Clinical Research Methods: From Idea to Publication

Saturday, May 11, 2013
May 11, 2013

Dear Colleagues,

On behalf of the course chairs, we welcome you to Toronto and to the ISAKOS Pre-Course: Clinical Research Methods: From Idea to Publication.

This Pre-Course will emphasize evidence based research methods and analytic techniques. The goal of the course is to provide attendees with the skills necessary to undertake their own high quality research projects. This didactic course will instruct attendees on the process of conceiving a research question, designing a study, analyzing data, and presenting results. Topics of presentation will include Conceiving an Answerable Research Question, Avoiding Bias in Clinical Research, Evaluating Total Joint Arthroplasty, Coordinating Large Multi-Center Observational Studies, Randomized Clinical Trials, and Basic Principles of Data Analysis and Statistics. This course is open to physicians and researchers of all specialties—not just arthroscopy, knee surgery and orthopaedic sports medicine.

We have assembled an international faculty, including experts from around the world, presenting on their areas of expertise. We thank them in advance for their time and their presentations.

Thank you for your participation, and we hope you find the ISAKOS Pre-Course: Clinical Research Methods: From Idea to Publication to be a valuable educational experience.

Best Regards,

Stephen Lyman, PhD, USA
Robert Marx, MD, MSc, FRCSC, USA
Pre-Course Chairs
Stephen Lyman, PhD, USA
Robert Marx, MD, MSc, FRCSC, USA

Faculty
Mohit Bhandari, MD, PhD, FRCSC CANADA
Warren Dunn, MD, MPH USA
Jon Karlsson, Prof SWEDEN
Bruce Levy, MD USA
Jacques Ménétrey, MD SWITZERLAND
Nizar Mohamed, MD,ScD CANADA
Norimasa Nakamura, MD, PhD JAPAN
Kurt Spindler, MD USA
Daniel Whelan, MD CANADA
Stefano Zaffagnini, MD ITALY
Financial Disclosure
Each participant in the ISAKOS Biennial Congress has been asked to disclose if he or she has received something of value from a commercial company or institution, which relates directly or indirectly to the subject of their presentation. ISAKOS has identified the option to disclose as follows:

1 – Royalties
2 – Speaker
3a – Employee
3b – Paid Consultant
3c – Unpaid Consultant
4 – Stock
5 - Research or Institutional Support
6 - Financial or Material Support
7 - Royalties (Publisher)
8 - Editorial or Governing Board of Medical or Orthopaedic Publication
9 - Board of Directors, Owner or Officer for Healthcare Organization

ISAKOS does not view the existence of these disclosed interests or commitments as necessarily implying bias or decreasing the value of the author’s participation in the ISAKOS Biennial Congress. An indication of the participant’s financial disclosure appears after their name, as well as the commercial company or institution that provided the support.

<table>
<thead>
<tr>
<th>Course Chairs</th>
<th>Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyman, Stephen L.</td>
<td>8 - Editorial Board, American Journal of Orthopaedics; 9 - Scientific Committee, ISAKOS</td>
</tr>
<tr>
<td>Marx, Robert G.</td>
<td>7 - Demos Health (The ACL Solution); Springer (ACL Revision textbook)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhandari, Mohit</td>
<td>3b - Amgen, Eli-Lilly, Moximed, Stryker, Smith &amp; Nephew; 5 - Stryker, Smith &amp; Nephew</td>
</tr>
<tr>
<td>Dunn, Warren R.</td>
<td>Nothing to Disclose</td>
</tr>
<tr>
<td>Karlsson, Jon</td>
<td>Nothing to Disclose</td>
</tr>
<tr>
<td>Levy, Bruce A.</td>
<td>3b - Arthrex; 7 - Arthrex, Biomet</td>
</tr>
<tr>
<td>Ménétrey, Jacques</td>
<td>Nothing to Disclose</td>
</tr>
<tr>
<td>Mohamed, Nizar</td>
<td>Nothing to Disclose</td>
</tr>
<tr>
<td>Nakamura, Norimasa</td>
<td>Nothing to Disclose</td>
</tr>
<tr>
<td>Spindler, Kurt P.</td>
<td>5 - Research grant from Smith &amp; Nephew</td>
</tr>
<tr>
<td>Whelan, Daniel</td>
<td>Nothing to Disclose</td>
</tr>
<tr>
<td>Zaffagnini, Stefano</td>
<td>6 - Aperion, I + Orthopaedics; 7 - Springer; 8 - Associate Editor, Knee Surgery, Sports Traumatology, Arthroscopy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ISAKOS Staff</th>
<th>Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson, Kathryn</td>
<td>Nothing to Disclose</td>
</tr>
<tr>
<td>Festo, Donna</td>
<td>Nothing to Disclose</td>
</tr>
</tbody>
</table>
CME Hours
The ISAKOS Sports Rehabilitation Concurrent Course: Global Perspectives for the Physical Therapist and Athletic Trainer is planned and implemented in accordance with the essential areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through joint sponsorship.

CME Accreditation
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through joint sponsorship of the American Academy of Orthopaedic Surgeons (AAOS) and the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS).

The AAOS is accredited by the ACCME to sponsor continuing medical education for physicians.

The American Academy of Orthopaedic Surgeons designates this live activity for a maximum of 8.25 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Course Objectives
Upon completion of this course, participants should be able to:

- To provide attendees with the skills necessary to undertake their own high quality research projects
- Evaluate clinical cases and practice evidence-based, informed orthopedic care.
- Demonstrate the application of current techniques, procedures and research
- Identify and analyze current research data pertaining to the Clinical Research
Agenda
PRE-COURSE AGENDA

8:00 - 8:10  Introduction
Pre-Course Chairs: Stephen Lyman, PhD USA
Robert Marx, MD, MSc, FRCSC USA

8:10 - 10:00 Session I: Conceiving and Preparing your Research
Moderator: Robert Marx, MD, MSc, FRCSC USA
8:10 - 8:40 Concieving an Answerable Research Question
Stephen Lyman, PhD USA
8:40 - 9:10 Avoiding Bias in Clinical Research
Daniel Whelan, MD CANADA
9:10 - 9:40 Evidence Based Medicine & Levels of Evidence
Stefano Zaffagnini, MD ITALY
9:40 - 10:00 Discussion
Stephen Lyman, PhD USA
Daniel Whelan, MD CANADA
Stefano Zaffagnini, MD ITALY

10:00 - 10:20 Coffee Break

10:20 - 12:10 Session II: Studies & Evaluation
Moderator: Jon Karlsson, Prof. SWEDEN
10:20 - 10:50 Case Controlled Studies
Jacques Ménétrey, MD SWITZERLAND
10:50 - 11:20 Registries for Evaluating Total Joint Arthroplasty
Nizar Mohamed, MD,ScD CANADA
11:20 - 11:50 Coordinating Large Multicenter Observational Studies
Kurt Spindler, MD USA
11:50 - 12:10 Discussion
Jacques Ménétrey, MD SWITZERLAND
Nizar Mohamed, MD,ScD CANADA
Kurt Spindler, MD USA

12:10 - 1:00 Lunch

1:00 - 2:50 Session III: Evaluation, Variables and Statistics
Moderator: Bruce Levy, MD USA
Stefano Zaffagnini, MD ITALY
1:00 - 1:30 Evaluation of Clinical Research Methods: Examples from the Literature
Robert Marx, MD, MSc, FRCSC USA
1:30 - 2:00 Operationalizing Variables
Stephen Lyman, PhD USA
2:00 - 2:30 Basic Principles of Data Analysis and Statistics
Stephen Lyman, PhD USA
2:30 - 2:50 Discussion
Stephen Lyman, PhD USA
Robert Marx, MD, MSc, FRCSC USA
ISAKOS Congress 2013: Pre-Course
Clinical Research Methods: From Idea to Publication
May 11, 2013 • Toronto, Canada

2:50 - 4:30  Session IV: Outcomes & Clinical Trials
  Moderator: Jacques Ménétrey, MD SWITZERLAND
  Stephen Lyman, PhD USA
2:50 - 3:20  Randomized Clinical Trials in Orthopaedic Surgery
  Mohit Bhandari, MD, PhD, FRCSC CANADA
3:20 - 3:50  Assessment of Biological Outcomes in Clinical Research
  Norimasa Nakamura, MD, PhD JAPAN
3:50 - 4:20  The Challenge of Surgeon Equipoise in Randomized Clinical Trials
  Bruce Levy, MD USA
4:20 - 4:30  Discussion
  Mohit Bhandari, MD, PhD, FRCSC CANADA
  Bruce Levy, MD USA
  Norimasa Nakamura, MD, PhD JAPAN

4:30 - 5:35  Session V: Presenting Data
  Moderator: Norimasa Nakamura, MD, PhD JAPAN
4:30 - 4:50  Presenting Data
  Warren Dunn, MD, MPH USA
4:50 - 5:10  Writing a Paper
  Jon Karlsson, Prof. SWEDEN
5:10 - 5:30  Discussion
  Warren Dunn, MD, MPH USA
  Jon Karlsson, Prof. SWEDEN

5:30 - 5:35  Closing Remarks
  Pre-Course Chairs: Stephen Lyman, PhD USA
  Robert Marx, MD, MSc, FRCSC USA
Session I

Conceiving and Preparing Your Research
A. What is a hypothesis?

- Miriam-Webster Dictionary: a tentative assumption made in order to draw out and test its logical or empirical consequences
- Wikipedia: a proposed explanation for a phenomenon.
- Last’s Dictionary of Epidemiology:
  1. A supposition, arrived at from observation or reflection, that leads to refutable predictions.
  2. Any conjecture cast in a form that will allow it to be tested and refuted.

B. The Scientific Method

- Initial observations
- Information gathering
- Objective
- Variables
- Hypothesis
- Design Experiments
- Perform Experiments
- Summarize Results
- Draw Conclusions

C. Hypothesis Generation

- Scientific Method requires that hypothesis be testable
- Criteria for “testable”
  - Measurable exposure and outcome
  - Operationalized definitions of exposure and outcome

D. Examples
Avoiding Bias in Clinical Research
Daniel Whelan, MD CANADA
Evidence-Based Medicine and Levels of evidence

Stefano Zaffagnini

Clinica Ortopedica e Traumatologica II – Laboratorio di Biomeccanica. Istituto Ortopedico Rizzoli - Bologna

Introduction

Evidence-Based Medicine (EBM) was rated as 1st of the top 15 medical breakthroughs in the last 160 years, before antibiotics, vaccines, noninvasive internal imaging, joint replacement and more...!!!!

WATTS BMJ 2007

Introduction

Clinical medical care should be based on high-level evidence. However, this is not always possible, but every attempt should be made to use the highest quality evidence available.

The strongest evidence supporting clinical evidence intervention is ...
- through RCT
- meta-analysis
- systematic review of RCTs

The Traditional Dogma

- We’ve always done it this way.
- The chief recommends this type of treatment, and he or she is as experienced as they come.
- This Rx is the best one, considering the circumstances and it appeared to be good at the time.
- We just thought we’d try this new technique. It’s written up in one of the journals, isn’t it?
- Under the circumstances, we did not have other options.

History of Decision Making

- PRE-SCIENTIFIC METHOD (<1900):
  - apprenticeship, eminence based, anecdotal or experience based
- BIOLOGICALLY PLAUSIBLE (modern era)
  - in-vitro science: biomech, cell, test-tube
  - in-vivo: translational or animal models
- EVIDENCE BASED MEDICINE (last 20+ yrs)
  - application scientific method clinical studies (epidemiology, statistics, patient-oriented outcomes)
EBM – What It Isn’t!!!

- Not a science with a long history
- Not a recipe or formula for how to practice
- Not based solely on evidence (considers personal experience, judgment, patient preferences)
- Not restricted to randomized trials and meta-analyses

Evidence-Based Medicine
What is it?

- Tool for finding evidence and analyzing its quality
- Promotes critical thinking and synthesis of the literature
- By default, evidence may (and likely will) change over time
- Provides guidance for informed medical decision making
- Identifies gaps in the evidence that can direct future research

KEY STEPS OF EBM

1) Formulate the problem and convert the information needs into a answerable question
2) Search in the most efficient way possible the best evidence that answer the questions (clinical examination, laboratory test, images, literature)
3) Appraise the evidence critically of both its validity and its applicability to current clinical question
4) Apply the results of this search to both clinical question and patient context
5) Evaluate above steps

EBM AT WORK

- Components of a good question:
  - Patient Characteristics
  - Intervention
  - Comparison
  - Outcome
- Finding evidences in literature (search high quality articles!)
- Integration with clinical expertise into practice
- Evaluation (self-evaluation!!!)

Evidence- Based Medicine: Why Is It Important?

1. BEST CARE of our patients:
   - reason we choose medicine as a profession
2. MONEY:
   - financial stability for employees of healthcare team
3. CONTROL:
   - ambiguity in treatment fuels legal system and allows insurance industry to DENY payment

EBM Is Here To Stay!

- Guyatt G “Evidence-Based Medicine”. ACP J Club 1991
- Requires a set of skills including efficient literature searching and the application of formal rules of evidence in evaluating the clinical literature
EBM Is Here To Stay!

- Structured abstracts (Haynes et al, Ann Int Med 1990) and secondary journals summarizing studies of high relevance and methodological quality (Haynes et al, Ann Int Med 1991)
- Evolving philosophy – does NOT ignore the importance of values and preference judgments that are implicit in every clinical decision

The Challenges for EBM

- Integration into clinical practice – producing relevant evidence through high quality research will continue indefinitely

The Challenges for EBM

- Manpower and resources to summarize evidence is considerable – 2015 to produce 10,000 Cochrane reviews to summarize existing evidence (Mallet and Clarke ACP J Club 2003)
- Knowledge translation may be our biggest challenge – ensuring that clinicians base their day to day decision making on the right principles and on current best evidence – How do we keep political and financial pressures from influencing translation into practice?

Hierarchy Treatment Studies - Levels of Evidence

Systematic Review/Meta-analyses*
Randomized Controlled Trials (Level I)
Cohort Studies (Level II)
Case Control Studies (Level III)
Cross Sectional Surveys
Case Reports/Series (Level IV)
Expert Opinion (Level V)
Anecdotal

*Level I = RCTs, Level II includes cohorts
Levels of Evidence

First assess primary research question!
Often the conclusions of many studies are not related to primary research question

**Levels of Evidence**

- **Therapeutic Study Type**
  - Assessing effect of specific treatment (can be randomized!)
- **Prognostic Study Type**
  - Evaluating effect of patient characteristics on the outcome of disease process
- **Diagnostic Study Type**
  - Assess if a specific test is related to presence/absence of a pathology
- **Economic Analyses**
  - Assess cost-effectiveness of a treatment
- **Decision Analyses**
  - Evaluate the outcome of a therapy to determine the ideal treatment

**Levels of Evidence**

**Level I**:

- **Therapeutic Study Type**
  - Randomized controlled trials (RCTs) with significant difference or not significant difference but narrow confidence interval
  - Systematic review of Level I RCTs
- **Prognostic Study Type**
  - Prospective studies
  - Systematic review of Level I studies
- **Diagnostic Study Type**
  - Testing of previously developed diagnostic criteria in consecutive patients
  - Systematic review of Level I studies
- **Economic and Decision Analyses**
  - Clinically sensible costs and alternatives (many studies)
  - Systematic review of Level I studies

**Level I example**:

- Same pathology
- 2 different treatments (2 groups)
- Randomization at last possible time point (e.g., at time of surgery)
- A priori power analysis to ensure adequate number of patients
- Specific primary outcome

**Levels of Evidence**

**Level II**:

- **Therapeutic Study Type**
  - Prospective cohort study
  - Lesser quality RCT (<80% follow-up, no blinding…)
  - Systematic review of Level II studies or Level I studies with inconsistent results
- **Prognostic Study Type**
  - Retrospective studies
  - Untreated controls from an RCT
  - Systematic review of Level II studies
- **Diagnostic Study Type**
  - Development of diagnostic criteria in consecutive patients
  - Systematic review of Level I and II studies
- **Economic and Decision Analyses**
  - Clinically sensible costs and alternatives (limited studies)
  - Systematic review of Level II studies

**Level II example**:

- Two groups of the same prospective cohort (based on age, sex or other…)
- Same pathology
- Same treatment
- Specific primary outcome
Levels of Evidence

Level III:

- **Therapeutic Study Type**:
  - Case-control study
  - Retrospective cohort study
  - Systematic review of Level III studies

- **Diagnostic Study Type**:
  - Study of non consecutive patients
  - Systematic review of Level III

- **Economic and Decision Analyses**:
  - Analyses based on limited alternative and costs; poor estimates
  - Systematic review of Level III studies

Level III example:

- Retrospective review of medical records
- Same pathology
- 2 different treatments (2 groups)
- Specific primary outcome
- A priori power analysis

Level IV:

- **Therapeutic Study Type**:
  - Case series

- **Prognostic Study Type**:
  - Case series

- **Diagnostic Study Type**:
  - Case-control
  - Poor reference standard

- **Economic and Decision Analyses**:
  - No sensitivity analyses

Level IV example:

- Retrospective review of medical record
- Same pathology
- Same treatment
- Various outcomes

Level V:

- **Therapeutic Study Type**:
  - Expert opinion

- **Prognostic Study Type**:
  - Expert opinion

- **Diagnostic Study Type**:
  - Expert opinion

- **Economic and Decision Analyses**:
  - Expert opinion

Level V example:

- Expert opinion
- Different pathologies
- Different treatments
- No specific outcomes
Levels of Evidence

Grades of Recommendation:

- Multiple studies more convincing than a single article!
- Grades of recommendation useful for guidelines

GRADE A: good evidence (Level I studies)
GRADE B: fair evidence (Level II or III studies)
GRADE C: poor quality evidence
GRADE I: insufficient or conflicting evidence

For the researcher:
Performing Level I studies is very difficult
Maintain methodologic transparency!

For the reader:
Level I studies and Grade A recommendation are synonymous of high validity of results

EBM and Levels of Evidences

The strongest evidence supporting clinical evidence intervention is …
- through RCT
- meta-analysis
- systematic review of RCTs

Randomised Trials

- Problems of performing RCTs
  - *structural, cultural and psychological resistance to the use of randomisation*
  - inherent variability of surgical methods (and skills), requiring very precise definition of indications, interventions, and quality control of all methods

Randomised Trials

- Problems of performing RCTs
  - *learning curves*, causing difficulties in timing (and surgical skills and experience), making RTCs of new techniques difficult
  - comparisons of surgical and non-surgical treatments (greatly different risks) difficult; in terms of patients’ acceptance (equipoise)
Randomised Trials

• Special considerations and problems
  - **commercial competition**
  - **personal prestige**
  - technique becomes widespread before any RCT is performed (e.g. shrinkage)

Randomised Trials

• Special considerations and problems
  - **life-threatening situations**
  - emergency surgery, often outside normal working hours
  - randomisation (and consent) difficult or impossible

Randomised Trials

• Special technical problems
  - **the learning curve**
  - bias, especially in randomisation between a well-known and an unfamiliar operation
  - bias against the unfamiliar one

Randomised Trials

• Special technical problems
  - **development vs research**
  - RCTs not always justified, e.g. small modifications to treatment
  - if a positive RCT would be needed to adopt each small improvement, many would in fact be rejected.

Randomised Trials

• Special technical problems
  - **patients´ acceptance ( equipoise)**
  - especially Type 3 trials (comparing surgical and non-surgical treatment) pose particular difficulties with equipoise of patients.

Randomised Trials

• Special technical problems
  - **blinding**
  - specific problems in surgical trials.
  - only a third of surgical trials include adequate blinding (patients, observers, surgeons)
REPORTING RCTs:
The CONSORT Checklist:
Guidance to how report the results of RCTs.
Flow diagram:
- Enrollement phase
- Allocation phase
- Follow-up phase
- Analysis phase
Title and abstract, introduction, Methods, Results, Discussion, Other information

REPORTING LEVEL II and III:
The STROBE Checklist:
To improve quality of observational studies.
- Title and abstract (1 item)
- Introduction: background and objective (2 items)
- Methods: study design, setting, participants, variables, measurement, bias, study size, quantitative variables, statistical methods (9 items)
- Results: participants, descriptive data, outcome data, main results, other analyses (5 items)
- Discussion: key results, limitations, interpretation, generalizability (3 items)
- Other information: funding (1 item)

Key message
Clinical care should be based on the best available evidence

Key message
An RCT, meta-analysis or systematic review is the best source of evidence on an intervention

Key message
All clinicians should be able to critically appraise the evidence

Key message
The method of a study is critical to the interpretation of the results
Key message

Study bias; the study may be biased in the method or in the interpretation
Session II

Studies & Evaluation
Case-control studies

Jacques Menetrey, Unité d’orthopédie et traumatologie du sport, Swiss Olympic Medical Center, Orthopaedic Surgery Service, University Hospital of Geneva, Faculty of Medicine, University of Geneva, Geneva Switzerland.

<table>
<thead>
<tr>
<th>Levels of Evidence for Primary Research Question</th>
<th>Types of Studies</th>
<th>Economic and Decision Analyses—Developing an Economic or Decision Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Randomized controlled trial</td>
<td></td>
<td>1. Clinically sensible costs and alternatives; values obtained from many studies; multivariable sensitivity analyses</td>
</tr>
<tr>
<td>a. Significant difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. No significant difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Narrow confidence intervals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Systematic review of Level I studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>were homogeneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Prospective cohort study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Poor-quality randomized controlled trial (e.g., &gt;80% follow-up)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Systematic review of Level II studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Level II studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Nonhomogeneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Case-control study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Retrospective cohort study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Systematic review of Level III studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case series (no, or historical control group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level V</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expert opinion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. All patients were enrolled at the same point in their disease course (inception cohort) with ≥80% follow-up of enrolled patients.
2. A study of results from two or more previous studies.
3. Patients were compared with a control group of patients treated at the same time and institution.
4. The study was initiated after treatment was performed.
5. Patients with a particular outcome (‘cases’ with, for example, a failed total arthroplasty) were compared with those who did not have the outcome (‘controls’ with, for example, a total hip arthroplasty that did not fail).

From Wright JG, Swiontkowski MF, Heckman JD J Bone Joint Surg 2003
Case-control studies are level III of evidence and are relatively rare in the orthopaedic literature.

The different types of studies we can use for an investigation are listed below.

**Type of studies**

*Observational:*
- Case series
- Case report
- Case control studies
- Cohort studies

*Experimental:*
- Randomized-Clinical Trial (RCT)

Studies can be:
- Retrospective
- Prospective
- Cross-sectional: survey one point in time
- Longitudinal: same patients over multiple points in time

**Case series**
- Retrospective, descriptive account of a group of patients with interesting characteristics
- Series of patients who have undergone an intervention

**Advantages:**
- Easy to construct
- Forum for presentation of interesting or unusual observations

Case control studies are a type of observational study useful in identifying risks factors associated with a specific outcome. Case-control studies are most useful when the research question addresses outcome that are rare or take a long time to develop. They are also indicated when randomization may be unethical.

**Strength and limitations of case control studies**:

- **Strength**
  - Facilitates the study of rare outcomes
  - Facilitates the study conditions with substantial time between exposure and outcome
  - Control groups can be matched according to known (or suspected) confounding factors
  - Allow for the study of multiple potential causes of an outcome of interest
  - Relatively inexpensive
  - Can be completed over a relatively short period of time periods

- **Limitations**
  - Inefficient when the exposure is rare
  - Information on exposure and history that is derived from interview is subject to recall bias
  - Selection of an appropriate control group may be challenging
  - Lack of randomization means that groups may suffer from an imbalance of confounding factors
- Can only study one outcome of interest
- Validation of exposure information is often difficult (or simply impossible)
- Cannot provide information on prevalence of the outcome of interest
- Unable to establish causality
- Methodology and correct interpretation of results may be challenging


To conduct a case-control study, one needs to follow a step by step process:
- Formulating a research question
- Identifying a potential risk factor
- Identifying the cases
- Identifying appropriate controls
- Data collection
- Institutional review board
- Statistical consideration
- Limiting bias
- Reporting a case-control study
References


Registries for Evaluating Total Joint Arthroplasty

Nizar N Mahomed, MD ScD FRCSC
Nicki & Bryce Douglas Chair in Orthopaedic Surgery
Professor, Department of Surgery, University of Toronto
Head, Division of Orthopaedics, Toronto Western Hospital
Director, Arthritis Program, University Health Network

Overview
1. History
2. Impact
3. Registries Today
4. Future

History
Early seventies...
- knee arthroplasty relatively uncommon procedure
- restricted for those with severe disability
- Limited literature abundant choice of implants (continuously being modified)

History
- 1975 - Swedish Orthopedic Association initiated nationwide multicenter study
- Recognition by orthopedic surgeons of difficulty in choosing optimal techniques or implants based on personal experience
- Aim: prospectively monitor knee arthroplasty surgery, and render information that could warn against suboptimal techniques and implants.

History: RCT vs. Registry
- RCTs are gold standard for assessment of clinical effectiveness
- But
  - strict inclusion and exclusion criteria limit generalizability
  - not practical when long-term follow-up is necessary, complication rates are low, and random assignment to treatment conditions is unethical

History: RCT vs. Registry
- Patient registries provide alternative to RCTs in these situations.
- Large registries provide comparisons of implants/techniques in real-world setting (i.e. implant survival assessed in patients with various comorbidities, different clinical practice patterns, etc).
Registries Objectives

- Early warning of inferior designs, present average results based on experience of many
- Main interest: failures and complications, rather than degree of benefit.
- Though function deteriorated with time, difficult to distinguish cause; procedure vs. confounding diseases and aging.
- Longevity thus became measured by the absence of failure → problem of defining failure and when it occurred.

Registries Objectives

- Terms success & failure were difficult to define
- Clearly unsuccessful cases were often caused by implant and fixation problems, or by local complications, requiring surgical intervention.
- Revision, therefore, indicated surgeon and patient agreed original problem not solved
- So, revision meant failure of primary surgery
- Revision is well-defined, thus revision and time-to-revision can be recorded.

Impact

- Findings from registries have influenced clinical practice and reduced revision rates.
- Demonstrated positive influence of registries on clinical practice has resulted in increased interest in the development of national/regional/local total joint replacement registries.

Historical Look at Joint Registries

Registries Today – Data Collection

Level I (International Society of Arthroplasty Registers minimum data set)
- Patient information (eg, name, gender, date of birth, diagnosis, health #)
- Surgeon name, National Provider Identifier
- Hospital name and NPI
- Procedural information, including implanted component catalog and lot #

Level II data
- Expanded procedural data (eg, approach, fixation, technique, OR time);
- Pre- and postoperative assessments (eg, DVT and infection prophylaxis, LOS, and Physician Quality and Reporting System information);
- ASA scores;
- Patient comorbidities (eg, obesity, coronary artery disease, diabetes);
- Complications (eg, neurovascular injury, PE, dislocation, MI, infection, fracture, renal failure, death).

Level III (PROM)
- 36-Item Short Form Health Survey (SF-36)
- Hip disability and Osteoarthritis Outcome Score (HOOS)
- Knee injury and Osteoarthritis Outcome Score (KOOS)
- Modified Western Ontario and McMasters University Osteoarthritis Index (WOMAC)
- Oxford Hip and Knee Scores
- Knee Society Knee Scoring System®
- Harris Hip Score

Level IV data include radiographic images
To date...

- Early warning of inferior designs and techniques
- Outcome analyses: mainly confined to the rate of revisions and complications – most research focused on this
- Further research benefits:
  - Data for separate studies on population undergoing arthroplasty
  - Studies on subsets of patients or implants

**Quality benefits**
- Comparisons possible between units and implants regarding patient selection → helps decision-making
- Reveals differences between regions or patient groups regarding results

**Political/economic benefits**
- Purchasers/authorities/clients more willing to provide financial support when
  - Effects of previous financing can be shown
  - Results of treatment can be documented
  - Improvement in quality with time can be demonstrated
- Future trends can be predicted
Today

- Hip and knee arthroplasty have become accepted as safe, reliable, cost-effective treatments
- Now, degree of success is of particular interest
- Studying other types of outcome measures, not based on failures, is underway
  - patient satisfaction, general and site/disease-specific health scores

Today

- In most patients who do not experience failure, grading of the success is possible → further enhancement of choice of implants and methods which optimally benefits patients.

Today → Future

- Despite proven effectiveness of TJR in relieving pain and improving function
  - Significant minority report little to no improvement or dissatisfaction
  - recent recall of ASR hip implants
  → exposed need for systematically monitoring patient-centered outcomes

Today → Future

- Given observed and expected exponential growth in TJR, systematic comparative effectiveness research is critical for informing patients, physicians, and policy makers about optimal practices.
- Critical need for longitudinal PROs to provide evidence to inform patient and clinician decisions about optimal timing, implant selection, surgical technique, functional outcomes.

Today → Future

- Example (2012) Agency for Healthcare Research and Quality (USA) funding
  Function and Outcomes Research for Comparative Effectiveness in TJR (FORCE-TJR).
  - FORCE-TJR:
    - national scope
    - representative of US practices
    - includes longitudinal PRO

Today → Future

DADOS - Integrated Informatics: IT-enabled Personalized Arthritis Care

- PACS Imaging - Ray, CT, MRI Reports
- CAIS/AIMES Medications (Consider MedRec project as another source)
- QR SOS - Implant information
Coordinating Large Multicenter Observational Studies
Kurt Spindler, MD USA
Session III

Evaluation, Variables and Statistics
Methodologic Problems: Examples from the Literature

Robert G. Marx, MD MSc FRCSC
Professor of Orthopedic Surgery and Public Health
Weill Medical College of Cornell University
Hospital for Special Surgery
New York, New York

Are all PUBLISHED papers perfect? No…

How to identify:

• Generalizability problems (inclusion / exclusion criteria)
• Methodologic flaws
• Data poorly interpreted or presented
• Conclusions that are inaccurate, or misleading with respect to the data

Papers selected:

• Excellent papers
• Top journals
• Useful information

Goal of this talk:
To point out flaws and limitations in these very well done studies to improve your ability to read the literature critically.

Inclusion criteria leading to generalizability problems

1.) A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee (J. Bruce Moseley, et al. NEJM, 347 (2): 81-88)
   • Inclusion and exclusion criteria could have been more clearly specified. Osteoarthritis score greater than 9 were excluded. “Severe deformity and serious medical problems” were excluded.
   • Generalizability is questionable since all patients were from the VA. Less than 10% were female.
   • Inclusion criteria and generalizability
   • Clinical relevance of the outcome measure

2.) Natural history of asymptomatic rotator cuff tears: A longitudinal analysis of asymptomatic tears detected sonographically (K Yamaguchi, et al. JSES, 10(3): 199-203)
   • 58 had unilateral symptoms with bilateral cuff tears.
   • 13 patients lost to follow up.
   • Out of 45 patients: 23 became symptomatic
     How is “symptomatic” defined? Not in methods!
     17/23 “symptomatic” either saw a physician or were taking medication
Visual Analog score in the symptomatic group = 4.0
(8 patients had a score of 1 or 2)
Asymptomatic group had a Visual Analog mean score of 1.1
Progression of tear defined as longitudinal or transverse ultrasound increase of 5mm
Is this within measurement error?
Authors state ultrasound is reliable tool. However, we do not know if 5mm is within measurement error.
Asymptomatic patients: 2/9 progressed
Symptomatic patients: 7/14 progressed (not statistically significant)
Conclusions are accurate
-Pain can develop in a large percentage of patients with asymptomatic tears
Authors acknowledge bias due to the fact that this is a study of the contralateral shoulder with a symptomatic cuff tear in the other shoulder.
-Cannot extrapolate results to a patient with bilateral asymptomatic shoulders or a unilateral asymptomatic cuff tear

Power and statistical significance
Arthroscopic Stabilization in Anterior Shoulder Instability: Collision Athletes Versus Noncollision Athletes
Nam Su Cho, et al.
Arthroscopy, 22(9): 947-953, 2006
•4/14 in contact athlete group
•1/15 noncollision athletes
•P = 0.11
•No sample size calculation.
•There is a difference but it is not statistically significant.
  -A power analysis should be performed to see if the lack of statistical significance was related to insufficient patient enrollment.

What is Power?
•The probability of concluding that there is a difference when in fact there is one.
•This is relevant:
  1) Before the study for sample size calculations
  2) After a negative study (no statistically significant difference) to make sure there were enough patients to support the conclusion.

<table>
<thead>
<tr>
<th>Truth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
</tr>
<tr>
<td>No Difference</td>
</tr>
<tr>
<td>Difference</td>
</tr>
<tr>
<td>1-β</td>
</tr>
<tr>
<td>α error</td>
</tr>
<tr>
<td>No Difference</td>
</tr>
<tr>
<td>β error</td>
</tr>
<tr>
<td>OK</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Result</th>
<th>Difference</th>
<th>No Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
<td>1-β</td>
<td>α error</td>
</tr>
<tr>
<td>No Difference</td>
<td>β error</td>
<td>OK</td>
</tr>
</tbody>
</table>
Power in negative studies

• Determine the chances you had to detect a true difference when the study result was negative.


Probably underpowered (need power analysis to be sure).

Is this clinically significant?

4/14 in contact athlete group
1/15 noncollision athletes

OR

400 / 1400 in contact athlete group
100 / 1500 noncollision athletes

(Is it statistically / clinically significant now?)

BIAS related to follow-up


• How good is the follow-up?
  - The author states the follow-up is 62% (see first paragraph of results)
  - See third paragraph of methods: sample size indicated 48 patients required
  - Of 135 patients, authors invited 79 patients who lived within a 150 mile radius of the clinic for follow-up.
    Of these, 49 returned for follow-up for a total follow-up of 49/135 (36.3%)

Inadequate control group leading to BIAS


• 500 patients: 433 followed algorithm
  67 did not follow algorithm

Results

• Algorithm patients had a 2.1% allogeneic transfusion rate
• When algorithm not followed: 16.4% allogeneic transfusion rate

Conclusion

• The use of this blood-conservation algorithm resulted in a significant reduction in the need for allogeneic blood transfusions.

• Algorithm: see page figure on p. 1513
- It is based totally on the pre-op hemoglobin:
  Patients with LOW pre-op hemoglobin get EPO
  (** these are the patients at highest risk of transfusion)

• See page 1514, bottom: 58/67 were included in the non-algorithm group was due to…
  REASON: non-implementation of treatment with EPO despite an algorithmic
  recommendation to do so.

• See Table 2:
  Baseline hemoglobin in algorithm group - 14.0
  Non-algorithm group hemoglobin - 11.6

• Algorithm group:
  • high hemoglobin = don’t need EPO (415)
  • Low hemoglobin = all got EPO (18)

• Non-algorithm group:
  • 58 of the 67 patients fit criteria for algorithm recommendation for EPO (ie: LOW
    HEMOGLOBIN)
    • BUT they didn’t get EPO

The two groups are very different and cannot be compared.

The Real Question
Were transfusion rates higher due to:
  1) the algorithm (NO!)
     OR
  2) lower pre-op hemoglobin in the non-algorithm group and the fact that EPO was
     not used in these patients

Relevance of the primary outcome
Glucosamine, Chondroitin, Sulfate, and the Two in Combination for Painful Knee
• Was the primary outcome appropriate?
  • The clinically important outcome was a 20% decrease in knee pain from baseline
to week 24.
  • A continuous variable (pain score) was converted to a dichotomous to response
    (yes or no).
    • See Table 2 (p 801): when pain was examined as a continuous variable,
      the effect was almost identical to Celebrex.
    • The selection of the primary outcome and how it is analyzed and interpreted is
      critical.

Letter to the Editor
• The primary outcome for the Clegg et al study was the response rate to treatment,
defined as a 20% decrease in the WOMAC pain score. At the end of the follow-up, the
  Celebrex had a 70.1% response to treatment compared to 66.6% for chondroitin and
  glucosamine—very similar response rates although statistically significantly different.
• When the raw data is examined for the WOMAC pain score, the numbers are almost identical, and the P values are the same at P=0.12 for both groups.
• The effect of Celebrex compared to the chondroitin and glucosamine compound is very similar for most of the other outcomes evaluated.

In view of these findings, I will strongly encourage my patients with osteoarthritis of the knee who are treated non-operatively to take chondroitin and glucosamine supplements, particularly if they are interested in avoiding the known and potentially dangerous side effects associated with non-steroidal anti-inflammatory drugs.

• All authors were listed and received either research support, fees for work on advisory boards, speaker fees, stock options or consulting payments from Pfizer, or had equity interests in Pfizer.
• Note conflict of interest statement and draw your own conclusions…

**Interpretation problem relating to Exclusion criteria:**
The results do not apply to patients who are excluded from the study!

A RCT of Arthroscopic Surgery for OA of the knee (Sandy Kirkley, et al. NEJM, 359, 1097-1107, 2008)

• Compared arthroscopy to non-op care for patients with OA
• Inclusion criteria: age 18 or greater, meniscal tear on MRI with at least KL grade 2 OA

The authors excluded:

• “large meniscal tears, as detected by clinical examination or, in a minority of cases, by MRI, in whom surgery was considered appropriate”
  - These exclusions made it less likely that the study would find a benefit to arthroscopic surgery as compared to non-operative care.

• OA knee is a continuum: from young active person with injury and large meniscal tear
  • For example; 46 yo female with twisting injury five months ago, with subsequent medial pain, limitation in function and large meniscal tear on MRI with minimal OA (eligible for the study)
  • The other extreme: 68 yo female with bone on bone OA, three degree varus deformity and inability to walk more than 5 blocks (Also eligible)
  - This patient would have likely been INCLUDED since they are not a good candidate for arthroscopy!

Is this study useful?
• Indicates that arthroscopy is not better than non-op care for knee OA.
• But it does not mean that there no use for arthroscopy in knee OA – since the authors excluded the patients they thought would do the best with surgery (ones they thought had large meniscal tears).
Wall Street Journal, September 11, 2008
“Common Knee Surgery Ineffective, Study Says”

Conclusion:
The literature must be read and interpreted with caution.
Read the paper and interpret the results for yourself – see if you agree with the authors.
Thank You.
A. What is a variable?

- Categorical
  - Binary
  - Nominal
  - Ordinal

- Continuous
  - True continuous
  - Interval

B. Defining your variables

C. Strategies for Data Capture

- Existing records
- Electronic hospital systems
- Direct Objective Measurement
- In-person interviews
- Phone interviews
- Paper-based questionnaires
- Web-based questionnaires

D. Data Systems

- MS-Excel
- MS-Access
- Web-based research data system
A. Descriptive Statistics

- Categorical Variables
  - Frequency Counts
  - Percentages
  - Observed v. Expected
  - 2x2 table

- Continuous
  - Means
  - Medians
  - Mode
  - Standard Deviation
  - Standard Error
  - Intra-quartile Range
  - Minimum/Maximum
  - Range

B. Inferential Analyses

- Bivariate Analyses
  - Categorical Outcome v. Categorical Exposure
  - Categorical Outcome v. Continuous Exposure
  - Continuous Outcome v. Categorical Exposure
  - Continuous Outcome v. Continuous Exposure

- Multivariable Analyses
  - Logistic Regression
  - Multiple Linear Regression
  - Repeated Measures Analyses

C. Special Analyses

- Validation Studies
- Correlations v. Predictions
Session IV

Outcomes & Clinical Trials
Randomized Clinical Trials in Orthopaedic Surgery
Mohit Bhandari, MD, PhD, FRCSC CANADA
Assessment of Biological Outcomes in Clinical Research
-Cartilage repair as a model-

Norimasa Nakamura, MD, PhD
Institute for Medical Science in Sports, Osaka Health Science University
Takashi Nishii, MD, PhD
Department of Orthopaedic Surgery, Osaka University Graduate School of Medicine
Shuji Horibe, MD, PhD
Department of Comprehensive Rehabilitation, Osaka Prefectural University
Konsei Shino
Sports Medicie Clinic, Yukioka Hospital

Assessment of endpoints in cartilage repair generally involves clinical endpoints as well as biological (structural) ones. However, the applicability of these endpoints depends on the characteristics of the investigational product and its method of implantation.

It is widely accepted that clinically meaningful endpoints, such as improvement in pain and physical function, provide the most persuasive evidence of efficacy and thus these clinical evaluation has been used as the primary endpoint. There are several useful clinical outcome scoring systems available such as, Knee Injury and Osteoarthritis Outcome Score (KOOS), IKDC Subjective Knee Evaluation Form-2000, Cincinnati Knee Rating System, Marx score, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for the assessment of cartilage repair.

On the other hand, biological and structural evaluation is in general regarded as secondary endpoints. However, these assessments are very important because such biological and structural data directly relate to the quality of repair tissue, which could potentially affect the longer term durability of repair cartilage and subsequently their longer term outcomes.

The following methods are generally used in clinical trials:

1) Arthroscopic evaluation to assess changes in the size, location, and grade of cartilage lesions both before and after intervention. ICRS grading system is widely used for the detection of the integrity of repaired tissue, the integration of implanted product to adjacent tissue, and of stiffness of the implant by tissue probing.

2) Histologic evaluation at both short (e.g., six months) and long term (e.g., two years) follow-up in a subset of subjects to assess: matrix zonal organization; cell density; cell morphology (i.e., chondrocytic vs. fibroblastic); collagen types and concentration; aggrecan concentration, size, and composition; other proteoglycan concentrations; noncollagenous protein concentrations; and inflammatory response.

3) Magnetic Resonance Imaging (MRI) to evaluate articular surface integrity, thickness and volume
of chondral surface, subchondral bone plate contour, thickness and volume of synovial membrane, and volume of synovial fluid. MRI has gained a major role in the assessment of cartilage repair. The introduction of high-field MRI to clinical routine makes high resolution and three-dimensional imaging readily available. New quantitative MRI techniques that directly visualize the molecular structure of cartilage may further advance our understanding of cartilage repair.

The present lecture will provide up-to-date information on the advancement in biological and structural assessments for cartilage repair.
Equipoise (what it means, willingness to acknowledge uncertainties)

Bruce A. Levy, M.D.
Department of Orthopedic Surgery
Mayo Clinic, Rochester, MN

I. What is Equipoise
A. Equi = equal, Poise = position. A state in which two options appear equally appropriate
B. Community ~ Clinical Equipoise
   1. Circumstances in which the community of clinical scientists deem both options appropriate
   2. Entry and exclusion criteria for RCT define a population in whom there is no solid evidence favoring one treatment or another
   3. Consensus on patient population in whom it would be ethical to randomize
C. Individual Equipoise
   1. Clinical circumstances in which the investigator deems either option clinically appropriate and ethically defensible

II. Uncertainty Principle
A. Based on experience, clinicians often have an intuition, belief or hunch.
B. Some surgeons will only offer patient the trial when uncertain which option is best.
C. Clinical Investigator’s Dilemma
   1. If the clinician has a strong intuition that a patient who is eligible for the trial would benefit from surgery, is it ethical to recommend randomization?
   2. Similarly, if the clinician feels that an eligible patient would unlikely benefit from surgery, is it ethical to randomize?
   3. Is uncertainty (lack of preference) required to justify randomization?

III. Ethical Framework
A. Some ethicists uphold the principle of uncertainty as ethical prerequisite.
B. Others uphold community equipoise as ethical standard.
C. Still others argue that the ethical requirement is for fully informed, non-coerced consent.

IV. Examples
A. MeTeOR Trial
B. Simulated MeTeOR Trial

V. Take Home Points
A. RCTs are essential to establishing a base of clinical evidence
B. Randomization is the cornerstone of RCTs
C. Failing to preserve community equipoise contributes to weak evidence base.
Session V

Presenting Data
Presenting Data
Warren Dunn, MD, MPH USA
It is not an exact science to either write or review a manuscript. Sometimes it is quite the contrary, but there are certain existing rules and if the authors stick to them they will find that success as scientific authors will come much easier.

We all know that every manuscript must be reviewed. In most cases not only once, but more frequently 2-3 times. The authors also need to be aware of the fact that a critical and constructive review is probably the best thing that can happen to a manuscript. With a standardized review process, the papers will be easier to read, flow better and in fact be more likely to be accepted for publication. Please note the key word “flow”, as this is a very important element when writing a manuscript. The most important aspects of a manuscript is in other words that it should flow well, be easy to read, not be too long and absolutely not be boring.

In general terms, the three most important issues that the editors/reviewers are concerned with are as follows

- **Length of the manuscript.** A common problem is that the manuscript is too long. In fact, probably all manuscripts are too long. What instead is important is to have the manuscript well focused.

- **Avoidance of repetitions.** This must be avoided at any cost. It might also be said like this: a manuscript should be as must long as necessary, but as short as possible.

- **Keeping a good flow.** The manuscript should flow well, be easy to read and to follow the text.

**GENERAL COMMENTS**

The first thing that should be done is to carefully read the “Instructions to Authors”. It is way too common that authors have not read them. A lot of trouble will be avoided if the instructions are read and followed thoroughly.
The most important question related to every manuscript is about the research question. Is it of interest, is it original or is it merely a repetition? Repetitions can be useful as when findings by one particular research group need to be confirmed by a second group. The question is if the manuscript brings anything new. If not, it will most probably be difficult to get the manuscript published.

We should as authors and reviewers always bear in mind that most – or even all - manuscripts are too long, especially clinical papers. When reading through the paper, it is almost always evident that it can be shortened without losing any scientific information. Furthermore, it is not necessary to repeat what everyone knows, like ”ACL injuries are very frequent” - why write this for the 1000:th time? - or ”Hip fractures are very common in elderly women” - we all know this very well.

Another thing to consider is if the English language is in good order. This is especially relevant if the authors are not native English-speaking. The rejection risk in such case is in fact much higher. The editors of some scientific journals sometimes reject a manuscript already from the beginning due to poor English, without any scientific review, but in such a case they often/always give the authors the opportunity to revise their English and resubmit. It may take time to correct the English and it may even cost some money. This can be done by professional companies, but it can also be a good idea to join forces with a native English-speaking colleague if possible.

2. TITLE

The title should be short and concise. It may very well be somewhat provocative. Sometimes, although not very frequently, the title may be given as question. In other words, what is new?

Common errors are that the title is either too short or too long; where being too long is much more common. Another common error is that the title is too neutral and does not say anything at all, like ”Two year follow-up after ACL reconstruction”. In this example the readers don not actually know what happened. However, even though the title may be provocative, it should never be offensive.

Sometimes, unfortunately not infrequently, the title does not match the content of the manuscript. The title should never include abbreviations or jargon and it should also be short and clear. If a long title is needed, maybe due to complicated study design, a subtitle could easily be used. What the title should describe the study and the main result in 250 characters, if at all possible.

3. ABSTRACT
The abstract should be short, in principle never exceeding one manuscript page. It should be of maximum of 300 words in most journals and it should be concise. The content should be as follows: what was done, what were the results and what conclusion was reached. In case of non-clinical studies, the clinical relevance must be added. The keywords and Level of Evidence should also be checked. Many journals request a structured abstract like Purpose, Methods, Results and Conclusion. Some journals add more items, like Hypothesis and Setting. An interesting note is that approximately half of the manuscripts submitted to any journal are incorrectly formatted and unstructured. Editors are not asking for a long background and the purpose should seldom be more than one sentence. They are also not asking for a hypothesis or a discussion either and therefore this should most often be avoided. Furthermore, the use p-values or references in the abstract should be avoided. Methods should be described in detail in the text body.

A common error is that the results in the Abstract are not the same as the reported results in the running text, the Results section. A good advice to avoid this is to write the Abstract as the last part of the paper. Also, what we often see is that the methods mentioned in the Abstract are different from what is stated in the Material and Methods section. The length of the Abstract should absolutely not exceed the limit allowed by the journal; as already mentioned, about one manuscript page as a general rule. Another error sometimes seen is that the conclusions drawn in the abstract are not the same as stated in the manuscript. In most cases the authors also add something to their conclusion that per se is correct, but is not supported by the data in their study. This must be avoided. It is therefore beneficial to add a few words about the relevance of the work at the end of the conclusion section, especially in case of an experimental study. Some journals ask for Clinical relevance as a separate section of the Abstract and that should then be followed.

What the abstract should clearly state is what the authors found and what they concluded. As a general rule the conclusions should be clinically relevant.

Many journals now require Level of Evidence (for all clinical studies). The detailed information about levels of evidence is always found in "Instructions to Authors". Sometimes, the exact level may be difficult to determine and therefore Editors are happy to answer questions in case the authors are in doubt. Some journals add items like "what is already known about this subject" and "what is new". This is another example of when “Instructions to Authors” is useful.

4. INTRODUCTION

It can sometimes be difficult to write the introduction, especially to get started. What is said in the introduction should be thought-provoking and interesting. The ideas should be supported by recent literature. All too often authors support their ideas with old references. Bankart
wrote his classic paper in 1923 and it has been cited thousands of times even though a lot has happened since then.

A relevant question is if the introduction provides the necessary background. A good question to look at is the necessity to do this study? Is there a gap in the literature? What is new in this particular area/field? Is the research question reasonable and of interest? Is the purpose clear? Is the hypothesis given? Please note that a hypothesis is not needed for an experimental study, only for clinical studies.

The most common error is that the introduction is too long, i.e. partly discussion which is not needed and only will lead to repetitions and not infrequently, the purpose/objective of the study is not reported well and the originality of the study is not mentioned at all. It is important to state why the study is important? On many occasions the introduction is way too long and contains material that is not related to the scope of the study. The material is in most cases correct and well thought-out, but has more or less nothing to do with this present study. Sometimes the introduction contains material that should be presented in other parts of the manuscript, for instance materials and methods, description of the cohort and/or discussion.

5. MATERIAL AND METHODS (Patients and methods)

When writing the manuscript the authors need to check if the description of the methods is correct. The most important question is whether the study can be repeated by other researchers by using the description in the methods section. If not, the methods section is simply not good enough and the manuscript will not be accepted. Is the patient cohort adequately reported, e.g. age, sex distribution, concomitant injuries, previous surgery etc.? Another very important question is if the randomization adequately described. If the randomization process is not described properly, this needs to be addressed.

The most common errors are that some methods are not reported, even though they are used and referred to in the results section. Vice versa, some reported methods are not used. In some cases, methods are reported first in the results section, which is an error that should always be avoided. A general rule is that the methods section and the results section must mirror each other. All that is in the methods section must be reported in the results section and vice versa. Sometimes methods are missing, not well reported, or do not relate to the results, and thus not allowing the ability of a repetition of the study by another research group.

Most clinicians are not statisticians and therefore the statistical methods are often incorrectly reported. If the study design is complicated, it could be a good idea to join forces with a statistician. Moreover, the accuracy of measurement methods must be carefully reported, for instance in terms of reliability (test - retest). This also has bearing on how the results are reported. Two or three decimals are as a rule not necessary and should be avoided. The main
reason of this is that the measurement accuracy is usually less than for instance 0.01 mm or 0.01 degree.

At the end of the methods section, the subheading “Statistical Analysis” must be added; check the “Instructions to Authors”. Under this subheading, all statistical methods must be described in detail. A common problem in many clinical studies is that the cohort is too small. This is not related to writing the manuscript, but a full sample size (power) calculation should still be given here. If not, reviewers and Editors will simply ask for it. Limited sample size leads to erroneous conclusions, due to so-called Type II error. Sample size calculation is one of the most important parts of any manuscript and it is often the section that reviewers check first. Inadequate power means or erroneous conclusions. In large clinical studies, drop-out analysis should be mentioned.

6. RESULTS

The Results section must be short. A good rule is one manuscript page maximum, without the repetition of the information in Tables and Figures. All too often the Results section has included the duplication in the Results, Figures and Tables, and sometimes in all of them. This is problematic; it destroys the flow and just makes the manuscript longer without making it any better, rather actually making it worse. The Results section must always be in harmony with the Material and Methods section, it makes the manuscript easier to read and follow. A general rule is to not use subheadings in the Results section and if this for some reason must be done, the subheadings used should be similar to the ones in the Material and Methods section and the Discussion.

Sometimes we reviewers can read numbers in the submitted manuscripts like 0.001 mm or 0.001 degrees, and in most cases those are just mean values and they actually report many more decimals than they have measured. This is not correct, of course, as only what is measured in this particular study is what should be reported and nothing else. An important note to have in mind is to reduce the decimal places as much as possible. Often one decimal is enough. This will in most cases both be more correct and increase the readability.

Now, what about p-values? Different journals have different rules. Some accept non-significant p-values, while others do not. As a general rule, the non-significant p-values should be kept to a minimum or entirely avoided. A simple rule for the author is to use (n.s.). The results should not be based on trends, for instance a number like 0.057 should be written as non-significant, and not ”almost significant”

7. DISCUSSION

The most common error in the Discussion is that it is too long. It is also not uncommon for it to be too general and not really related to the findings of the study. As a general rule, the Discussion section should not exceed 3 manuscript pages. Authors should always start with a
short paragraph, possibly 1-2 sentences, about the most important findings. Thereafter, the findings must be put into context by comparing them with the findings of other researchers. What is similar and, more importantly, what is different? For all basic science studies, authors must mention the clinical relevance of the findings, especially if writing a paper in a clinically oriented journal. A good question to ask is how the findings can be helpful in the day-by-day clinical work.

Second to putting the findings into context is to honestly report the limitations of the study. This must be done and is in fact something that many Editors check first in a new submission. If limitations are not mentioned and discussed, the Editor will invariably think that the author might be hiding something. The limitations are important and should never be hidden. They often create new and significant scientific questions. The limitations should be stated near the end of the Discussion section. It must be remembered that all studies have limitations and that they should be discussed.

At the end of the Discussion, the clinical relevance of the study should be mentioned. This is where the conclusions are drawn from the authors own study, and not from other studies.

8. CONCLUSION

Only the findings of own study should be concluded and nothing else. No discussion and no general message should be written here. It is important to not be general, vague or to base the conclusions on feelings or general knowledge. Instead tell the readers in 2-3 sentences what have been found out. Way too often the Conclusion section is just an extended Discussion, so to avoid this; conclusions must be drawn from the authors’ own study and not from other and more general papers. Hard facts must be used, never trends. Trends may be discussed in the Discussion section, but never in Conclusion. What is concluded must be statistically significant.

9. REFERENCES

In this there are three common errors, with the first two being more common;

I. Incorrect format. This should be easy, the only thing needed is to read and follow “Instructions to Authors” carefully. It should be remembered that journals have different instructions and may have different citation systems. Even though this should be clear, approximately 50% of all manuscripts have incorrect reference format. Whether the reference format is correct or not is sometimes the first thing Editors check in a new manuscript. Some Editors claim that “if the references are not correct, then the rest is probably not correct either”

II. References are not up to date. There may be several reasons for this, the most common is probably that the study (for instance prospective cohort)
started several years back and the references were never updated during the study period. Another reason is that many researchers know the old classic references best and only use them. This will not do, of course. All Editors check for recent publications and they must be added. Otherwise the authors risk to miss important information and it will lead to a smaller chance of getting the paper published.

III. Incorrect citations. This invariably means that the authors have not read the paper.

A sound advice is to update the references just before submission. Recent and relevant citations always make the manuscript better.

10. TABLES AND FIGURES

First of all; no information already found in the manuscript should be repeated. Second, figures and tables should have added value show something that is not found in the rest of the manuscript. Figures should be clear, which means no drawings by amateurs and the figure legends must be such that key ideas and key facts are pointed out in the figure legend. Every figure should be possible to read as a ”stand-alone figure”. Combined figure and figure legend should give the reader a take-home message. All the same can be said for tables. Tables should mainly be used to give the most detailed information that is not found in the Results section.

11. REVIEWER’S CONCLUSION

This guide may appear to be complicated, but don’t worry. If you carefully follow these guidelines, the likelihood of succeeding in publishing your manuscript is much greater than if you ignore them. What to remember is that first of all, always start out by carefully reading the ”Instructions to Authors”. They are detailed on purpose. But they are less complicated than you might think and help you more than you probably could imagine. The good news is that if you have decent research question, and carefully follow the rules of writing the manuscript, it will most probably be accepted.