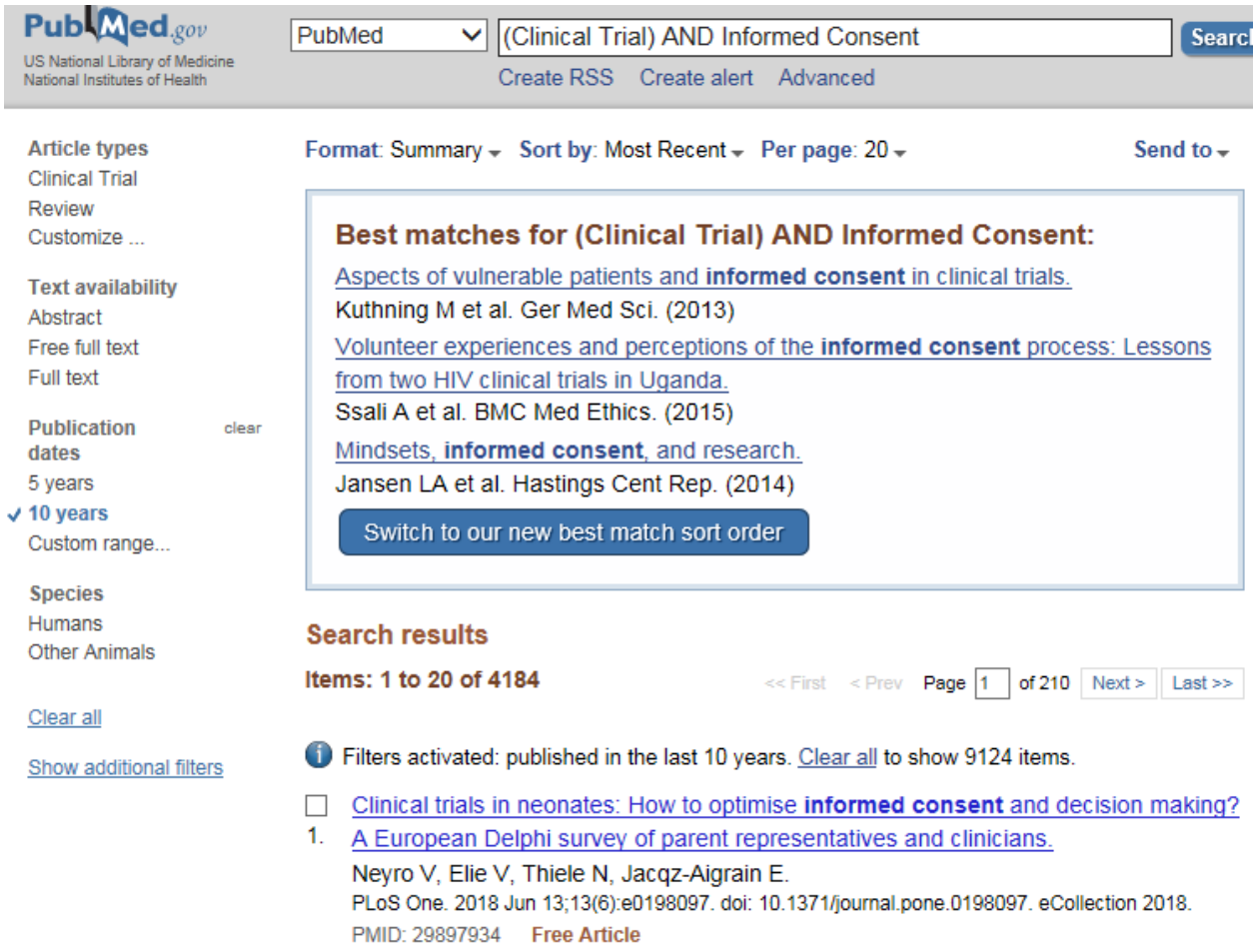

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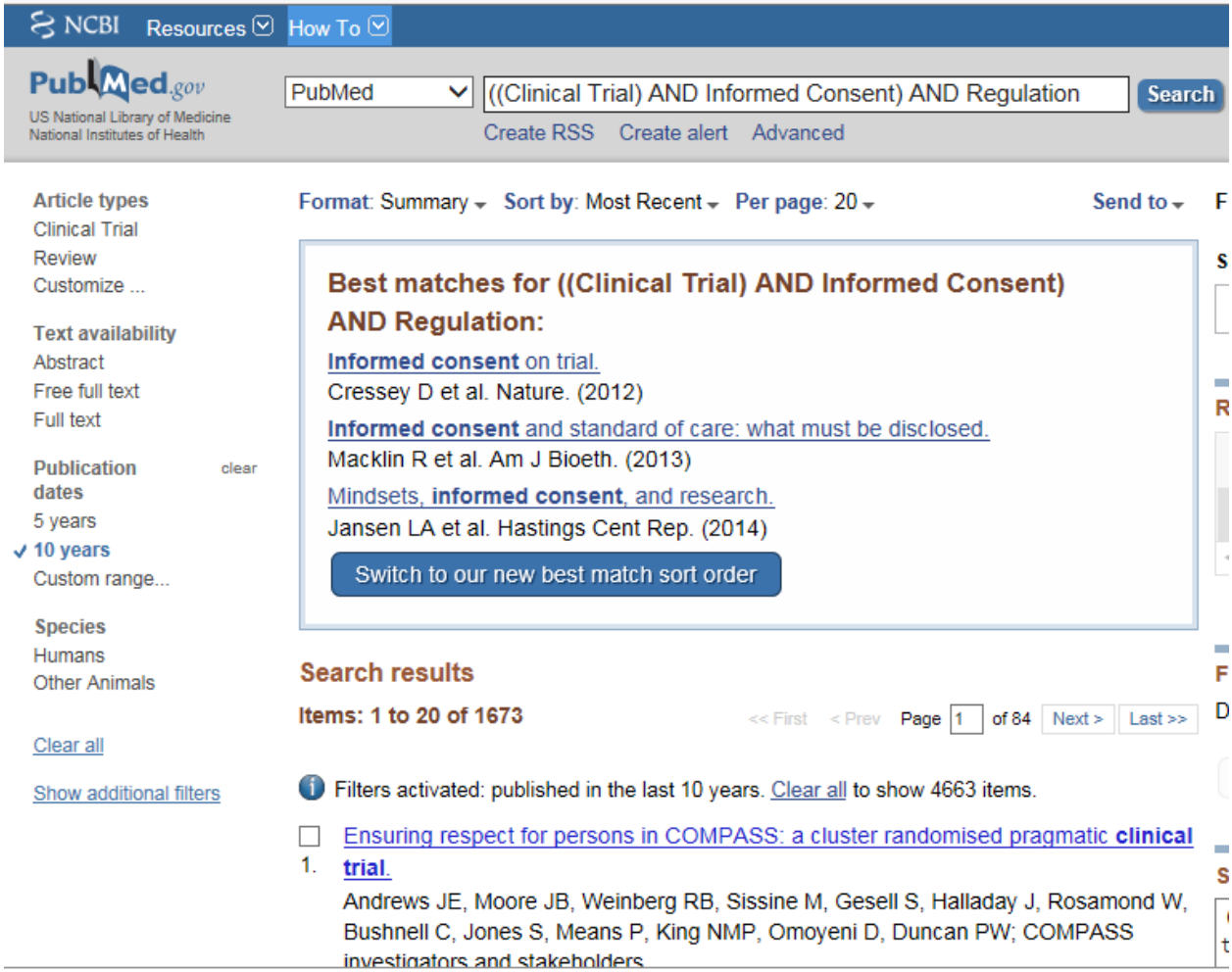

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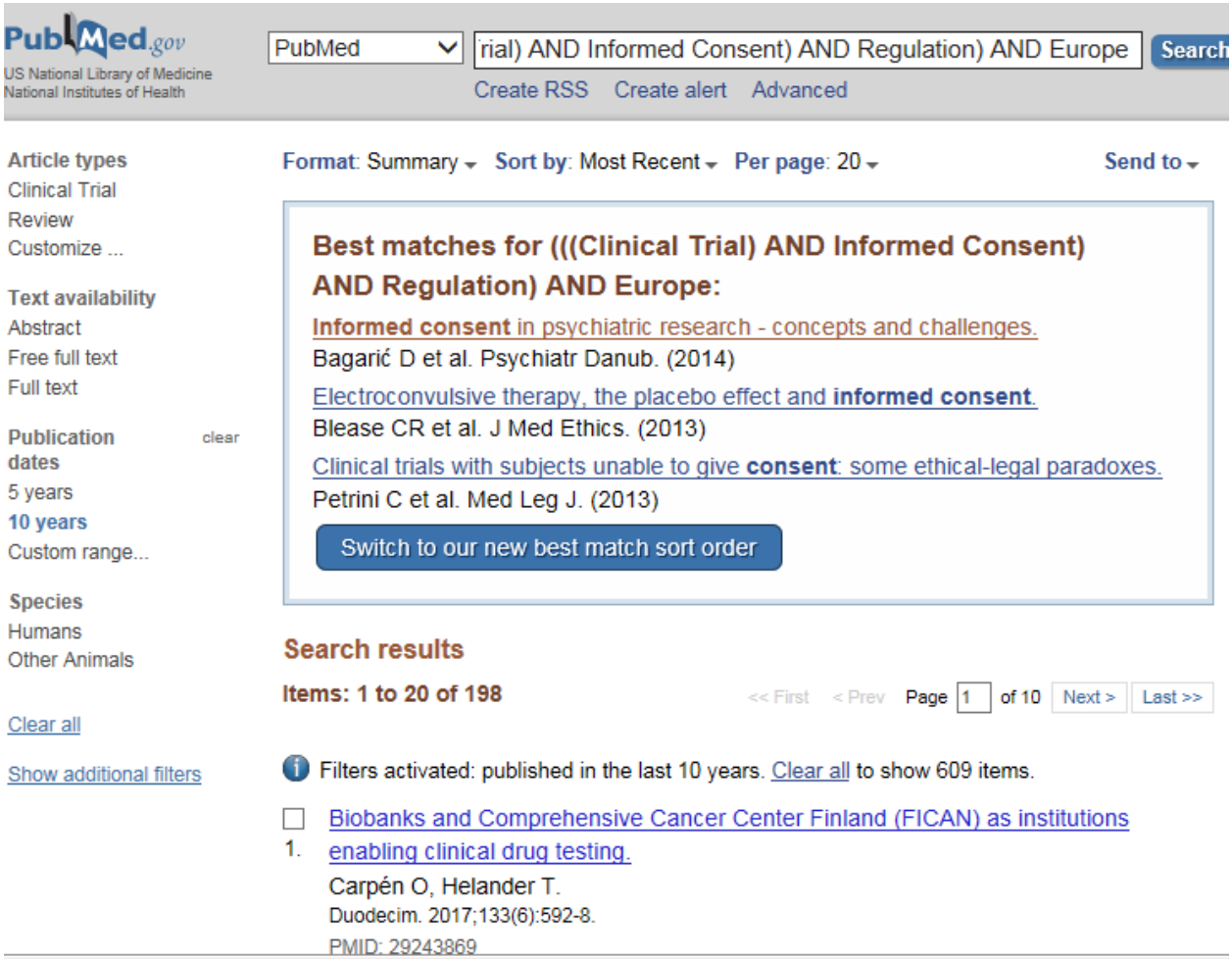

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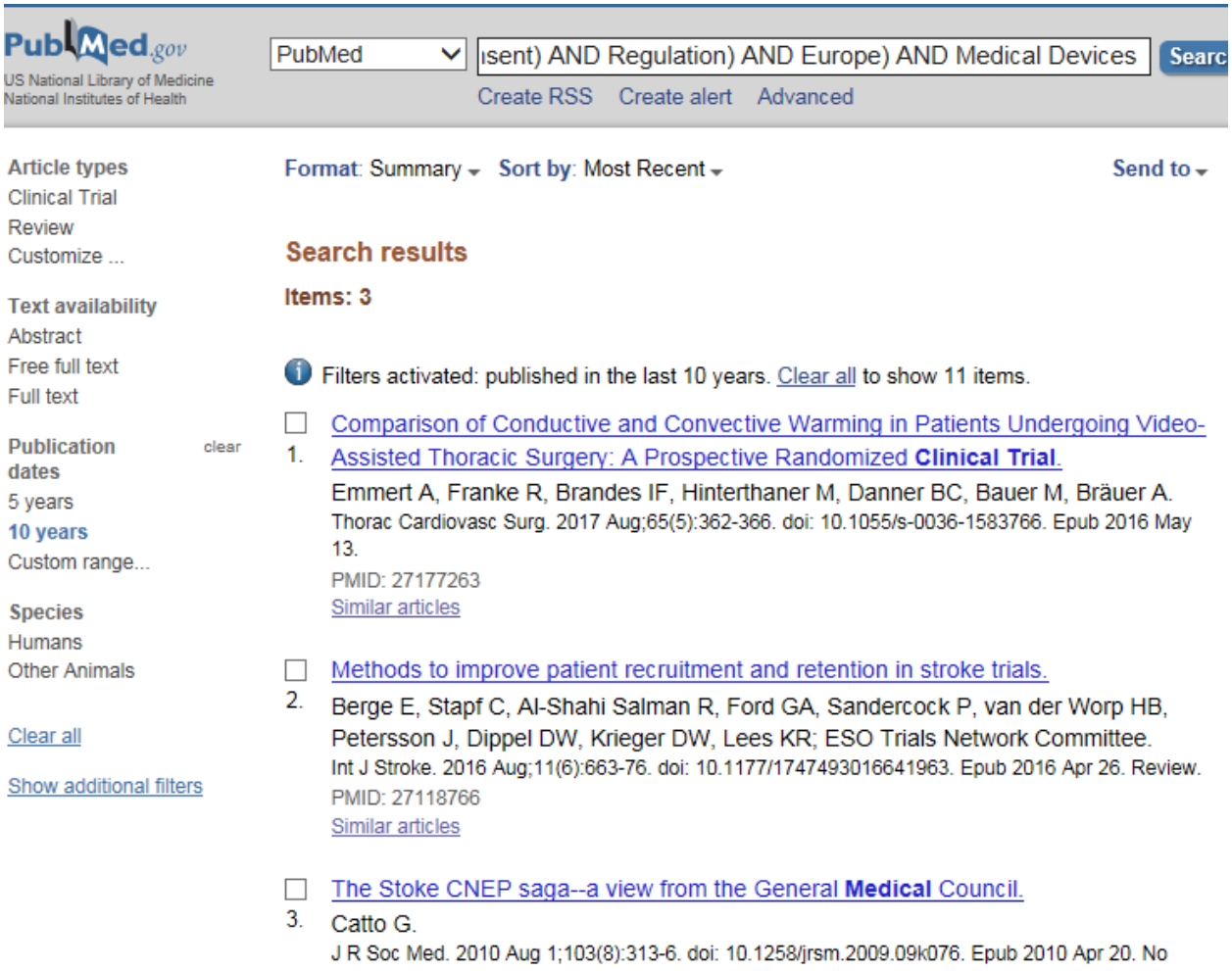

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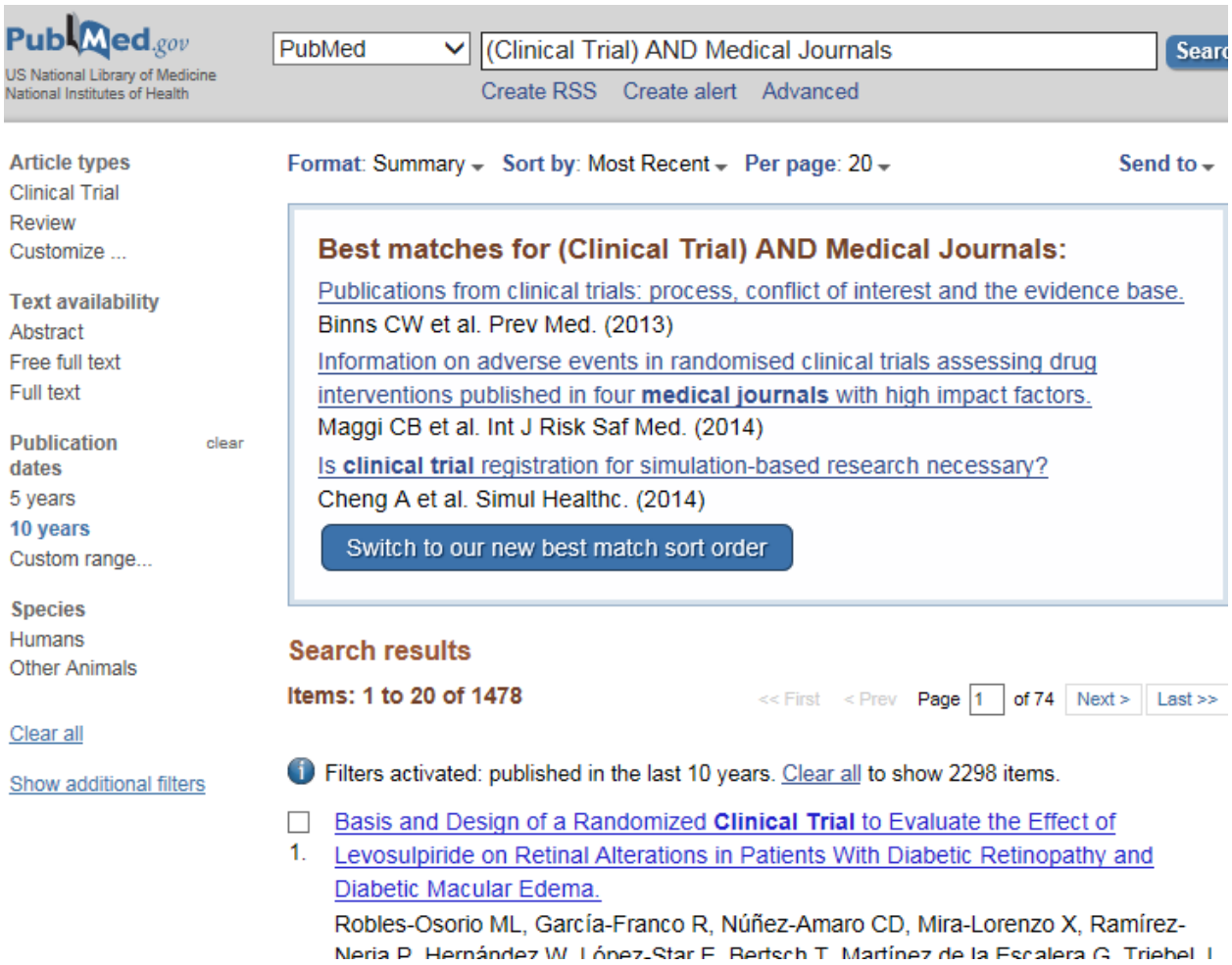

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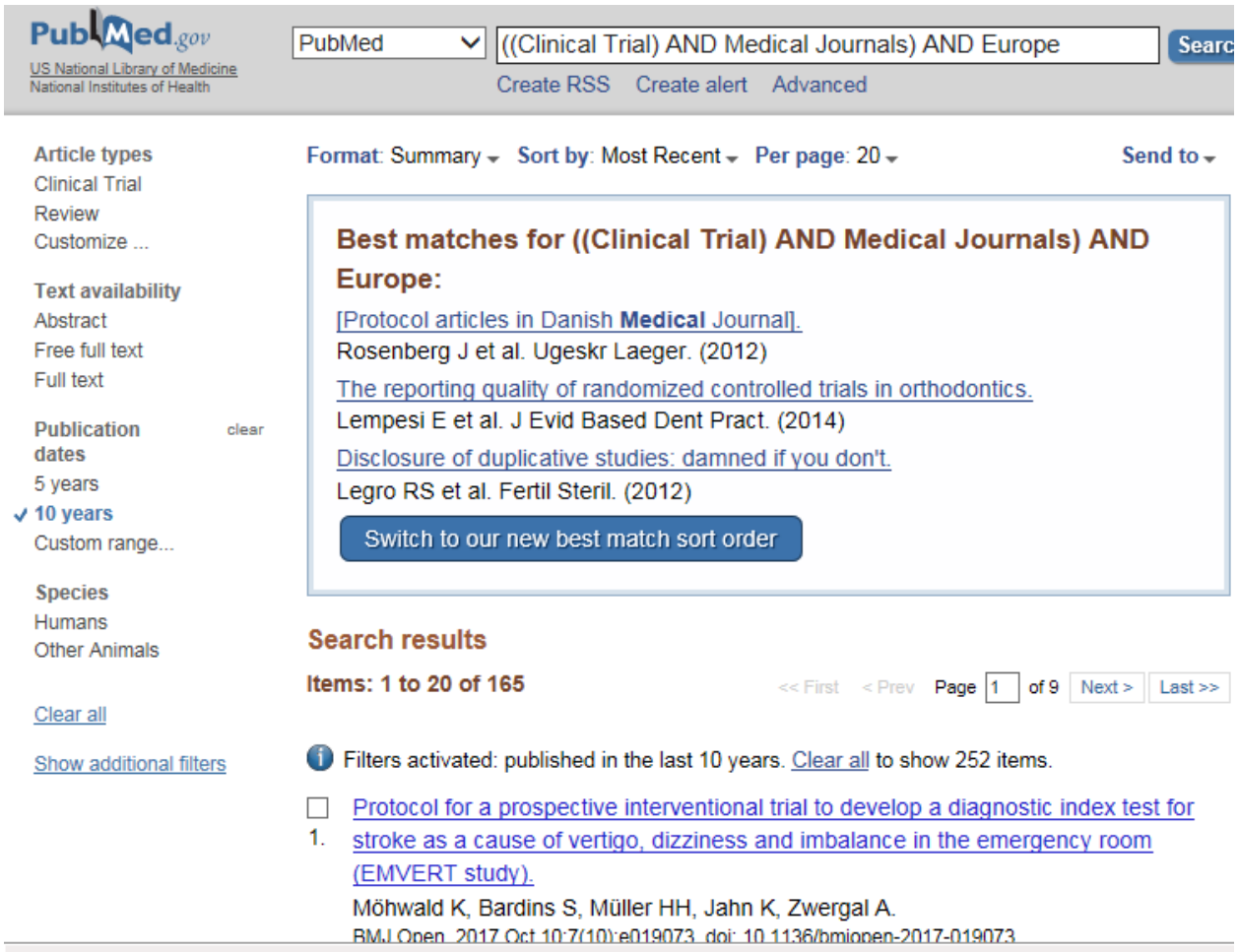

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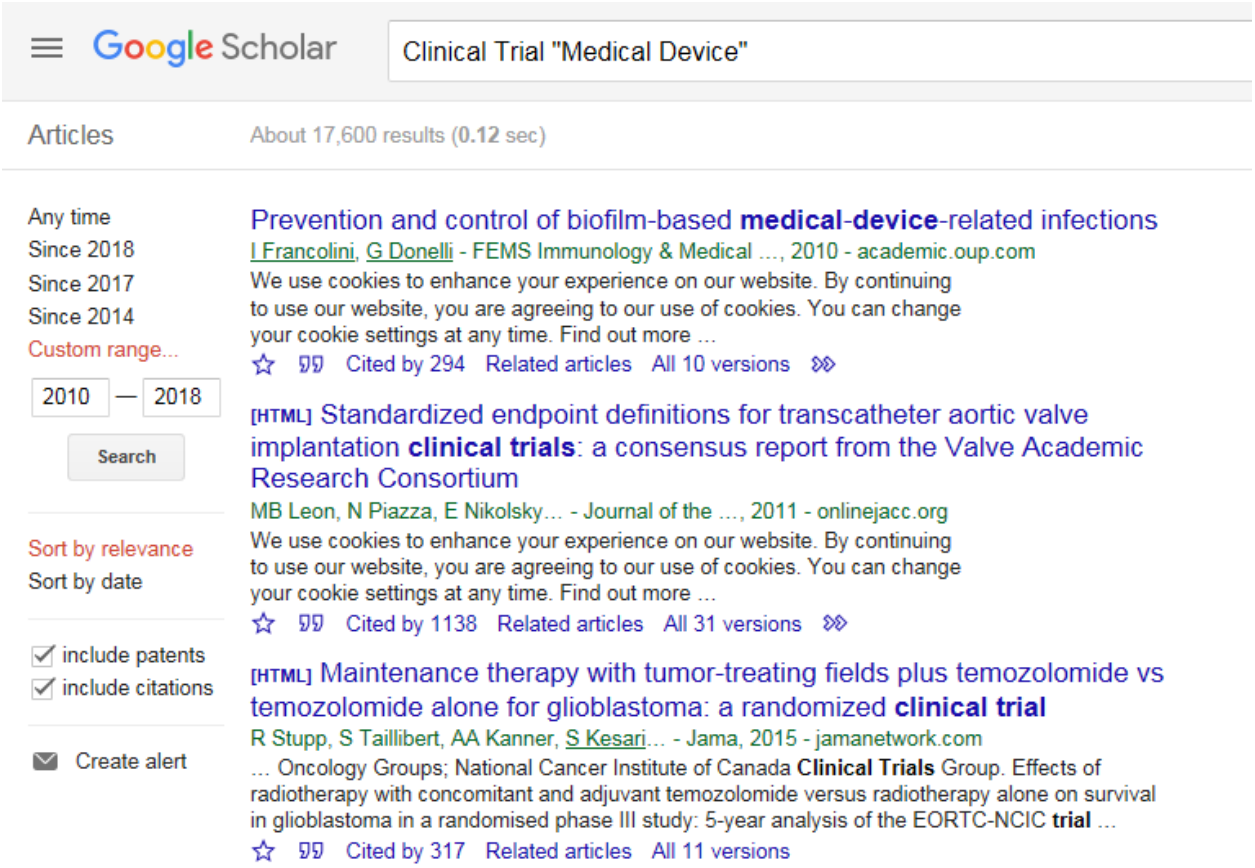

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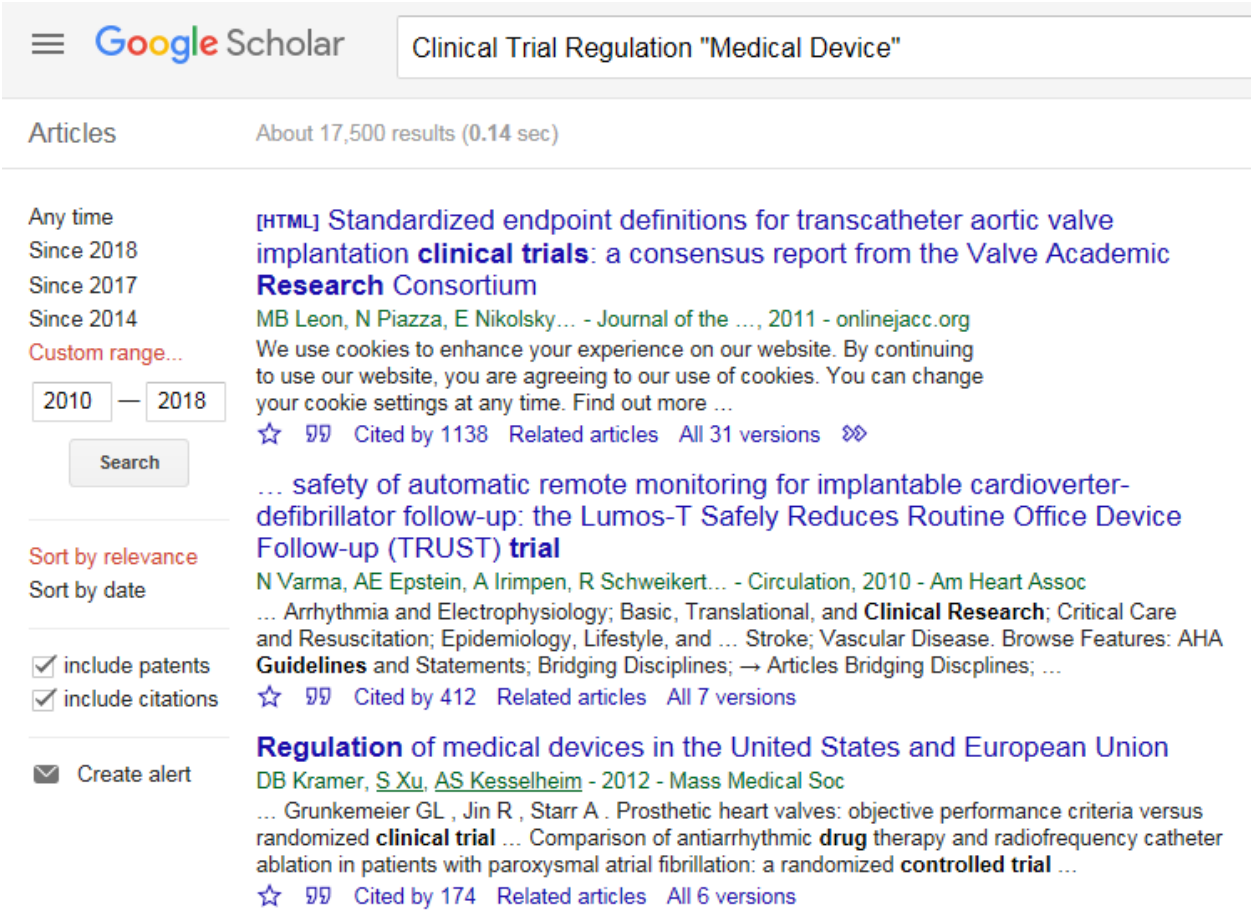

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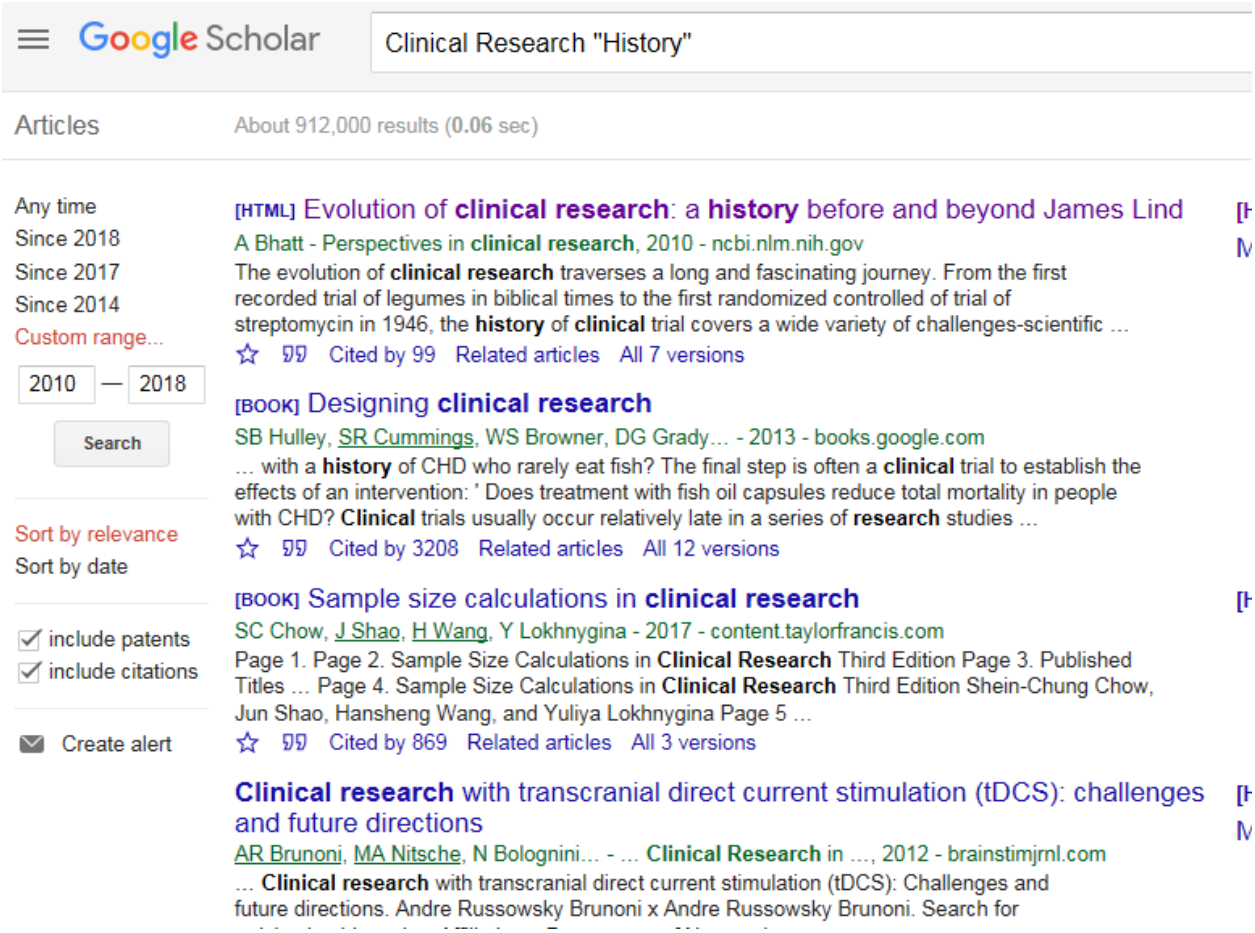

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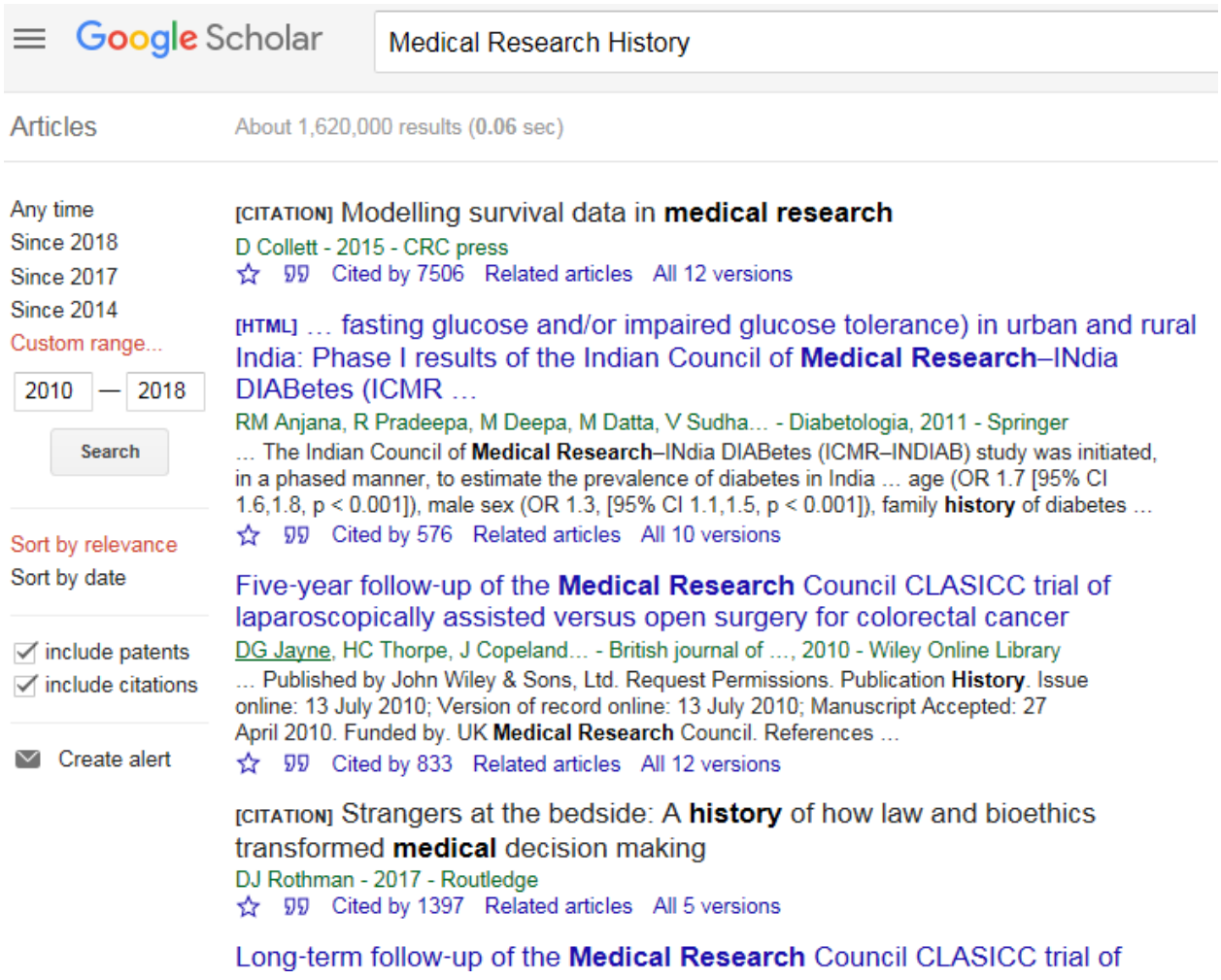

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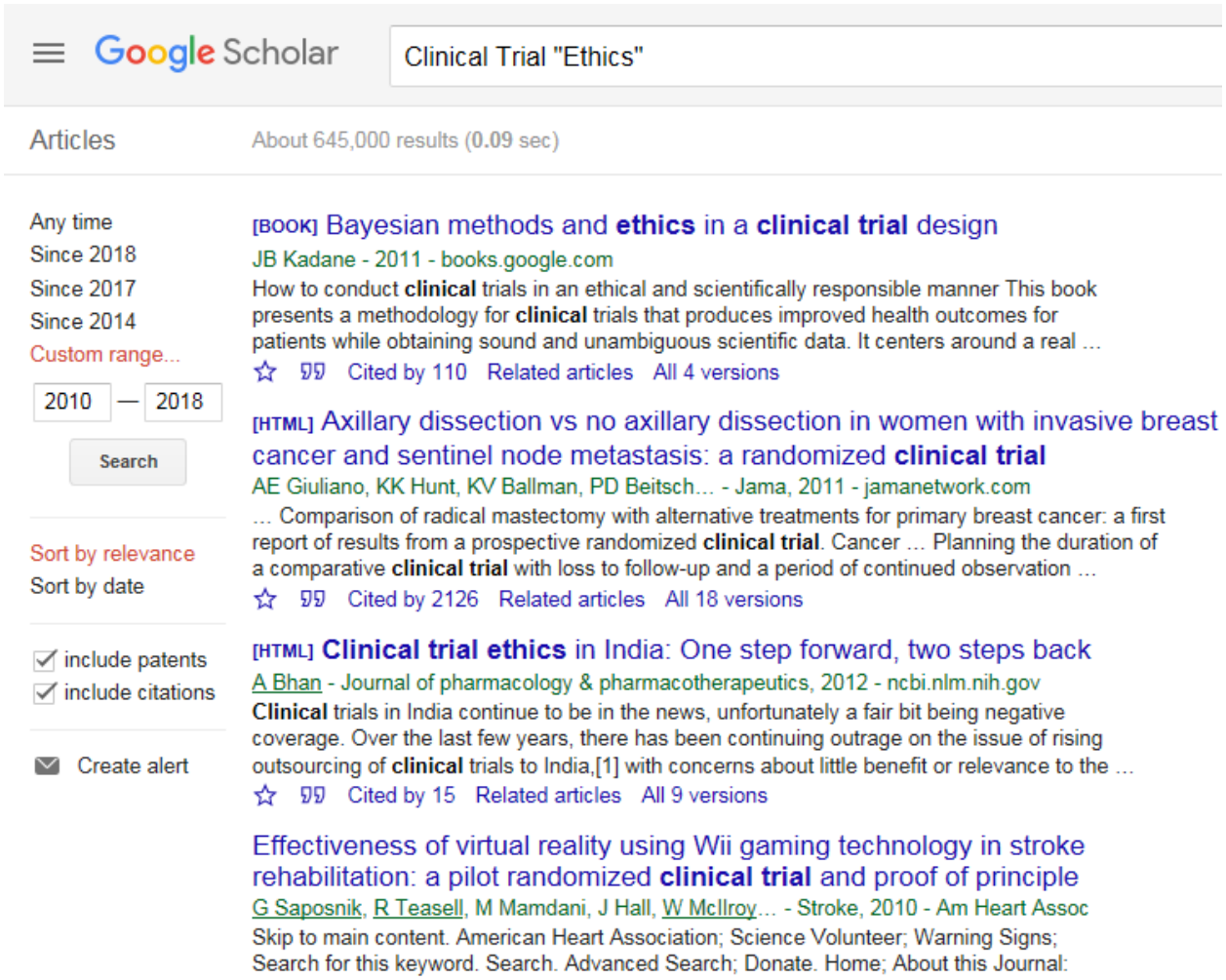

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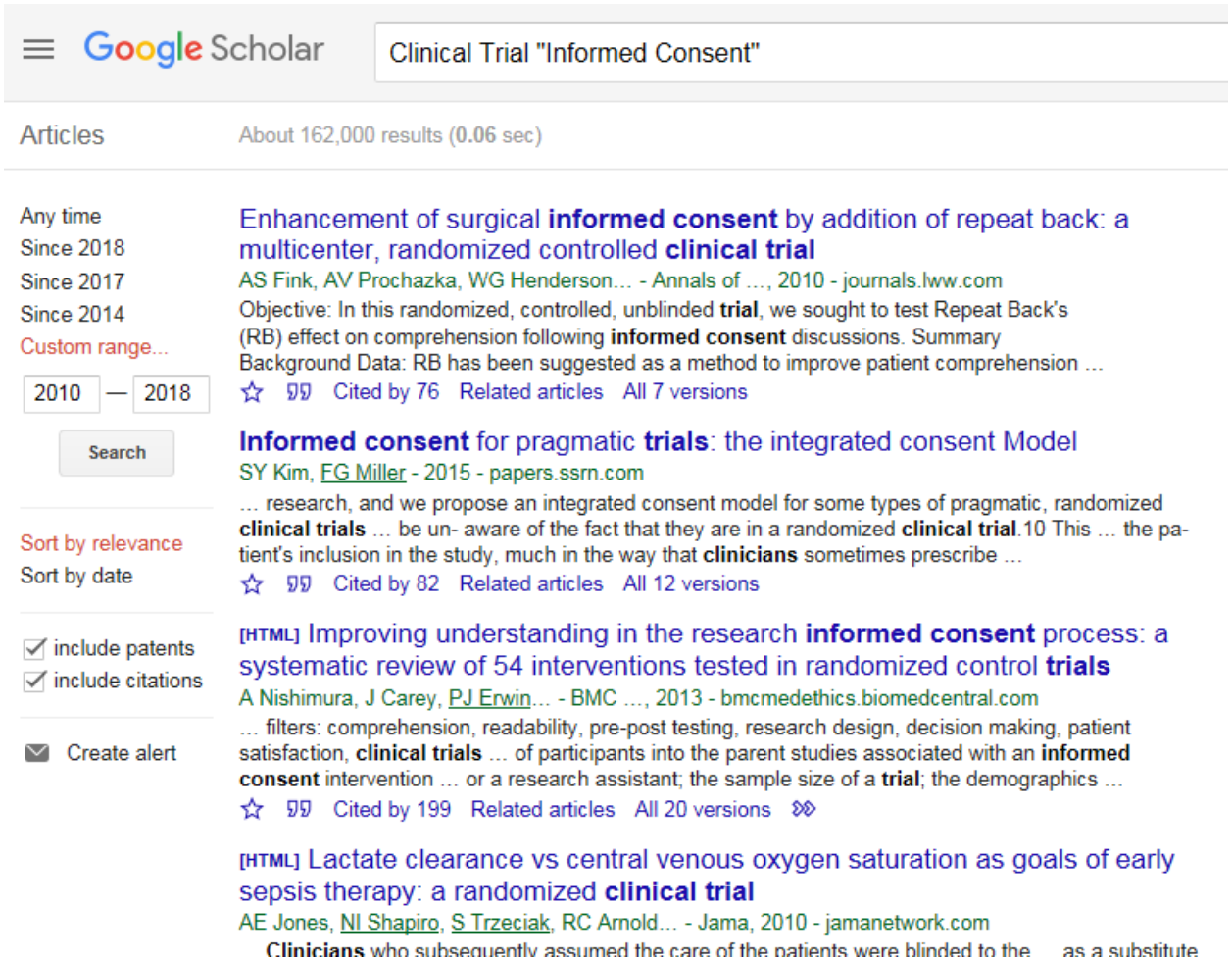

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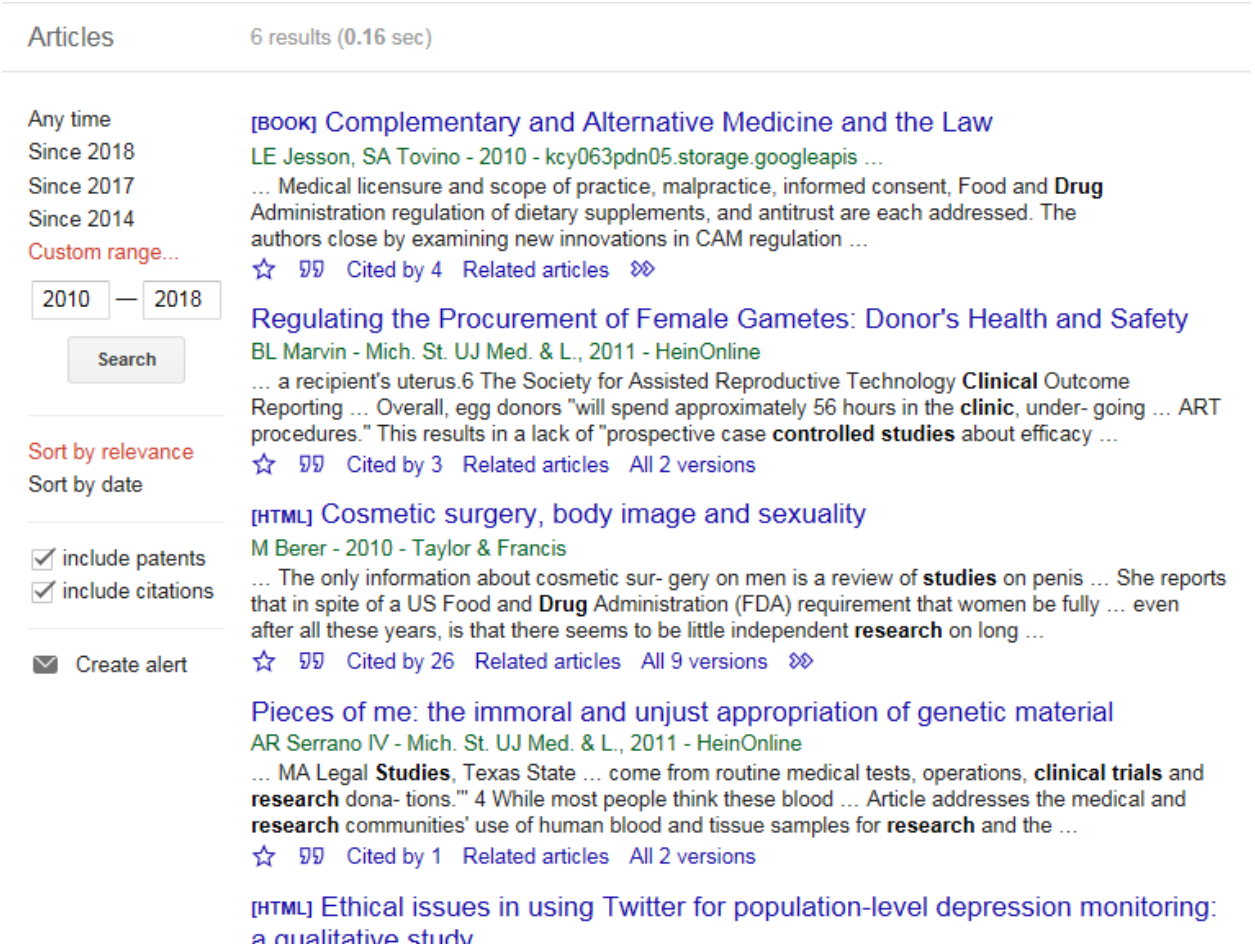

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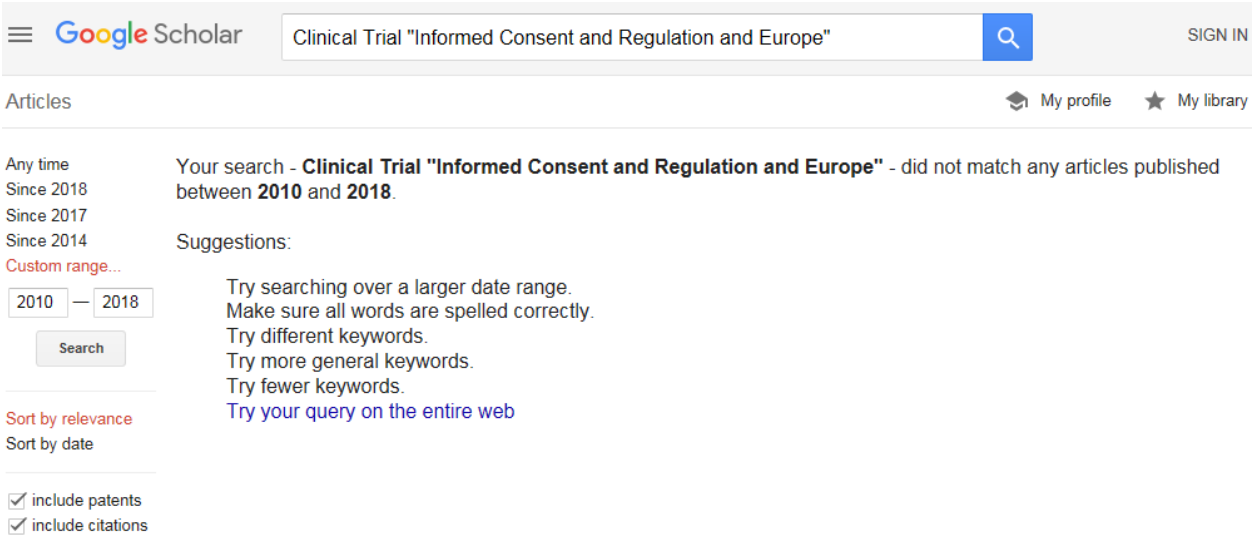

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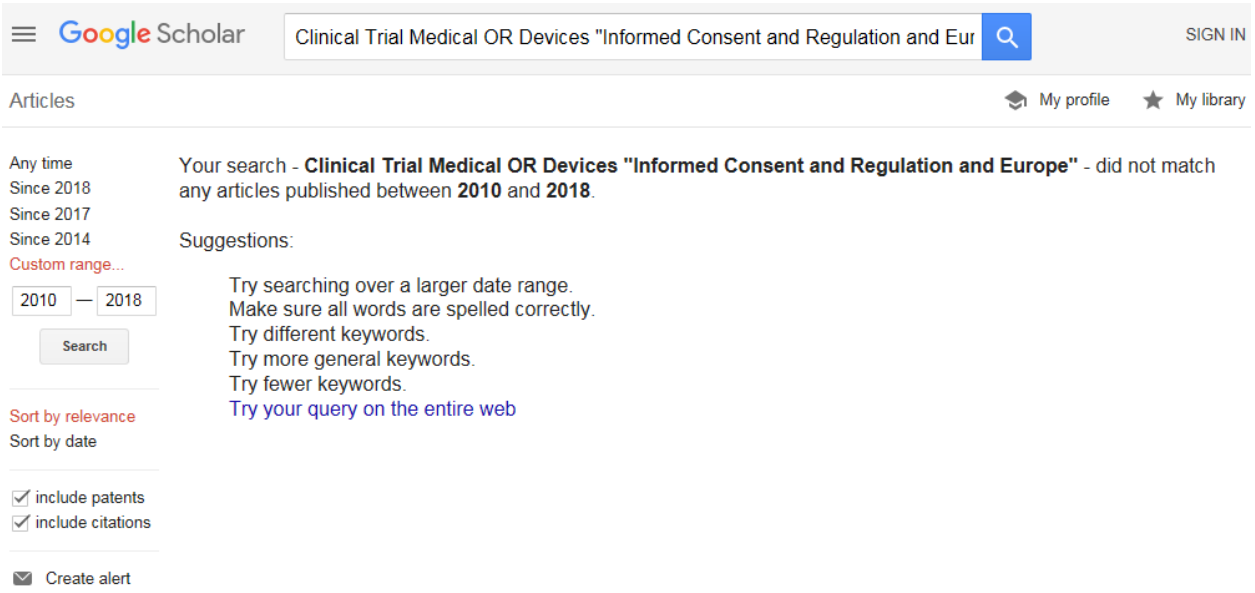

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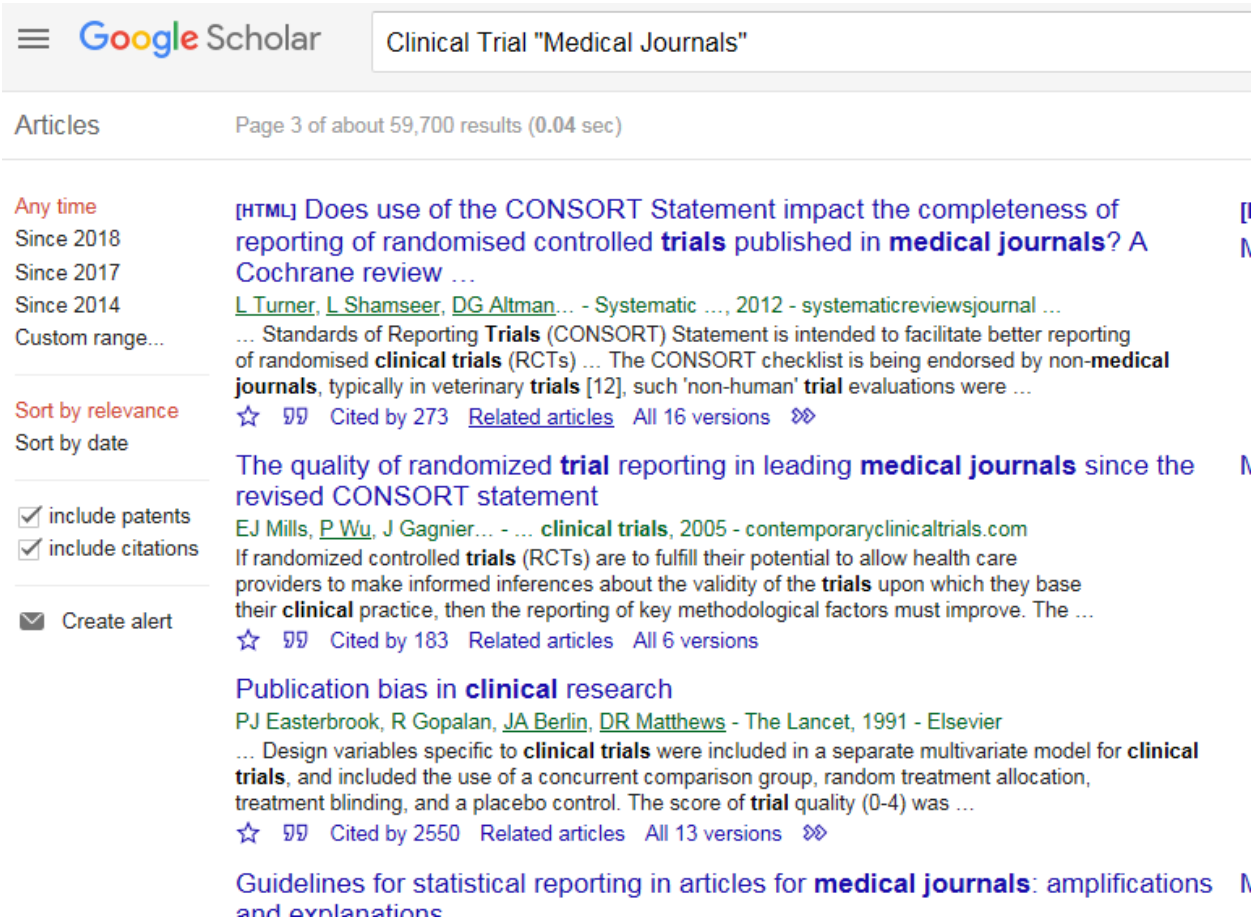

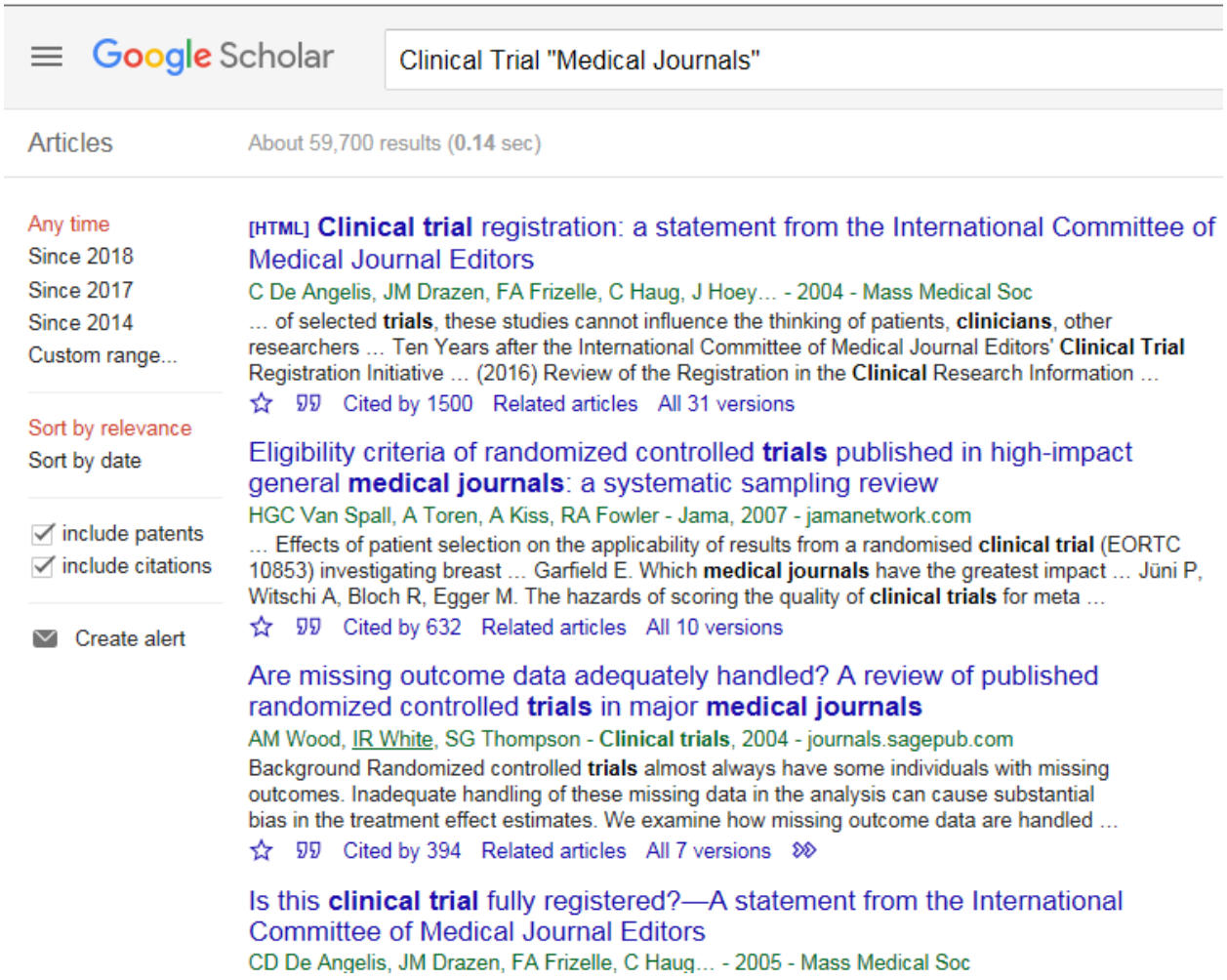
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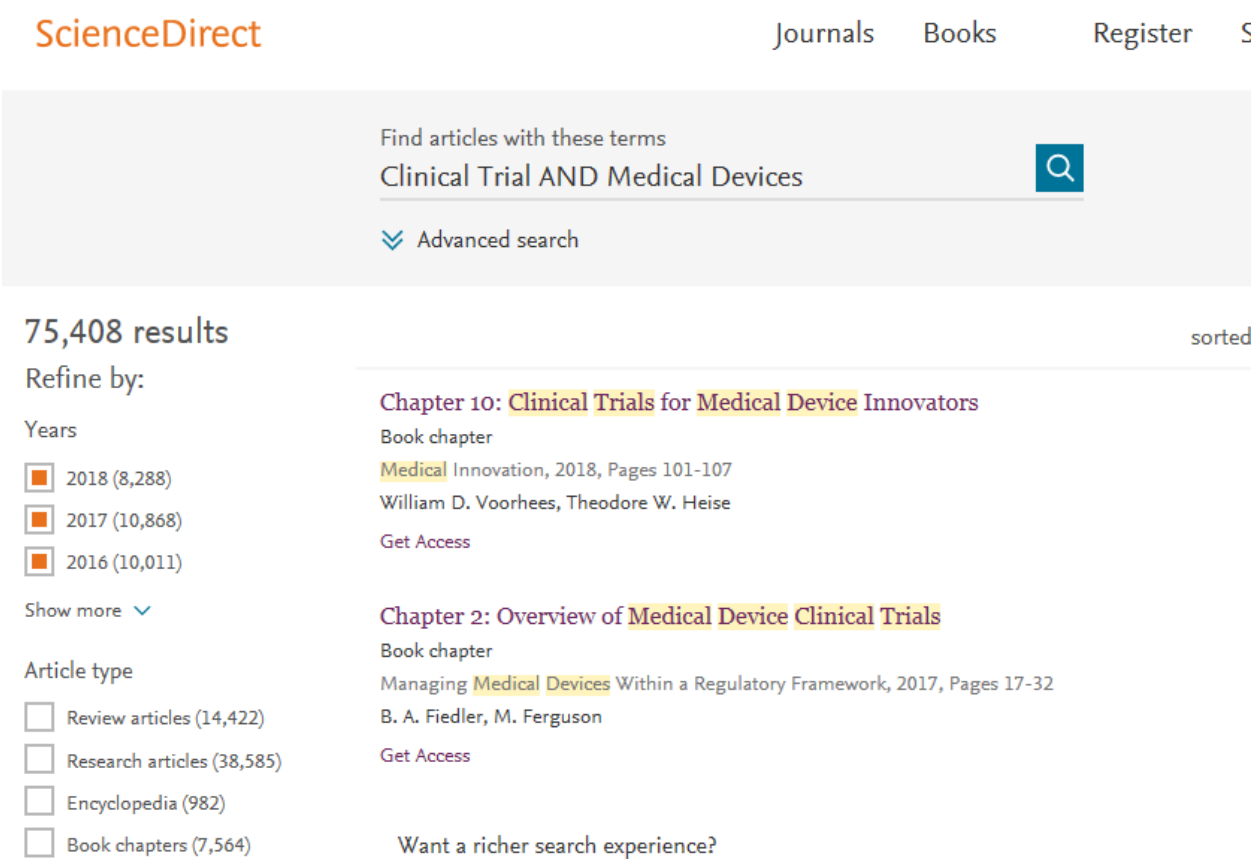

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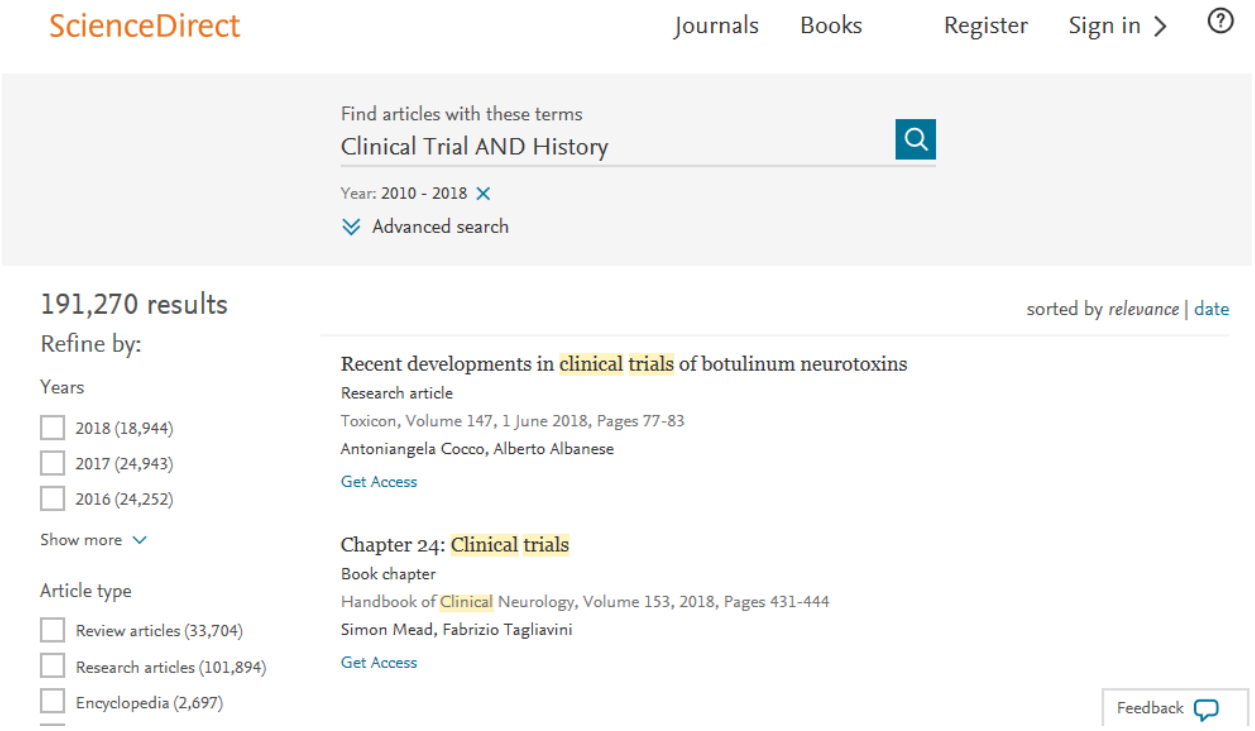

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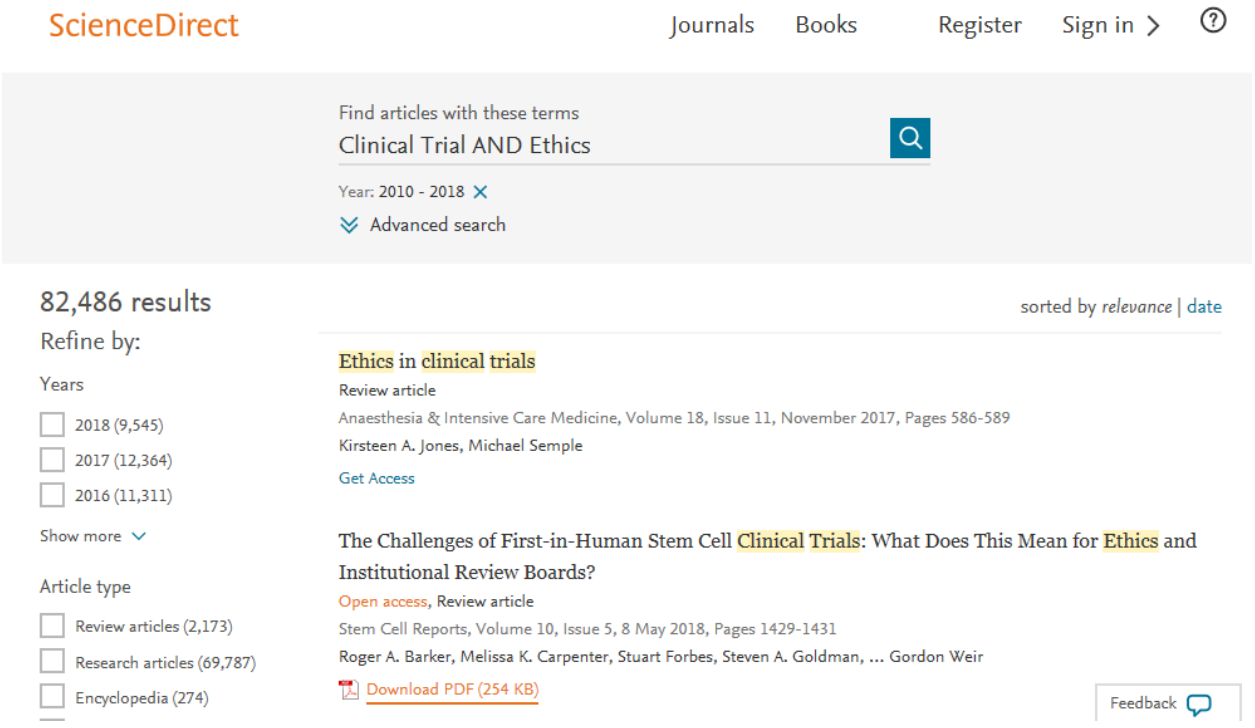

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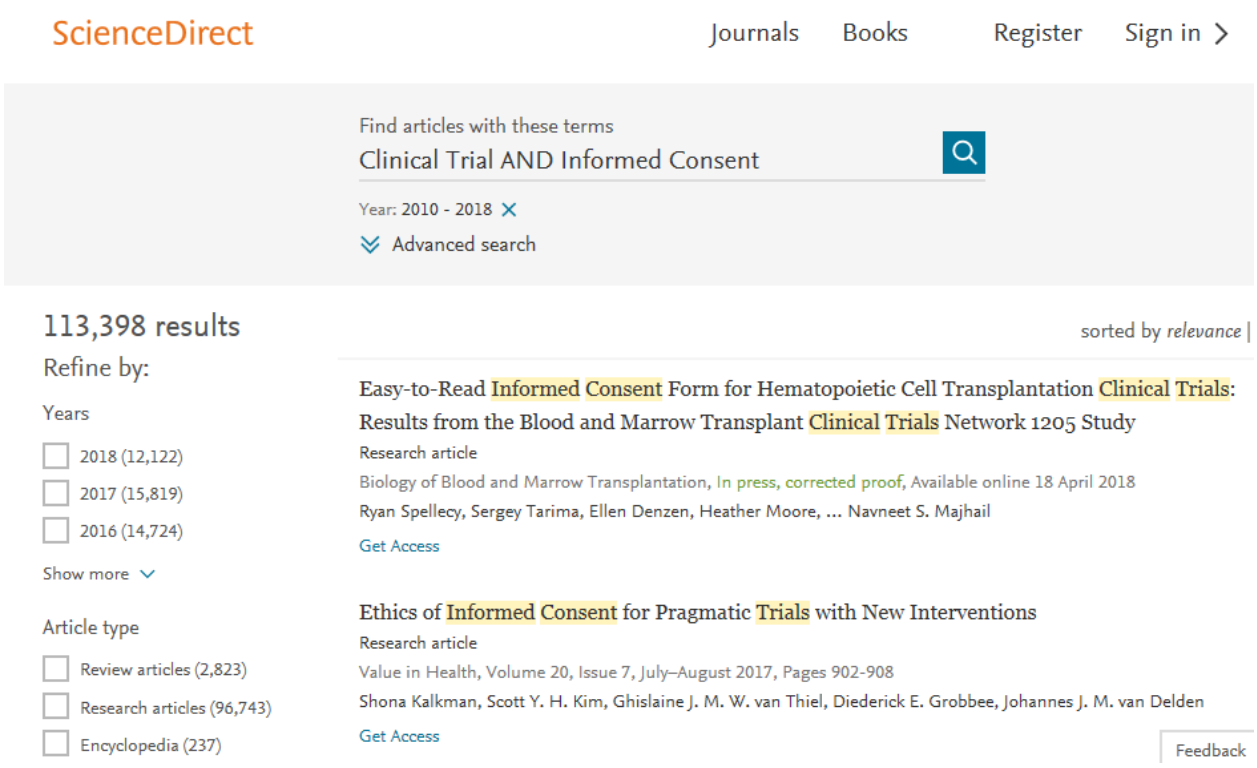

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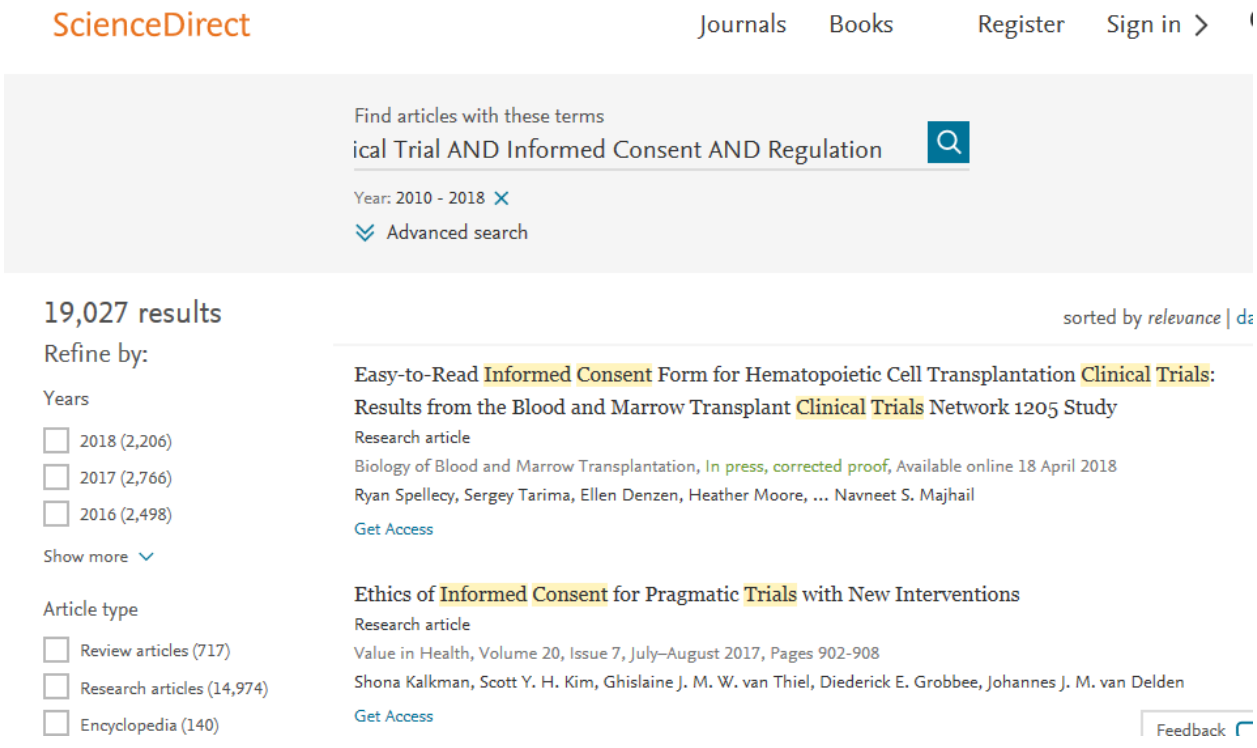

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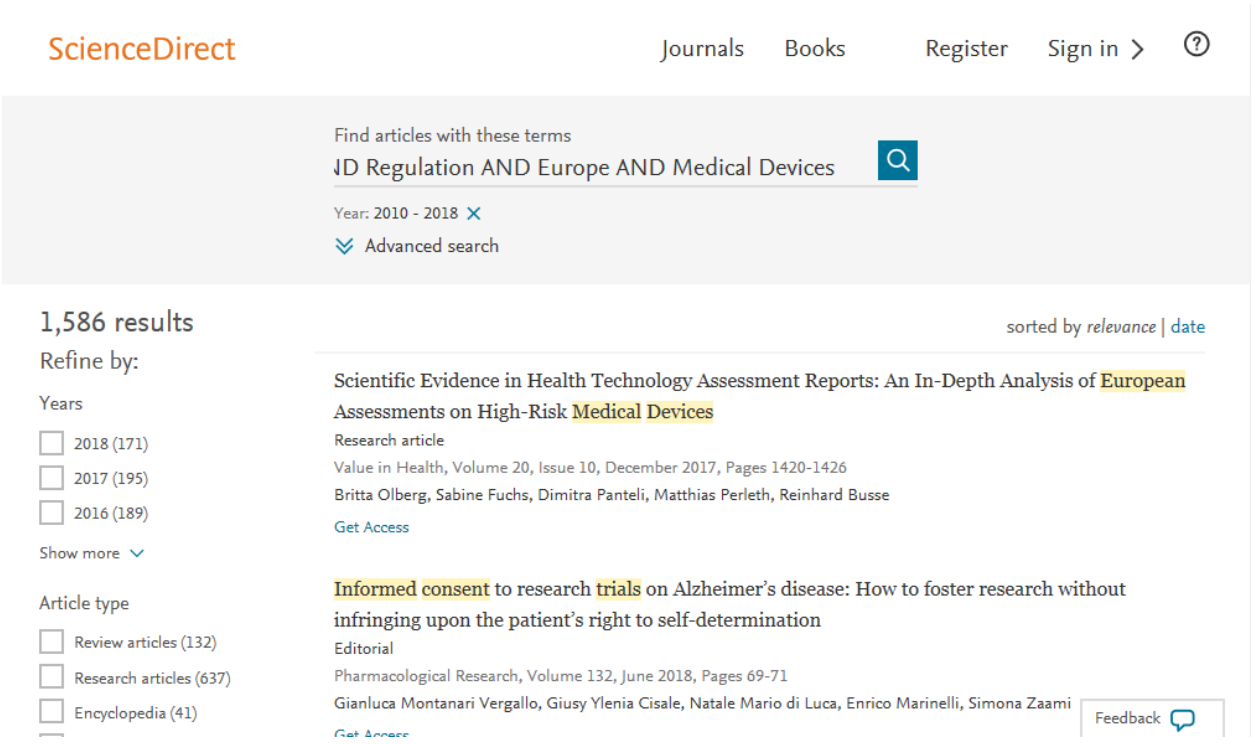

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