Designing Your First Clinical Investigation

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Thanks to Robert O’Toole, Mohit Bhandari, Herman Johal
Outline

• Think of a topic
  • Vet the question
  • Identify the impact
• Identify your goals
• Preparation
  • Literature review
  • Build a team

• Execution
  • Methodology
  • Funding opportunities
  • Research Support
  • Mentorship
• Long term considerations
Case Example

• You want to do a study to determine whether patients receiving NSAID require less opioid medication.
Before you start: Decide why you’re doing this!

• It’s a long road

• What are your motivations? Goals?
  • Improving patient care
  • Growing reputation
  • Career advancement
  • Teaching
  • Enjoy pure research

• Be honest with yourself. Involve your mentors and family.

• Multiple valid career paths.
Goals

Medical student research
Resident research
Fellow research
Faculty research
Local presentations
National presentations
Publish in lower tier journal
Publish in higher tier journal
Get industry grants
Get federal funding
Be a site for multi-center studies
Lead multi-center studies
What should you focus on?

Think of a topic:

- What do you see at your institution a lot?
- What are you good at?
- What do you see that’s unusual?
- Find a knowledge gap in the literature
Vet the question

• Do your homework. Answer 3 questions before proceeding:
  • Is it Redundant? – Has it been done before?
    • Literature review
  
  • Is it Realistic? – Can it be accomplished with the resources at your institution?
    • Case volume? Follow up?
  
  • Is it Relevant? – If successful, how will the information change clinical practice?
    • What actionable information can you discover?
Perform an extensive, methodical literature review

- Doing this in a reproducible, detail-oriented way will save work in the long run and serve for the foundation of all the writing required

- Multiple examples of reference matrices available
Perform an extensive, methodical literature review

• Pick a good reference management tool and commit to it
  • Endnote
  • Mendeley
Formulate “The Question”

• Frame the research around a specific, testable hypothesis

  • **Bad**: Geriatric pelvis fractures have a high mortality rate
    • not testable? What is “high”?

  • **Better**: Geriatric pelvis fractures have a one year mortality rate comparable to geriatric hip fractures

• The core of research design will hinge on addressing this question

• Alternative framing: Think about what it would take for a study to prove your hypothesis *wrong* → do that study!
Develop specific aims

- Required for grant writing
- Useful exercise even when not applying for funding
- Should be:
  - Based on specific hypotheses
  - Not interdependent
  - Incrementally more ambitious
- A useful exercise to determine what “success” will look like at the conclusion of the study
Case Example - Develop specific aims

• Aim 1: Determine whether patients who received Ketorolac treatment require less opioid medication throughout their hospital and post-operative course.

• Aim 2: Determine if early scheduled administration of Ketorolac will reduce the inflammatory cytokines and patient morbidity.

Beware of being vague, having sequential aims dependent on one another, having too many aims, over burdening your research facility and staff
Determine your outcome of interest

- Based on the optimum way to test your specific aims / central hypothesis
  - Functional scores:
    - Patient rated outcome measures (PROM)
    - Performance based measures (PBM)
  - Radiographic measurements
  - Clinical outcomes:
    - Death, infection, readmission, fixation failure, etc

- Selecting an appropriate primary outcome measure may be the most important step in study design
  - Reliability? Validity? Responsiveness?
Case Example - Outcome of interest

• Aim 1: Determine whether patients who received Ketorolac treatment require less opioid medication throughout their hospital and post-operative course.
  • Patients' subjective pain score (Visual Analog Score)
  • Morphine Milligram Equivalent intake
  • Group 1: Treatment vs Group 2: Placebo

• Aim 2: Determine if early scheduled administration of Ketorolac will reduce the inflammatory cytokines and patient morbidity
  • IL-6, IL-10, IL-1
  • Secondary outcome: morbidity, hospital length of stay, ARDS/SIRS, Pneumonia
Build a team – Getting started

• Bring in the help you realistically need to execute the research plan

• Balance of time, funding, expertise, and assigning credit
Build a team – Study staff

• Research coordinator
  • Requires funding, can act like an extension of the PI to keep paperwork, enrollment moving
  • Early in career, you may need to be your own coordinator!

• Research Analysts/Assistants
  • Cost money, need funding

• Medical students / Residents
  • A good resource for labor to help
  • Be realistic with them about their availability, your expectations
  • What is their reward! - academic credit
  • Requires supervision to ensure data integrity
Build a team – Statisticians

• A crucial resource

• Involve them *before* the study starts (e.g. power analysis)
  • Use them to help develop/build your data collection sheet

• Frequently require funding, sometimes can get short amounts of time

• They rely on *you* for clinical context and relevance
  • Provide them a detailed understanding of the medical details.
Build a team – Mentorship

- Whatever you’re about to start, chances are others have some similar projects in the past
  - Inside your institution: know the ins-and-outs of getting work done at your center
  - Outside your institution: can give you big picture guidance on how to set up your study to maximize the chance of success

- Learn from others’ mistakes so you don’t have to make the same ones

- Lean on mentors when you hit bumps in the road and unexpected problems

- NEVER BE AFRAID TO ASK FOR HELP – you will learn and gain respect
Case Example - Build a team

• Principal Investigator (PI) – You
• Co-PI – Mentor/Expert in the field
• Key Personnel:
  • Pharmacist-clinical studies
  • Statistician
  • Immunologist – Cytokine analysis
  • Clinical Study Coordinator
• Study Personnel:
  • Medical Students/Residents
  • Research Assistants: help with patient enrollment
Choose a Methodology

• What methods have been used before?

• What other validated ways exist to answer the question
Identify the Level of Evidence

• Prospective or retrospective?

• Pick minimum Level of Evidence to answer your question meaningfully

• Not everything needs a level 1 RCT

### TABLE 1. Levels of Evidence by Study Type

<table>
<thead>
<tr>
<th>Level</th>
<th>Therapeutic</th>
<th>Prognostic</th>
<th>Diagnostic</th>
<th>Economic and Decision Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>High-quality RCT with statistically significant difference or no statistically significant difference but narrow confidence intervals</td>
<td>High-quality prospective study (all patients were enrolled at the same point in their disease with &gt;80% follow-up of enrolled patients)</td>
<td>Testing of previously developed diagnostic criteria in a series of consecutive patients (with universally applied reference “gold” standard)</td>
<td>Sensible costs and alternatives, values obtained from many studies, multi-way sensitivity analyses</td>
</tr>
<tr>
<td>Level I</td>
<td>Systematic review of level I RCT (and study results were homogenous)</td>
<td>Systematic review of level I studies</td>
<td>Systematic review of level I studies</td>
<td>Systematic review of level I studies</td>
</tr>
<tr>
<td>Level II</td>
<td>Lower quality RCT (&lt;80% follow-up, no blinding, or improper randomization)</td>
<td>Retrospective study</td>
<td>Development of diagnostic criteria on the basis of consecutive patients (with universally applied reference gold standard)</td>
<td>Sensible costs and alternatives, values obtained from limited studies, multi-way sensitivity analyses</td>
</tr>
<tr>
<td>Level II</td>
<td>Prospective comparative study</td>
<td>Higher quality prospective study (patients enrolled at different points in their disease or &lt;80% follow-up)</td>
<td>Systematic review of level II studies</td>
<td>Systematic review of level II studies</td>
</tr>
<tr>
<td>Level II</td>
<td>Systematic review of level II studies</td>
<td>Systematic review of level II studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level III</td>
<td>Case-control study</td>
<td>Case-control study</td>
<td>Study of nonconsecutive patients (without consistently applied reference gold standard)</td>
<td>Analyses based on limited alternatives and costs, poor estimates</td>
</tr>
<tr>
<td>Level III</td>
<td>Retrospective comparative study</td>
<td></td>
<td>Systematic review of level III studies</td>
<td>Systematic review of level III studies</td>
</tr>
<tr>
<td>Level III</td>
<td>Systematic review of level III studies</td>
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</tr>
<tr>
<td>Level IV</td>
<td>Case series</td>
<td>Case series</td>
<td>Case-control study</td>
<td>No sensitivity analyses</td>
</tr>
<tr>
<td>Level V</td>
<td>Expert opinion</td>
<td>Expert opinion</td>
<td>Poor reference standard</td>
<td></td>
</tr>
<tr>
<td>Level V</td>
<td>Expert opinion</td>
<td>Expert opinion</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Trials Design

• Clinical Case Series – Level IV EBM
  • Easy to do
  • Requires few resources
  • May be prospective (best) or retrospective
  • Need a priori protocols, well defined inclusion/exclusion criteria
  • Will have a selection, recall, performance and expertise bias
  • Useful as a pilot study – generate hypotheses, power calculation for future studies, evaluate novel surgical techniques
Clinical Trials Design

• Case controlled
  • Two groups – cases versus control
  • Retrospective
  • Compared for risk factors, characteristics of patients, fracture, disease, treatment
  • Get Odds ratio, regression analysis
  • Simple, cheap, good for rare outcomes
  • Will have a selection, recall, performance and confounding bias
Clinical Trials Design

• Cohort Study
  • Two groups – exposed and unexposed group
  • Prospective – allocation naturally at baseline and followed
    • No recall bias, match for confounding variables, standardize eligibility and outcomes
    • Resource intensive, selection, detection, performance bias and attrition
    • Less strength in treatment effect inferences (vs. RCTs)
  • Retrospective - where exposure characteristics identified retrospectively (i.e. by type of treatment) and followed forward for the development of the outcome interest
Database study

- Multiple large national / international databases exist with data that can be “mined”
  - NSQIP, TQIP, Medicare payor database, PearlDiver, etc

- Pros
  - Very large sample size
  - Global uniform sample can eliminate expertise bias

- Cons
  - Only as good as the data coded into it: “garbage in = garbage out”
  - Can become descriptive studies = just defining incidence and event rates, no core underlying clinical question answered
  - Most of the low hanging fruit may have already been explored

- Only pursue a large database study if:
  - You have a clearly defined clinical question
  - The data captured in the database is extremely well suited to address the question
  - You have expertise or access to experts in the complex statistical methods required
Clinical Trials Design

• Randomized Controlled Trial
  • Highest quality evidence
  • Identify study prospectively and randomize based on strict inclusion/exclusion criteria
  • Mitigates selection and confounding bias
  • Efficacy and effectiveness may be determined
  • Needs proper strict randomization
  • Blinding if possible
  • Are expensive, time consuming

Power Analysis – How many patients do you need?

• Do this before starting!
  • Need to have a clearly defined primary outcome, a sense of what a clinically meaningful difference would be

• Should be done with the help of a statistician

• Retrospective studies: Often a sample of convenience
  • How do you know when you have enough patients?
Minimize Bias

• Selection Bias
  • Error due to difference in study groups leading to differences

• Recall Bias
  • Increased likelihood of patients with an adverse outcome to recall exposure

• Detection Bias
  • Differential assessment of outcome by assessors due to knowledge of treatment

• Performance Bias
  • Systematic differences in care between groups independent of the intervention

• Attrition Bias
  • Difference in patients who drop out of a study compared to those who remain

• Expertise Bias
  • Differential ability of treatment providers between interventions
Case Example - Methodology and Power Analysis

• Prospective Randomized Clinical Trial

• Double Blinded:
  • Neither research team nor patient aware of treatment group

• Single Center vs Multicenter: Do I have the sample size?

• Power Analysis: STATISTICIAN TO THE RESCUE
  
  • **Aim 1:** Utilizing a two-tailed t-test, a sample of 100 patients (50 per group) will be 90% powered to detect between group difference in opioid consumption.

  • **Aim 2:** A preliminary power analysis (using SAS Proc Power) shows that a sample size of 100 per group gives a power of 90% to detect a 20 percentage point difference in frequency of bacterial pneumonia and a power of 82% to detect a 15 percentage point difference in frequency of ARDS
Register your clinical trial

- Prospective clinical trials should be registered at Clinicaltrials.gov
  - Most institutions have a liaison that can help with that process
  - Should be registered *before* you start data collection
Funding

• Levels:
  • Intramural
    • Hospital Specific Startup Funds
  • Extramural
    • Pharmaceutical (disclosure and internal bias)
    • Society level (OTA, AO North America, MAOA, OREF)
  • Large Scale
    • NIH
    • Department of Defense
    • PCORI
Funding

• Be Prepared for Rejection
  • It is a process
    • Rejected
    • Recommend Changes
    • Reapply
  • Successful researchers average 8 rejections before 1 acceptance

• How bad do you want it?
• It is a learning experience – each rejection teaches you something
Case Example - Funding

• OTA Full Faculty Grant ($80K over 2 years)
  • Obtain pilot funding
  • Seed money for preliminary data
  • Demonstrate feasibility

• NIH RO1 / DoD Grant ($2 mil over 4 years)
  • For fully powered study
  • Multicenter trial
Ethics - IRB

• Not just a chore
• Opportunity to write the Intro and Methods for manuscript
• Doing a good job now saves work in the long run
• Save templates for future studies
• Ask for help
• The IRBs are for you and your patient’s protection – do not fight but cooperate with them
Data collection

• Time put into good data collection preparation pays for itself at the end of a study!
  • Agree on a format and make a standardized form that forces data to be entered correctly (i.e. minimize free text responses)
  • Put data into a single secure location that everyone on the study knows
  • For multicenter studies, consider data management software designed specifically to coordinate clinical trials (e.g. REDCap)
Equipment/Infrastructur

• What does my institution have:
  • High volume
  • Obesity
  • Geriatric
  • Opioid Epicenter

• What other departments are doing excellent research at my institution:
  • Physiology
  • Engineering
  • Microbiology

• Focus on your strengths and collaborate with others that have similar goals
Research Support from Department

• Not required but helps

• You need:
  • Seed Money
  • Resources: access to team personnel, lab
  • Time: “nights and weekends”
Case Example: Equipment/Infrastructure

• Research support: given 15% protected research time/DOE

• Equipment:
  • Support from Chair
  • Access to patients
  • Research coordinator/personnel to enroll patients
  • Investigational Drug Service to administer treatment
  • REDCap to assess patient outcome
  • PROMIS patient outcome scores
Courses to become a better researcher

• AAOS
• OREF
• USBJI – YII (Young Investigator Initiative)
• Local Hospital
• NIH Grant Writing Workshops
• Volunteer for Research Committees
Best Way to Become a Better Researcher

• Ask for Help

• Build relationship with mentors

• Seek out and collaborate with other good researchers

Dr. Bhandari

Dr. Tornetta

Dr. Obremsky
Ready?

• Follow through on what you planned

• Research should be:
  • Realistic
  • Achievable
  • Meaningful

• Anything that gets funded MUST get completed
  • Summary Report
  • Build a reputation
# Case Example - Ready

## Table 3: Tentative time table of the proposed project

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Inpatient</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily Screen</td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
<td>Day 4</td>
<td>Day 5</td>
<td>Discharge</td>
<td>2 Week</td>
<td>6 Week</td>
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<tr>
<td>Inclusion/Exclusion Review</td>
<td>X</td>
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<tr>
<td>Informed Consent</td>
<td>X</td>
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<tr>
<td>Blood Sample</td>
<td>X X X X X</td>
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<tr>
<td>Ketorolac Intervention</td>
<td>X X X X X</td>
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<tr>
<td>MME</td>
<td>X X X X X</td>
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<tr>
<td>Pain Assessment</td>
<td>X X X X X</td>
<td>X X X X</td>
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Reliability

• Be a reliable person in the “multicenter study”
• Say “yes” to stuff that is clinically meaningful for you
• Complete the task in timely fashion
• Support other researchers around you
Reality

• Your abstracts will be rejected
• Your grants will be rejected
  • may not even be scored
• Your publications will be rejected
• You will not be 100% successful, but remember it is a process with a steep learning curve
Research Reputation

• If you build it they will come!!

• You will be successful

• You will be part of a reliable network of researchers
Do you *really* want to do this?

Big picture:
Will never make you rich but will make you happy

- Short term: Money loser

- Long term: Good chance – money loser
  - If you do it well – could be positive for you
  - Big winner → institution (med school)
Thanks!