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

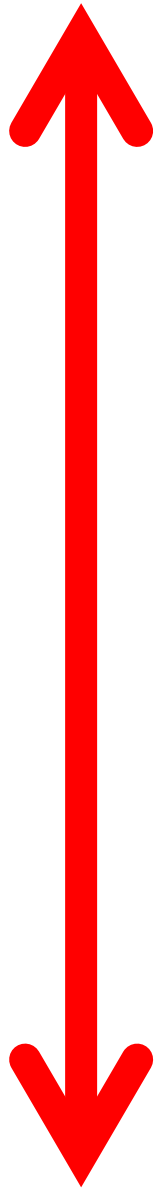
Publish in higher tier journal

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**

Number	PMID	Title	Authors	Year	Journal	Level of Evidence	Study Type	Country	Reviewer	Number of Patients (N)	Number of Tibiae (N)	Mean Age	Male (N)	Female (N)	Co-Morbidities, if listed 1 = Yes 0 = No
1	31801382	Three-Stage Masquelet Technique and One-	Q W		Foot and Ankle Int				BL						
2	31787329	A load-sharing nail - cage construct may improve outcome after induced	Gavaskar AS et al	2019	Injury	2	Prospective	India	BL	26	21	36	15	6	-
3	31771787	Risk factors associated with recurrence of extremity osteomyelitis	Wang X et al	2019	Injury	3	Retrospective	China	BL	424	259	37.9	351	73	
4	31579540	Induced-Membrane Technique in the Management of Posttraumatic Bone	Azi ML et al	2019	JBJS Essent Surg Tech		Surgical Technique		BL						
5	31451864	Masquelet technique for open tibia fractures in a military	Mathieu L	2019	Eur J Trauma Emerg Surg	4	Retrospective	France	BL	15	15	39	12	3	-
6	31403558	Intramedullary Nails Yield Superior Results Compared With Plate	Morwood MP et al	2019	JOT	3	Retrospective	US	BL						
7	31275548	The Masquelet induced-membrane technique: an option for a	Ley P et al	2019	J Surg Case Rep	4	Case Report	UK	BL	1	1	32	1	0	-
8	30905983	Role of Beta Tri-calcium Phosphate-based Composite Ceramic as Bone-	Gupta S	2019	Indian J Orthop	2	Prospective	India	BL	42	16	39.75	40	2	-
9	30639175	Very long-term results of post-traumatic bone defect reconstruction	Masquelet AC	2019	Orthop Traumatol Surg Res	4	Retrospective	France	BL	18	14	33	12	6	-
10	30562247	Results of the Induced Membrane Technique in the	Giotikas D	2019	JOT	4	Retrospective	France	BL	7	7				-
11	30526950	The Masquelet technique in the treatment of a non-infected open	Detitri S	2018	Injury	4	Case Report	Italy	BL	1	1	33	-	1	1
12	30280216	Induced membrane technique for the treatment of severe acute tibial bone	Ronga M	2019	Int Orthop	4	Case Series	Italy	BL	3	3	37	3	-	0
13	30214526	Masquelet induced membrane technique for treatment of rat chronic osteomyelitis	Cui T	2018	Exp Ther Med		Animal		BL						
14	29886150	Management of septic non-union of the tibia by the induced membrane	Siboni R	2018	Orthop Traumatol Surg Res	4	Retrospective	France	BL	19	19	53.9	14	4	1
15	29241817	Salvage of congenital pseudarthrosis of the tibia by the induced	Pollon T	2018	Orthop Traumatol Surg Res		Pseudoarthrosis		BL						
16	28839352	Reconstruction of traumatic bone loss using the induced membrane technique: preliminary results about	Kombate NK	2017	J Orthop	4	Case Series	Africa	BL	3	3	33.6	2	1	
17	28744608	Reconstruction of osseous defects using the Masquelet technique.	Saxer F	2017	Orthopade		Not in English	Switzerland	BL						
18	28639529	Circular external fixation and cemented PMMA spacers for the treatment of complex tibial fractures and defects: results with	Van Niekerk AH	2017	J Orthop Surg (Hong Kong)	3	Retrospective	Hong Kong	BL	24	24	35.1	16	8	
19	28634897	Influence of Surface Roughness and Spacer Texture on Bone Regeneration: A Canine Study	Luangphakdy V	2017	Clin Orthop Relat Res		Animal Study		BL						
20	28606128	Outcomes of cement beads and cement spacers in the treatment of bone defects associated with post-	Qui XS	2017	BMC Musculoskelt Disord	3	Retrospective	China	BL	40	33	37.75	33	7	
21	28536801	Induced membrane technique using beta-tricalcium phosphate for	Sasaki G	2018	Int Orthop	3	Retrospective	Japan	BL	5	5	39	5	0	

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

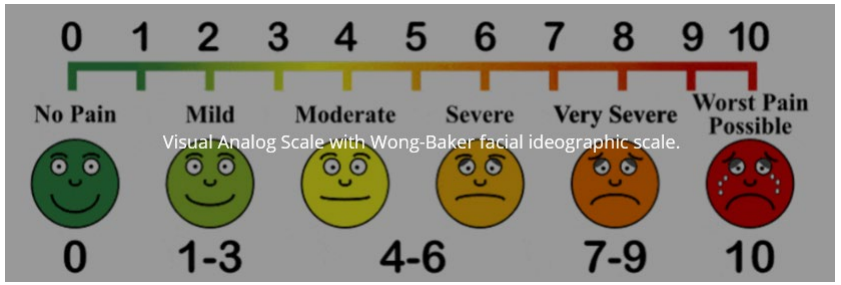
Determine your outcome of interest

- **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**

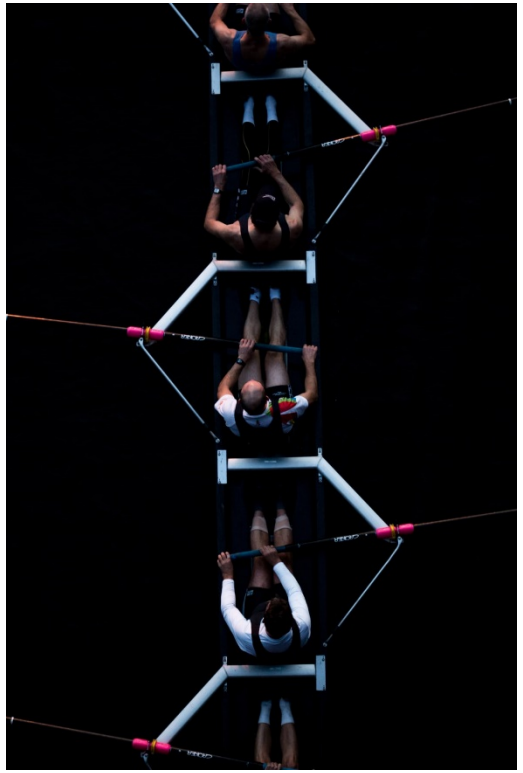


Visual Analog Scale with Wong-Baker facial ideographic scale.

- **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

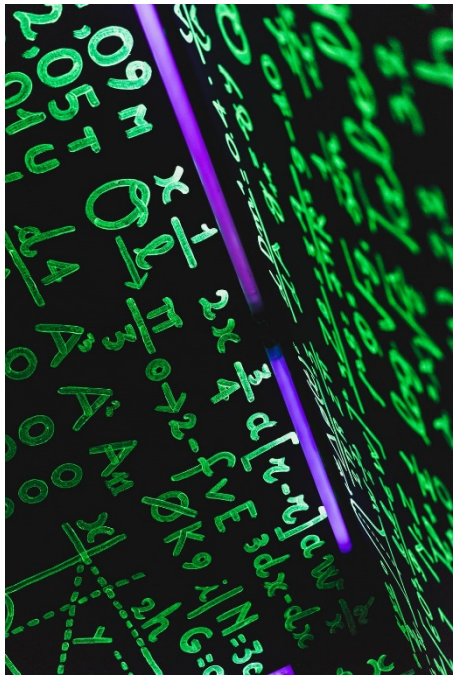
- **Bring in the help you realistically need to execute the research plan**
- **Balance of time, funding, expertise, and assigning credit**



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

	Type of Studies			
	Therapeutic	**Prognostic**	**Diagnostic**	**Economic and Decision Analyses**
Level I	• High-quality RCT with statistically significant difference or no statistically significant difference but narrow confidence intervals • Systematic review of level I RCT (and study results were homogenous)	• High-quality prospective study (all patients were enrolled at the same point in their disease with >80% follow-up of enrolled patients) • Systematic review of level I studies	• Testing of previously developed diagnostic criteria in a series of consecutive patients (with universally applied reference "gold" standard) • Systematic review of level I studies	• Sensible costs and alternatives, values obtained from many studies, multi-way sensitivity analyses • Systematic review of level I studies
Level II	• Lesser quality RCT (<80% follow-up, no blinding, or improper randomization) • Prospective comparative study • Systematic review of level II studies or level I studies with inconsistent results	• Retrospective study • Untreated controls from an RCT • Lesser quality prospective study (patients enrolled at different points in their disease or <80% follow-up) • Systematic review of level II studies	• Development of diagnostic criteria on the basis of consecutive patients (with universally applied reference gold standard) • Systematic review of level II studies	• Sensible costs and alternatives, values obtained from limited studies, multi-way sensitivity analyses • Systematic review of level II studies
Level III	• Case–control study • Retrospective comparative study • Systematic review of level III studies	• Case–control study	• Study of nonconsecutive patients (without consistently applied reference gold standard) • Systematic review of level III studies	• Analyses based on limited alternatives and costs, poor estimates • Systematic review of level III studies
Level IV	Case series	Case series	• Case–control study • Poor reference standard	• No sensitivity analyses
Level V	Expert opinion	Expert opinion	Expert opinion	Expert opinion

RCT, randomized control trial; systematic review, combination of results from 2 or more prior studies; prospective, study was started before the first patient enrolled; retrospective, study was started after the first patient enrolled; case–control study, patients identified for the study on the basis of their outcome (cases) and compared with those who did not have the outcome (controls); case series, patients treated one way with no comparison group of patients treated another way.

Adapted with permission from Introducing Levels of Evidence to the Journal *J Bone Joint Surg Am.* 2003;85:1–3.

Slobogean G, Bhandari M. Introducing levels of evidence to the Journal of Orthopaedic Trauma: implementation and future directions. J Orthop Trauma. 2012 Mar;26(3):127-8.

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 persue 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**

Busse JW, Bhandari M, Schemitsch EH. Randomized trails in surgery. Tech Orthop 2004; 19:77-82

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

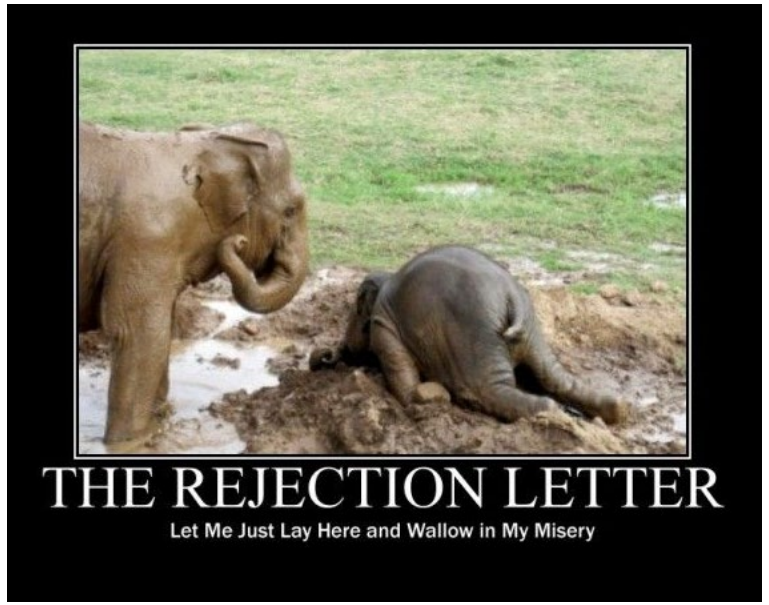
- **Prospective clinical trials should be registered at Clinicaltrials.gov**
  - **Most institutions have a liaison that can help with that process**
  - **Should be registered *before* you start data collection**

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

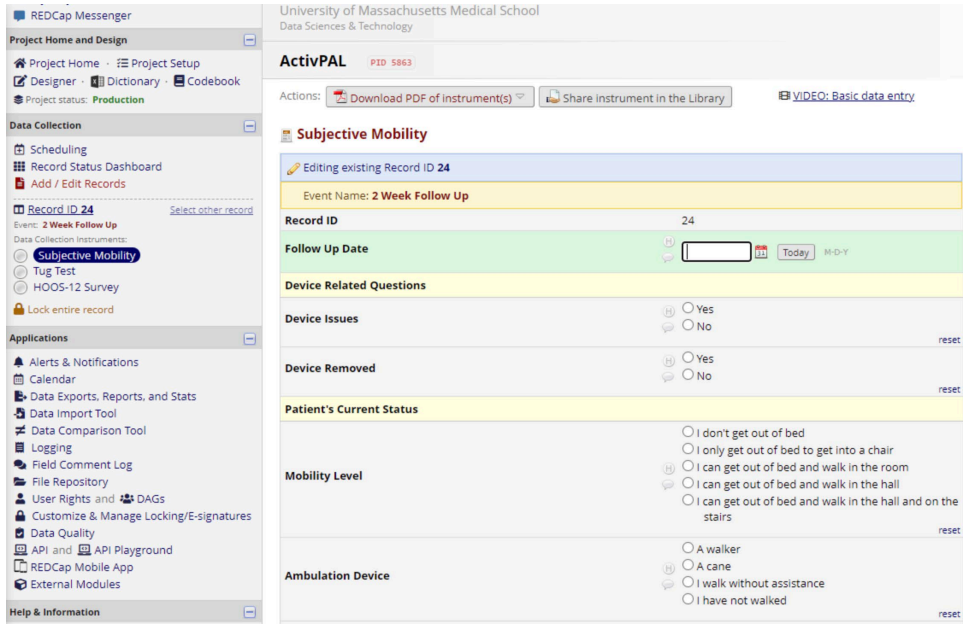
- Not just a chore
- Opportunity to write the Intro and Methods for manuscript
- Doing a good job now saves work in the long run
- Save templates for future studies
- Ask for help
- The IRBs are for you and your patient's protection – do not fight but cooperate with them

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)**

8. Blood glucose level

8.1 Blood glucose level monitored during surgery?	○ Yes - in mg/dL ○ Yes - in mmol/L ○ No
8.1.1 Maximum blood glucose level measured during surgery	_____ (mg/dL or mmol/L)
8.1.2 Frequency of measurement	○ Constantly ○ Every X minutes ○ X times
8.1.3 Please specify X	_____
8.2 Blood glucose level monitored postoperatively?	○ Yes - in mg/dL ○ Yes - in mmol/L ○ No
8.2.1 Maximum blood glucose level measured postoperatively	_____ (mg/dL or mmol/L)
8.2.2 Frequency of postoperative glucose monitoring	○ More than once a day ○ Once a day ○ Less frequently than once a day



Equipment/Infrastructure

- **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**

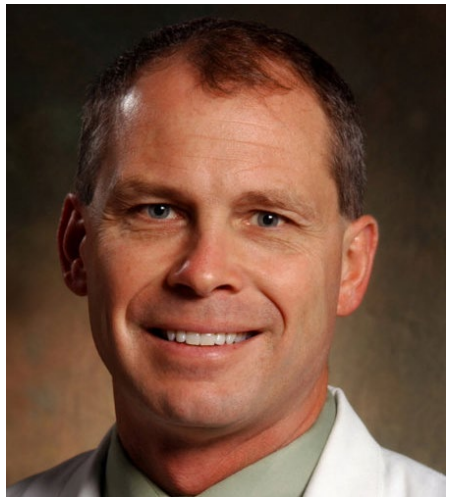
Best Way to Become a Better Researcher

- **Ask for Help**
- **Build relationship with mentors**
- **Seek out and collaborate with other good researchers**

Dr. Bhandari

Dr. Tornetta

Dr. Obremskey



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

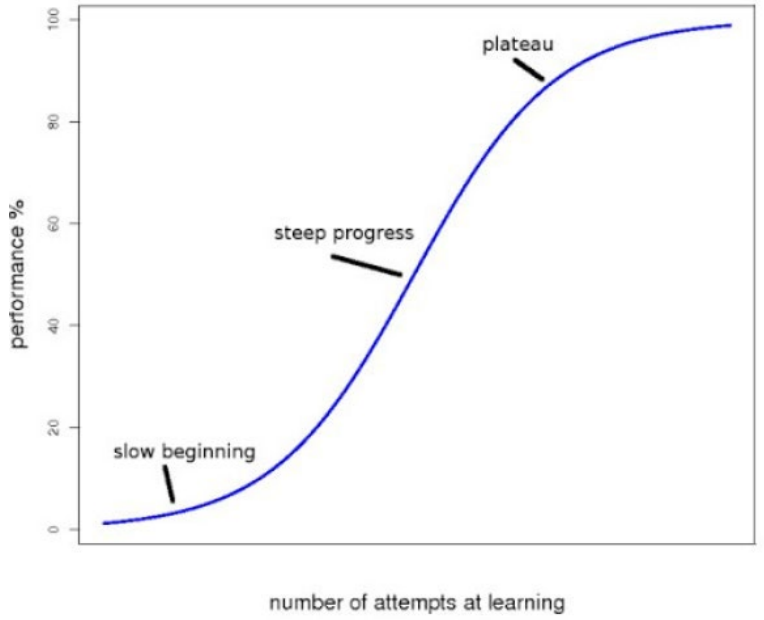
Table 3: Tentative time table of the proposed project												
	Inpatient							Outpatient				
Procedures	Daily Screen	Day 1	Day 2	Day 3	Day 4	Day 5	Discharge	2 Week	6 Week	3 Month	6 Month	12 Month
Inclusion/Exclusion Review	X											
Informed Consent	X											
Blood Sample		X	X	X	X	X						
Ketorolac Intervention		X	X	X	X	X						
MME		X	X	X	X	X	X					
Pain Assessment		X	X	X	X	X	X	X	X	X	X	X
SMFA						X			X	X	X	X
BPI							X					

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 remem 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!