Surviving a Site Audit: Tips for Good Clinical Practice in an Implant Trial

Esther M.M. Van Lieshout, PhD, Stephanie M. Zielinski, MD

Esther M.M. Van Lieshout, PhD

Dept. of Surgery-Traumatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands. E.vanlieshout@erasmusmc.nl

Stephanie M. Zielinski, MD

Dept. of Surgery-Traumatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands. S.zielinski@erasmusmc.nl

Correspondence address:

E.M.M. van Lieshout

Erasmus MC, University Medical Center Rotterdam

Department of Surgery-Traumatology

P.O. Box 2040

3000 CA Rotterdam

The Netherlands

Phone: +31.10.7035010

Fax: +31.10.7035039

E-mail: e.vanlieshout@erasmusmc.nl

Abstract

The number of clinical trials involving implants for trauma and orthopedic surgery is increasing. The International Conference of Harmonization-Good Clinical Practice (ICH-GCP) guideline has been developed in order to assure that the rights, safety, and well-being of trial subjects (*i.e.*, patients) are protected. Not performing a trial according to legal requirements including this guideline is no longer acceptable, and trial audits are increasingly being performed as an independent quality check for data validity and credibility. This manuscript provides an overview of the Guideline for Good Clinical Practice in the context of conducting an implant trial in trauma and orthopedic surgery. As long as all guidelines are adequately adhered to and all paperwork is in order, there is no reason to fear a trial audit.

Keywords:

RCT, trauma surgery, orthopedic surgery, clinical trial, GCP

I. THE PRINCIPLES OF ICH-GCP

The ICH-GCP guideline, which has its origin in the Declaration of Helsinki, is an international ethical and scientific quality standard for the design, conduct, recording, and reporting of trials involving human subjects (2, 3). The guideline provides a unified standard for clinical research in the European Union, Japan and the United States, in order to facilitate mutual acceptance of clinical data by regulatory authorities in these jurisdictions.

The key principle of the ICH-GCP guideline is the ethical conduct of a trial (2). No trial can be initiated before all foreseeable risks and inconveniences are weighted against the anticipated benefit for the individual trial subject and society. The safety and well-being of the trial subjects should always prevail over scientific interest (2). Medical device GCP includes the following key items: (1) Appropriate clinical trial documentation as defined by ICH-GCP; (2) Medical Ethics Committee approval of the trial; (3) Ethics committee supervision and review of amendments and adverse events; (4) Written clinical trial study report about the study outcome. If applicable, competent authority approval should also be obtained.

II. DESIGNING THE TRIAL AND WRITING THE STUDY PROTOCOL

Clinical trials should be scientifically sound, and described in a clear, detailed protocol (2). The protocol should provide detailed information on the rationale, aims, objectives, design, proposed analyses, methodologies, data analyses, and conduct of the trial. Table 1 provides an overview of key topics to be mentioned in the protocol. Local authorities may also require that the applicable ethics issues are adequately addressed in the protocol.

All relevant literature related to the efficacy and safety of the implant should be summarized in the protocol. The best approach for assessing available literature data is by

performing a systematic review and/or meta-analysis. Commonly used electronic databases include MEDLINE, EMBASE and CINAHL. Depending on the topic, recent systematic reviews may already be available in the Cochrane library. The conduct of a meta-analysis helps to systematically appraise the available evidence, and will provide guidance in formulating a testable research question for the trial.

In surgical study protocols attention should also be paid to surgeon related aspects. The individual skills and habits of the orthopedic trauma surgeon participating in a clinical trial may influence the outcome of the trial. Therefore, it may be important to standardize key elements of the intervention for both the treatment group(s) and the control group in order to reduce bias due to variation in techniques and skills of participating surgeons.

There are several options for reducing technique-associated bias, each with related advantages and disadvantages. These options include: (1) all surgeries are being done by the same surgeon; (2) obliged teaching sessions prior to the trial; (3) auditing surgical performance throughout the trial; and (4) stratifying patients by surgeon at the time of randomization. For specific interventions it may also be better to determine a priori how may procedures each participating surgeon should have performed in his/her entire career and/or in the last year prior to trial startup.

Similar to the standardization of surgical and technique associated factors, guidelines regarding peri-operative care (*e.g.*, thromboprophylaxis, antibiotic prophylaxis, optimization for surgery, pain medication) and after-treatment (*e.g.*, physical therapy) should be specified in the protocol if relevant for the trial.

Availability of experienced surgeons is critical when it comes to the ability to enroll patients at any time. Any site participating in a trial should have a team with adequate skills,

expertise and equipment available for participation. Trials involving acute traumatic injuries may require the prompt availability of a skilled surgical team.

Other key aspects of a methodologically sound study design are randomization, allocation concealment, and blinding (4-8). Randomization ensures that both known and unknown prognostic factors are equally distributed in the treatment and control group. Allocation concealment prevents undermining of random, unpredictable assignment sequences resulting in overestimated treatment effects (4, 8). In surgical trials, blinding of patients and surgeons may not be feasible. Blinding of outcome assessors should be aimed at as much as possible, as treatment effects are known to be over-estimated in unblinded studies (4, 7, 9, 10). If applicable, one might consider blinding of radiographs by superimposing the implants used in either trial arm (11). Blinding of the surgical site could be achieved by covering it with the same band-aid, regardless of the intervention.

It is becoming more common to publishing the trial protocol prior to or immediately following trial startup. Early publishing of the trial protocol may lead to higher protocol adherence, and at the same time may set a higher threshold for any post-hoc protocol revisions and amendments. In the future, more scientific journals may also request submission of the trial protocol together with the final manuscript in order to identify protocol deviations.

III. ETHICS APPROVAL AND TRIAL REGISTRATION

Clinical trials are closely supervised by legal authorities. All clinical trials that involve an intervention on patients must be approved by a supervising ethics review committee before permission is granted to run the trial. After receiving this permission, the trial should be conducted in compliance with ICH-GCP, strictly following the study protocol.

An ethics review committee is an independent body of medical professionals, and lay members. Usually this committee is called a medical research ethics committee (MREC or EC), or Institutional Review Board (IRB) for the US. An independent ethics committee can be consulted if the local investigator's hospital or institution has no MREC or IRB. The legal status, constitution, and responsibilities of ethics committees may differ from country to country.

The mandate of the ethics review committee is to safeguard the rights, safety, and well-being of all research participants. Ethics committees review the study protocol, the case report forms, the study budget and trial participant payment, the consent form, and any other study documentation in order to ensure that the trial is justified, safe, that the patients are properly informed about the research, and that adequate facilities and resources are available. Table 2 provides an overview of trial documents to be reviewed by the ethics committee. They may request changes in study procedures or in the explanations given to the patient (*e.g.*, patient information brochure or consent form).

In the US and most European countries, the local ethics review committee must certify that site (principal) investigators and their staff have adequate knowledge on ICH-GCP before they can conduct clinical trials. Attending an ICH-GCP course is often compulsory for the principal investigator.

For multicenter trials, one MREC or IRB will act as primary, central ethics review committee. They perform a full review of the study documents and should approve the trial prior to its startup. Local MRECs or IRBs should only advice on feasibility of the trial at that particular site. International trials require a central ethics review committee in every participating country.

Once the trial has been approved by the ethics review committee, it is necessary to continue to communicate regularly with the MREC or IRB. Investigators are obliged to submit an annual update report on the progress of the study and any new safety information related to the study. Also, all amendments to the protocol, consent form, and case report forms must be promptly reported. Amended documents cannot be implemented before approval of the ethics review committee has been obtained.

In addition to ethics approval, legislation in some countries requires registration of trials in a public trial register. An overview of primary registries that meet the requirements of the International Committee on Medical Journal Editors (ICMJE) is given in Table 3.

IV. INFORMED CONSENT AND RECRUITMENT

Ensuring informed consent from the participants is a major cornerstone of ethical human subject research. In compliance with ICH-GCP guidelines, every trial subject should give his/her informed consent prior to clinical trial participation (3). Consent is considered 'informed' when given by a person who understands the purpose and the nature of research, what is required from the participant and what may be the potential benefits and risks resulting from the study. If the patient is unable to consent for him/herself, researchers can seek consent from the patient's legally authorized representative. Who is entitled to act as legal representative may differ between countries, depending on local legislation.

If limited numbers of trial subjects are to be expected at a single site, it may be preferable to choose for a multicenter approach, thereby reducing the time needed for trial subject enrolment. As a consequence, the process of obtaining MREC or IRB approval will take more time to complete, as local feasibility of the trial needs to be tested by a local ethics review

committee at each participating site.

V. ADVERSE EVENT REPORTING

If during the trial an adverse event is encountered, this should be reported to the local MREC or IRB. An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a trial-specific product (*e.g.*, implant, medical device or pharmaceutical product) and which does not necessarily have a causal relationship with this treatment. (3). A serious adverse event is an adverse event which results in death, is life-threatening, requires in-patients hospitalization (or prolongs existing hospitalization), results in persistent or significant disability of incapacity, or is a congenital anomaly or birth defect (3). A non-serious adverse event is any adverse event that does not meet the criteria of a serious adverse event. Many review boards require serious adverse events to be reported within 24 hours and non-serious adverse events to be reported within 48 hours, in compliance with ICH-GCP guidelines. If applicable, adverse events should also be reported to the data safety and monitoring board.

VI. THE RESEARCH TEAM

The medical care given to, and medical decisions made on behalf of trial subjects should always be the responsibility of a qualified physician (3). However, the overall conduct of the trial and the trial-related activities may involve a dedicated research team. Each individual in this team should be qualified by education, training, and experience to perform his or her respective tasks (3). A single center trial requires a different team than a large, international trial involving multiple sites per country. Multicenter trials usually have a central project office or methods

center that coordinates and overseas the trial. Requirements and responsibilities of key persons and groups within the team are given below.

A. Site Principal Investigators and Site Investigators

If a participating clinical site has more than one surgeon enrolling patients into the trial, one investigator from each site should be designated as the site principal investigator (PI). The PI is the medical practitioner or licensed medically qualified person conducting the study in accordance with the protocol. The site PI serves as the primary contact for the sponsor or central methods center, and is responsible for all communication with the local MREC or IRB. The site PI should also ensure correct documentation in case report forms and patient hospital records to enable source data verification. In multicenter trials, the site PI also attends investigator meetings and conference calls regarding the trial.

A site PI may appoint any number of co-investigators who are given the responsibility to actually conduct the trial as defined in the clinical investigation plan. The site investigators are responsible for enrolling patients into the trial, following the study protocol, and following patients according to the study protocol.

In addition to the site investigators, the site PI may also appoint a dedicated clinical research coordinator to manage the day-to-day trial activities at the clinical sites. These include regular communication with the local ethics committee, assisting with the patient enrolment, completing case report forms, scheduling patient follow-up appointments, and entering data into a database or submitting data to the central methods center. The clinical research coordinator and the site PI work closely together to ensure compliance and data quality.

B. Sponsor

The sponsor is the organization that has initiated the trial. This could be a medical industrial company or a hospital. The sponsor and the local site PIs are jointly responsible for writing a site-specific patient information brochure and informed consent form that accurately informs the potential subjects about the true risks and potential benefits of participating in the study, while at the same time presenting the material as briefly as possible and in ordinary language.

Throughout the clinical trial, the sponsor is responsible for: (1) accurately informing the local site (principal) investigators about any relevant news on the trial; (2) monitoring the results of the study as they come in from the various sites, as the trial proceeds; and (3) collecting adverse event reports from all site investigators in the study, and for informing all the investigators of the sponsor's judgment as to whether or not these adverse events were related to the study treatment.

C. Steering Committee

The sponsor may appoint a Steering Committee that will be responsible for the overall design and conduct of a trial. This committee consists of the principal investigator(s), the biostatistician and trial methodologist, and other key investigators. It communicates with the Data Monitoring Committee, the Central Adjudication Committee, and the site PIs. At the completion of the trial, the Steering Committee maintains responsibility for the final data analysis and publication (12).

D. Data monitoring committee (DMC)

In larger clinical trials, a sponsor will use the services of a DMC, known in the U.S. as a Data Safety Monitoring Board (12). This is an independent group of health care professionals who are

completely independent of the investigators and who have no financial, scientific, or other conflict of interest with the trial. The DMC members should have adequate expertise in clinical trial methodology, biostatistics, and regulatory guidelines like ICH-GCP. The DMC reviews unblinded data related to the conduct of the study (*e.g.*, recruitment rates, non-compliance, and protocol violations), carries out evaluations of serious unanticipated adverse events, evaluates pre-planned interim analyses for efficacy, safety, and the triggering of statistical warning rules. The DMC has the power to recommend termination of the study based on their review.

E. Central Adjudication Committee (CAC)

The CAC is designated to review important study end-points reported by the trial investigators to determine if they meet protocol-specified criteria. Site investigators should provide them with all relevant information such as X-rays, surgical reports, and clinical notes. If feasible, the CAC should be blinded to treatment allocation where ever possible in order to reduce bias and random error in determining outcome events (4, 7, 12). This committee is optional and can be beneficial in surgical trials, in which the intervention(s) cannot be blinded.

VII. DATA MANAGEMENT AND TRIAL MONITORING

Following initiation of a clinical trial, progress and quality of the collected data should be monitored in detail. The purposes of clinical trial monitoring is to verify that the rights and well-being of human subjects are protected, to verify that the reported clinical trial data are accurate, complete, and verifiable from source documents, and to verify that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH-GCP, and with the applicable regulatory requirement(s).

Although the sponsor holds the overall responsibility of the trial, it is the responsibility of the site PI and the site investigator(s) to provide complete and high-quality data. A sponsor may appoint monitors to oversee the conduct of the trial or hire a Contract Research Organization (CRO) for that purpose. The monitor continuously conducts the in-process quality control for the trial, checks the performance of the trial and its compliance with the overall legal requirements and ICH-GCP. The monitor represents the sponsor, periodically visits the trial sites and reviews the data through source data verification (*i.e.*, reviewing the collected data against the medical records and reports pertaining to the trial subject).

ICH-GCP guidelines dictate that all clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification (3). All data concerning a trial participant should be stored in a folder, in which each document should have the subject's unique identifier. In compliance with regulatory requirements regarding privacy and confidentiality protection, subjects should be given a unique identification number (3). A common numbering system is a combination of the trial acronym (or protocol number), followed by the site number and subject number.

Data collection may be challenging, both in single as in multicenter trials. Coordinating centers increasingly use centralized computer data collection systems that can be fax-based or Internet-based (1, 13). Data should be checked for missing information, implausible data, and inconsistencies at an early stage. Any problem encountered should be corrected as early as possible. This is primarily the task of the local research coordinator. Failure to resolve problems urgently will violate the ICH-GCP guideline and can result in termination of the trial by the authorities as a worst-case scenario.

VIII. REGULATORY DEVICE TRIALS

Regulatory device trials allow for the clinical evaluation of (new) medical devices, determining whether or not they can be safely and effectively used in patient care (14).

In the US, the Food and Drug Administration (FDA) must give approval to all clinical trials involving new medical devices that pose a significant risk to patients. Depending on the assigned level of risk (*i.e.*, class I, II, III), a clinical trial involving an approved medical device for a new indication not covered by the initial marketing approval may also require FDA approval (15). In the EU, all medical devices must be identified with the CE (Conformité Européenne; in English European Conformity) mark. There are numerous 'Agreements on Mutual Recognition of Conformity Assessment' between the EU and other countries such as the USA, Japan, Canada, Australia, New Zealand and Israel. Regulatory trials must function in compliance with governmental regulations. Legislation may vary considerably between countries.

Participation in a regulatory trial is more complex and time-intensive than participating in a non-regulatory trial. Regulatory trials require an even stricter adherence to ICH-GCP. In practice, the administrative workload will be higher and details must be recorded, sometimes to the extreme.

IX. TRIAL AUDITING

Following in-process quality checks by a trial monitor or DMC, auditing or inspection is the second line of defense for trial compliance. The ICH-GCP guideline defines an audit as a systematic and independent examination of trial-related activities and documents for industry-sponsored trials. An audit can be requested by the sponsor, but also by formal bodies such as the

ethics committee. The aim of the audit is to ensure that trials are conducted in compliance with the trial protocol, the sponsor's standard operating procedures, and all applicable guidelines and regulatory requirements. In other words, auditing is critical in ensuring that the collected data is credible and reliable. Audits are conducted at the time of screening, halfway during the trial and at the trial closure.

Clinical trial audits are performed by regulatory authorities, trial sponsors, or organizations nominated by the trial sponsor (3). The regulatory authorities in the United States and European Union perform audits of the sponsor, manufacturing plants, and study sites. Study sites always receive advanced written notification of an audit, allowing them sufficient time to prepare for the audit. Auditing uses a structured agenda and clearly defined objectives. The auditor will provide a checklist of documents and data that should be available, along with a list of persons to be present during the audit.

Any issues identified that could result in major non-compliances should be properly addressed by the site PI immediately after they have been identified. Negative audit findings may vary in severity from deficiencies in essential trial documentation that can easily be rectified, to errors in consent procedures and investigator fraud. Serious discrepancies may lead to termination of a trial at a study site or legal proceedings against an investigator.

As audits can be very stressful for investigators, they need to be thoroughly prepared. Organizing training sessions or pre-investigational site visits may reveal any problems that might be encountered during the actual audit, and will enable the site PI the chance of a timely solution. As long as all members of the research team conduct the trial in agreement with ICH-GCP guidelines and other regulatory requirements, they have nothing to fear.

X. REFERENCES

1. Bhandari M, Schemitsch EHM. Beyond the Basics: The Organization and Coordination of Multicenter Trials. Techniques in Orthopaedics 2004;19:83-87.
2. European Medicines Agency. Guideline for Good Clinical Practice. European Medicines Agency, London, UK [http://www.emea.europa.eu/], 2002.
3. International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Harmonized Tripartite Guideline: Guideline for Good Clinical Practice: (ICH-E6). 1996.
4. Schulz KF. Assessing allocation concealment and blinding in randomised controlled trials: why bother? Equine Vet J 2005;37(5):394-5.
5. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. Jama 1995;273(5):408-12.
6. Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. Bmj 2008;336(7644):601-5.
7. Schulz KF. Assessing allocation concealment and blinding in randomised controlled trials: why bother? Evid Based Nurs 2001;4(1):4-6.
8. Schulz KF, Altman DG, Moher D. Allocation concealment in clinical trials. Jama 2002;288(19):2406-7; author reply 2408-9.
9. Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. Bmj 2001;323(7303):42-6.

10. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001;135(11):982-9.

11. Karanicolas PJ, Bhandari M, Walter SD, Heels-Ansdell D, Guyatt GH. Radiographs of hip fractures were digitally altered to mask surgeons to the type of implant without compromising the reliability of quality ratings or making the rating process more difficult. J Clin Epidemiol 2009;62(2):214-223 e1.

12. Bhandari M, Joensson A. Clinical Research for Surgeons. 2009.

13. Zlowodzki M, Bhandari M, Driver R, Obremskey WTM, Kregor PJM. Beyond the Basics: Internet-Based Data Management. Techniques in Orthopaedics 2004;19:88-93.

14. McKay PJ, Resendes S, Schemitsch E, Bhandari M. What is involved in a regulatory trial investigating a new medical device? J Long Term Eff Med Implants 2007;17(2):165-71.

15. The U.S. Food and Drug Administration. Device Advice; available on the internet: www.fda.gov/cdrh/devadvice/ide/index.shtml.

Table 1. Content of the trial protocol

- Title of the project
- Names, qualifications and addresses of the sponsor (*i.e.*, trial initiator)
- Justification and rationale of the trial, including literature overview
- Objectives of the trial, including testable hypothesis
- Inclusion and exclusion criteria
- Details on randomization, blinding and treatment allocation
- Definition of the interventional procedures
- Details on the implant tested
- Anticipated adverse events and related risks associated with the implant
- Definition of perioperative care, after-treatment and any other trial-specific treatments*
- Detailed overview of outcome assessment, including justification
- Detailed list of data to be collected, including procedures how to collect these
- Required sample size, including statistical justification
- Definition of statistical methodologies to be applied
- Details on handling and storage of data and documents
- Details on public disclosure and publication
- Detailed list of literature references

* Only if applicable

Table 2. Overview of trial documents to be reviewed by the ethics committee

- Application form, including names and qualifications of participating surgeons
- Study protocol
- Investigational brochure and other documentation related to the trial (*e.g.*, Standard Operations Manual)*
- Information sheet for research participants
- Consent Form for research participants and/or their legal representative
- Data collection booklets/Case Report Forms/questionnaires
- Promotion material (*i.e.* study posters or pocket cards)
- Details on radiology and/or toxicology safety
- Details on payment to trial participants
- Letters of agreement and/or contract with sponsor*
- Up-to-date, dated and signed Curriculum vitae (CV) of the principal investigator, all co-investigators and independent physician
- Trial termination criteria*

* Only if applicable

Table 3. Primary Registries in the WHO Registry Network

Registry	Website
Australian New Zealand Clinical Trials Registry (ANZCTR)	http://www.anzctr.org.au/
Chinese Clinical Trial Register (ChiCTR)	http://www.chictr.org/
Clinical Trials Registry - India (CTRI)	http://www.ctri.in/Clinicaltrials/index.jsp
German Clinical Trials Register (DRKS)	http://www.germanctr.de/
Iranian Registry of Clinical Trials (IRCT)	http://www.irct.ir/
ISRCTN.org	http://www.isrctn.org/
Japan Primary Registries Network (JPRN)	http://www.isrctn.org/
The Netherlands National Trial Register (NTR)	http://www.trialregister.nl/trialreg/index.asp
Pan African Clinical Trial Registry (PACTR)	http://www.pactr.org/
Sri Lanka Clinical Trials Registry (SLCTR)	http://www.slctr.lk/

Primary registries in the WHO Registry Network meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration. Primary Registries meet the requirements of the ICMJE (International Committee on Medical Journal Editors) are listed, along with their websites.

(Source: http://www.who.int/ictrp/network/primary/en/index.html).