Send Orders for Reprints to reprints@benthamscience.net

The Open Spine Journal, 2013, *5*, 1-5

Open Access

Clinical Trials for New Implants in Spinal Surgery. The Oxford Experience

D. Rolton*, C.Thakar and C. Nnadi

Nuffield Orthopaedic Centre, Windmill Road, Oxford, UK

Abstract: Surgical implants have come under increasing scrutiny in recent years. A number of high profile failures have highlighted the importance of quality assurance and research that supports their use. Well designed clinical trials provide an objective way of assessing the effectiveness and safety in human subjects that can then be evaluated by the wider orthopaedic community. This article highlights some of the problems with current implant regulations and the stages in designing a clinical trial for an orthopaedic implant.

Keywords: Clinical Trial, Implants, Spinal Surgery.

INTRODUCTION

Orthopaedic surgeons are regularly presented with new devices and implants by commercial companies which propose new benefits and advantages to existing designs. In an ideal world each implant would come with long term clinical data which references long term outcomes and potential complications to support their use. In reality this is rarely the case and orthopaedic surgeons are often criticised for the lack of well-designed clinical trials to support their practice. In recent years there have been well documented cases of early implant failure within the arthroplasty community leading to significant repercussions for the orthopaedic community at large [1-3]. The pressure of commercialism for implants to succeed has resulted in some implants entering the market place without necessarily the supporting evidence for their use. This contrasts with the extent of clinical trial data required from the pharmaceutical industry. Given the current health economic climate, there is now a greater need to ensure public safety and confidence in the implants that we use whilst striving for improved clinical and cost effectiveness. Whilst costly in the short term, emerging research exists supporting the cost benefit of clinical trials to the public health [4].

The recent early failure of the ASR hip has once again questioned the research and attention that goes into approving orthopaedic implants before their use in human subjects. The orthopaedic industry is not alone with these concerns; increased rupture rates of PIP breast implants that are said to have affected 35000-45000 women worldwide also highlighting problems with inadequate regulation of the implant industry as a whole.

The arthroplasty community has responded to these concerns by setting up national joint registries, which can pick up trends towards early failures and implant problems on a national scale. The 9th Annual report from the National Joint registry [5] revealed an unacceptable failure rate of 24.2 % at 7 years for the ASR. Tighter regulation and use of clinical trial data may have led to earlier detection of the ASR failings.

The potential for long term patient morbidity due to implant failure in spinal surgery would appear higher given the location and nature of the surgery. Bearing surfaces have now become a reality in spinal surgery with the advent of disc replacements, which are gaining popularity despite the lack of long term data to support their use. Spinal registries such as the European Spine Tango and more recently the British Spine registry have been set up but remain in infancy.

Surprisingly, regulations for introducing an implant to the market differ between Europe and America. Worryingly there are a number of examples of implants that were rejected by the Food and Drug Administration (FDA) but were approved by the EU (1) such as the ASR hip and PIP breast implants. In Europe the level of clinical data required for a new device can be minimal and is often at the discretion of the Notified Bodies. There is no need for proof of clinical efficacy prior to general use in Europe, unlike in the pharmaceutical industry. There are three main risk based categories for medical devices. The level of risk to the patient increases from Class I to III. Device classification depends on intended use of the device and indications for use. Orthopaedic devices are class III as they "support or sustain human life, are of substantial importance in preventing impairment of human health, or which prevent a potential, unreasonable risk of illness or injury." A CE (European conformity) mark is granted by a number of notified bodies in individual European countries and is the only prerequisite for an implant entering the market. The CE mark may remarkably be awarded based on clinical evaluations based on existing technologies rather than the actual evaluation of the new device!

*Address correspondence to this author at the Nuffield Orthopaedic Centre, Windmill Road, Oxford, UK; Tel: 01865 741155;
E-mails: danrolton@hotmail.com

1876-5327/13

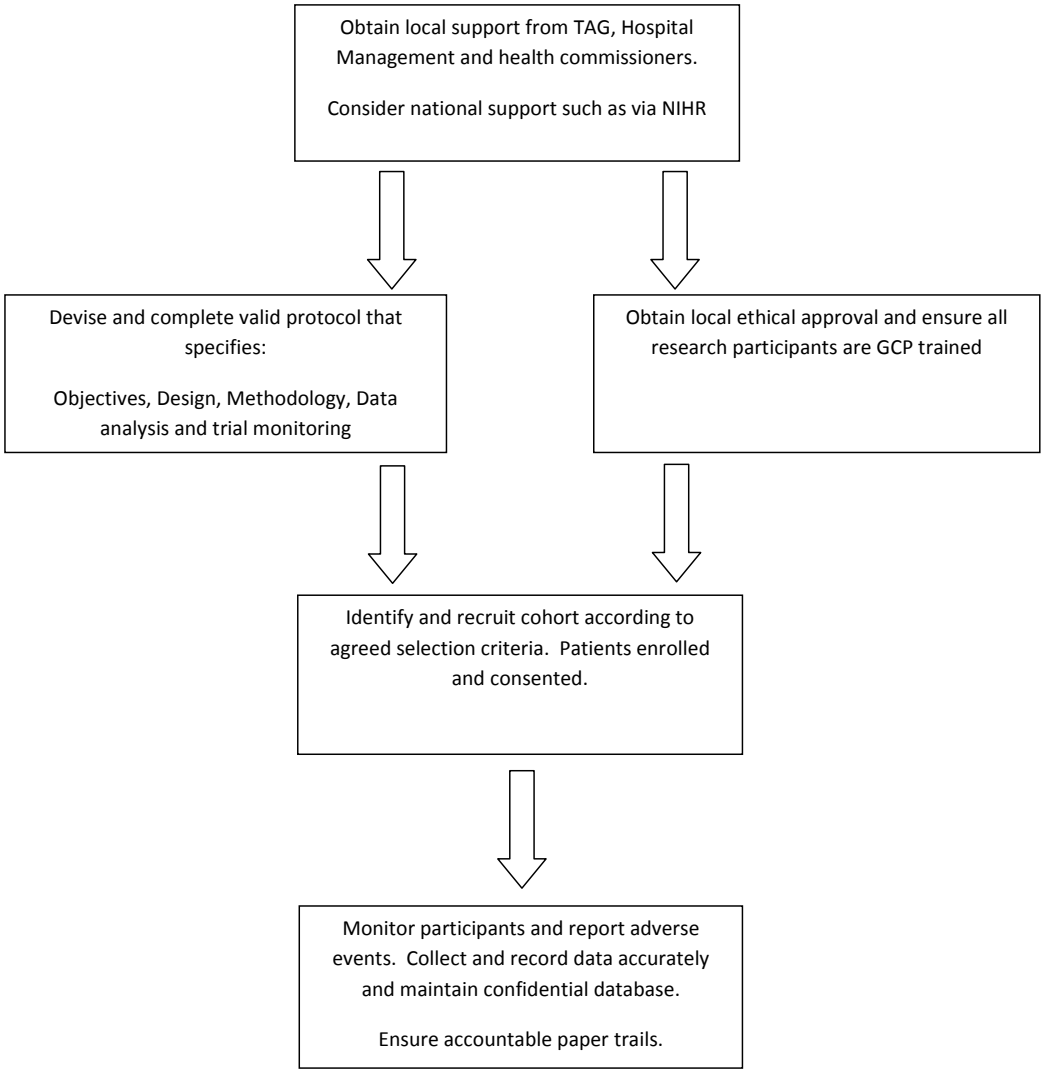

Fig. (1). The challenges and processes in setting up a clinical trial.

In North America, the requirements for implant approval are greater. Class III medical devices are available for general use after going through one of two possible routes: Pre-market authorisation or premarket notification (510(k)) and is regulated by the FDA. The former route involves proof that the device is both safe and effective for its intended use. The latter involves demonstration that the medical device is substantially equivalent to an existing product on the market known as the predicate device. If the FDA approves the device through 510k, the manufacturer may market the device immediately without the need for clinical data in many cases. Ninety percent of medical devices on the North American market have been approved through the 510(k) route and is seen by many as the easier route to bring an implant to market in the US.

Both the European and American systems specify some form of post market surveillance as part of their approval however the manner in which this occurs is not rigorous. We believe post market surveillance should be done in a regulated environment such as provided by a clinical trial. This allows surgeons to evaluate the risks and benefits of a device and also enhances both surgeon and patient decision making in treatment choices. The lack of well designed clinical trials in orthopaedics is not for want of enthusiasm about research but mainly due to the often burdensome process involved in undertaking this. The Oxford Spine Unit has recently introduced a new medical device for treatment of Early Onset Scoliosis (EOS). This device introduced a new concept in managing EOS with the possibility of significantly minimising morbidity in a paediatric population. This article details the challenges and processes in setting up a multicentre trial in the United Kingdom and is summarised in Fig. (**1**).

SETTING UP A TRIAL FOR A NEW IMPLANT

Before a new implant or technology can be introduced into a hospital in the UK approval needs to be obtained locally from a Technology Advisory Group (TAG).

Approval for the use of a new technology is based on a number of parameters including clinical effectiveness, safety, cost, ethics and competency. Once the premise has been accepted by the hospital management team funding streams for the treatment must also be agreed with local health commissioners.

Once the concept has local support the next to step is to address how the clinical effect and safety of the new technology can be scientifically evaluated. Around the world there are different levels of beaurocracy and rigors in setting up a clinical trial. In the UK researchers should be familiar with Good Clinical Practice (GCP) as a legal requirement set out be the Medicines for Human Use (Clinical Trials) Regulations 2004 [6]. GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve participation of human subjects. It is based on a number of principles set out by the International Conference for Harmonisation of GCP. Compliance with GCP ensures first and foremost that study participants (patients) are protected and secondly, that the data produced is credible. There are a number of bodies both locally and nationally that can help set up and support clinical trials. In the UK the authors have used the National Institute for Health Research (NIHR) via the Clinical Research Network in conjunction with the local university. These bodies can help with study design, documentation and gaining ethical approval.

ETHICAL APPROVAL

Any study involving human subjects should be done with ethics approval. The Declaration of Helsinki was first adopted in 1964. It provides guidance to physicians and other participants in medical research involving human subjects. Its principles are based on patient safety, risk management, informed consent and compliance with research protocol. There is a specific section dedicated medical devices to be used in the study. The manufacturer details along with device identification name and number are mandatory. Length of time since the device came into use must be stated. The key questions to be addressed include:

1. Is this a new device?
2. Is the device being used within its CE market intended purpose?
3. Is the device being used outside the terms of its CE market intended purpose?

STUDY DOCUMENTATION

Protocol

The study protocol sets out the objective, design, methodology, statistical considerations and organization of a trial. The protocol details every facet of the study and covers everything from scientific justification through to publication policy and data handling. The key scientific questions to be answered and the exact methodology are included in easily understandable language so that it can be scrutinised by ethics committees and local health boards. The protocol sets out what the researchers will adhere to during the course of the study and any change may need approval by the Ethics Committee.

Patient Information Sheet (PIS)

This details in an easy to understand format in plain English what the study is about. It should discuss treatment options as well as risks and benefits. It should also provide assurance to the patient that opting out or staying in the study will not affect their standard of care. Different groups may require different leaflets such as those for children under the age of 5 may include pictures and videos.

CONSENT FORM

This is separate to the normal clinical consent forms. It should contain a short title of the study, name of Principal Investigator (PI), ethics reference number, date and version number. A signature is taken from the participant or on behalf of the participant in the case of a minor, and from the person taking consent. A copy is given to the participant, one is stored in the research site file and one is kept in the medical notes.

GENERAL PRACTITIONER (GP) LETTER

It is important that the GP is made aware that their patient is undergoing procedures which are not standard clinical practice.

CASE REPORT FORM (CRF)

These forms are used to collect study data.

Data and Document Storage

Data and document storage is a key aspect of the study design. All the documentation described thus far must be stored and kept in the Trial Master File (TMF). These allow evaluation of the conduct of the study and quality of data produced. The TMF is looked after by the Chief Investigator (CI) who has overall responsibility for the research including that carried out at the other sites in multicentre studies. The study may be subject to audit by the sponsor, Medicines and Healthcare Products Regulatory Agency (MHRA) or local research and development. In a multi-centre study each local site has an investigator site file (ISF) containing essential documents.

SAFETY REPORTING

In any study safety of the research participants is of primary concern. In paediatric spine surgery most implants have not been through a premarketing authorisation process. They may have been tested in the laboratory or on animal models but this by no means guarantees how they will react in a human subject. Adverse event reporting is mandatory for any clinical trial. Learning from adverse events promotes good practice and enhances the ethical and scientific quality of the research. Most importantly, it promotes an honest open evaluation of the implant that safeguards other patients.

Recruiting and Consenting Patients for the Trial

Participants are usually identified during outpatient consultations. As part of a structured research trial there must be a clear consent process. Consent relies on a competent individual confirming their readiness to take part in a study having fully understood all the aspects. Consent is an on-going process and not just at the point a signature is

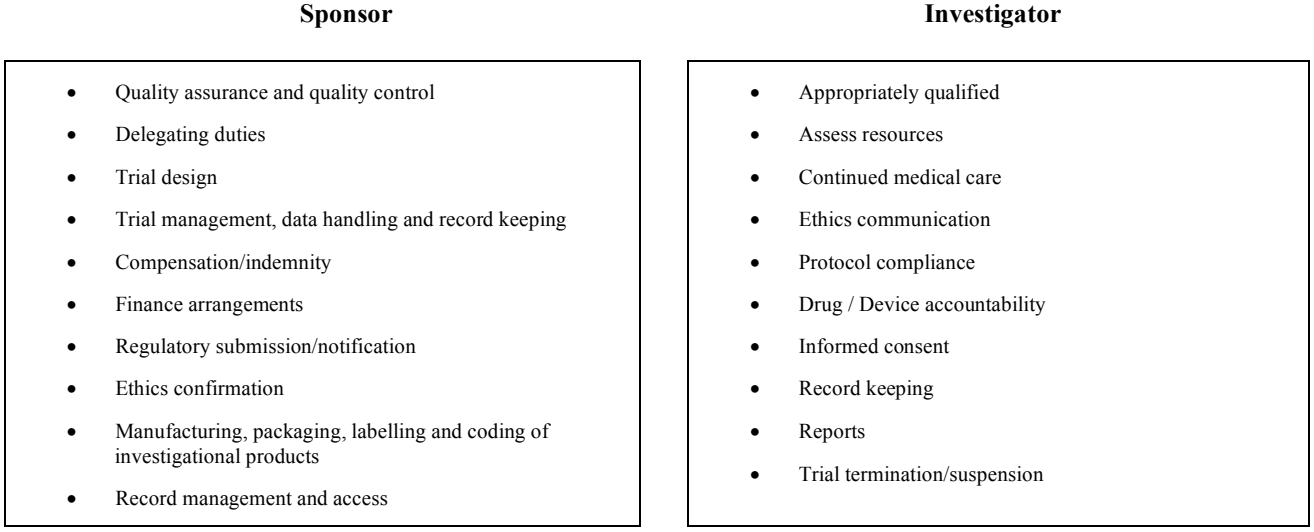

Fig. (2). Responsibilities of sponsor and investigator.

placed on the dotted line. Depending on how participants are identified, an ethics approved invitation letter may be given to determine if they are interested and want more information. All potential participants should receive a patient information leaflet and be given sufficient time to consider the information before consenting the participant to the study. This should be conducted as a separate interview by a researcher who has a thorough understanding of the study. It is important that participants understand that they can withdraw consent at anytime without their care being affected. A copy of the signed form is given to the participant, one goes into the medical records and one into the TMF. In the case of vulnerable participants such as children, a responsible adult should give consent on their behalf.

Consent indicates willingness to take part but not enrolment. This distinction is made by entering details onto an enrolment log. It should also be written in the medical notes. A sticker placed on the front of the medical notes detailing name of study and enrolment date is good practice. Participants should also be given credit cards which indicate they are in the study and also contain contact details. The GP will also be notified of their enrolment in the study.

Running and Monitoring the Trial

Once the study is up and running consideration then needs to be given to monitoring, data collection and audit trails. Time management and organization are essential tools to run any study. Allowing enough time to see participants and to organise the necessary paperwork are key. Having access to dedicated research clinics, fellows and nurses can make the administration of a study more manageable. Delegation of different responsibilities should be recorded in the delegation log and therefore research team members should be on hand to collect data. During the study monitoring visits are undertaken by the sponsor to endure the accuracy of the data and safety of the subjects. Both sides have a responsibility to make sure the study is run according to stated protocol, guidelines and regulations. Any breaches in protocol are subject to audit review. The responsibilities of the sponsor and the investigator are summarised in boxes 1 and 2 of Fig. (**2**).

All data and any changes must be recorded meticulously so as to leave a legible paper trail. As stated previously, consent is an ongoing process, confirmation of this should be sought on a continuous basis throughout the study. Any adverse events and concomitant medications must be diligently recorded.

SUMMARY

The way in which a trial is set up and run is just as important as the clinical question that intends to be answered by the research. Valid results and meaningful conclusions cannot be founded without solid methodology. The ideal clinical trial obtains reliable, accurate clinic data whilst ensuring that the participants are well informed and safe throughout. The processes set out above aim to achieve this. Setting up a trial and establishing all of the pathways and documentation set out above can take many months. The trial set up by the senior author mentioned previously took over 9 months to establish before any patients could be recruited. The time and resources that go into setting up a clinical trial may explain the paucity of prospective research that supports orthopaedic implants. From our experience in setting up a trial aimed at assessing the outcome of a device it would appear that most of the processes are designed with drug therapies in mind. Some of the set procedures, particularly those regarding adverse outcomes, have had to be modified to bear more relation to implant research. The previous high profile failures seen in orthopaedic implants have occurred when apparently minor alterations have been made to existing designs. With the introduction of any new implant or technology that brings with it new concepts in spinal surgery the need for prospective well designed research is vital to fully evaluate its use and ensure safety before it is rolled out on a larger scale.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENT

Declared none.

REFERENCES

[1] Cohen D. Out of joint: the story of the ASR. BMJ 2011; 342: d2905.

[2] Thomas SR, Shukla D, Latham PD. Corrosion of cemented titanium femoral stems. J Bone Joint Surg Br 2004; 86(7): 974-8.

[3] Langton DJ, Jameson SS, Joyce TJ, *et al.* Accelerating failure rate of the ASR total hip replacement. J Bone Joint Surg Br 2011; 93(8): 1011-6.

[4] Gray M. Evidence-Based Healthcare and Public Health. 3rd ed. PA, USA: Churchill Livingstone 2008; p. 448.

[5] National Joint Registry. Available from: http://www.njrcentre.org.uk/njrcentre-/Reports, Publications and Minutes/Annual-reports/tabid/86/ Default.aspx [Accessed: June 2013].

[6] gcp.admin.ox.ac.uk [Internet]. [cited 2013 Apr 20]. Available from: http://gcp.admin.ox.ac.uk

Received: May 14, 2013 Revised: June 17, 2013 Accepted: June 25, 2013