Designing & publishing your research

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SIPRESS
"Daddy works in a magical, faraway land called Academia.
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COLLECTION

What makes a good research question?

- The question is clearly defined. (Not "What happens after X?" but "What is the frequency with which Y happens after X?)
- The animal model/patient population/disease process/independent and dependent variables/endpoints are clearly defined.
- The answer is not already known! You MUST review the literature.
- However, variations on a theme are acceptable if they progress the field. (large animal model vs. mice, diabetic vs. non-diabetic, male vs. female, rural populations)
- You can access enough animal, patient, or subject material to answer the question
  - Sample size calculations (calculators available online)
  - Easier to start: Look at similar sorts of published papers to see their "n"
- You care about finding the answer!

Designing the study: Animal models

- Your primary research question is often about HUMANS, unless you are a purely veterinary researcher. However, you may not be able to study humans!
- Choose a relevant & feasible animal model
- Does the animal model adequately model the disease or physiology you wish to study?
  - Review the literature
  - Consider validation against human benchmarks (e.g. relevance of wound healing studies of "diabetic" mice with serum glucose 400-500 mg/dl)
- Is the animal model practical for you (availability, cost, experience, etc.)?
- Can you measure what you want to measure in the model you've chosen?
- Now, reformulate your research question into a testable hypothesis about the animal model
- Do you have the right control(s)?
- Consider: species, strain, age, gender, health status of animals
- NIH now specifically requires that you analyze male and female separately
- Be sure you have defined your variables clearly

Designing the study: Human studies

- Define your hypothesis carefully and specifically
- Inclusion criteria assure your sample will test your hypothesis
- Exclusion criteria avoid weird stuff and are essential for safety for prospective trials, but
  - Decrease sample size
  - May restrict real world applicability
- What data will you collect? How will you handle missing data?
- How valid is your data source?
- Remember you need IRB approval

Designing the study: Sample size

- Sample size calculators are available on-line
- Multiple endpoints require different sample sizes, so think carefully about what's most important to you.
- Choose the LARGEST sample size of the calculations for your primary endpoint(s)
- Sample size calculation requires estimates of baseline, variation from baseline, standard deviation of the data, study power desired
- Because these are artificial, also look at previous similar studies' sample sizes
- Estimate complication/failure/mortality rates
- Will you include or exclude incomplete data?
- Are you going to have a male group and a female group? Other subgroups?
- Now revisit the sample size!

From your notebook…..

- A subgroup analysis of a recent large trial of a new antihypertensive drug suggests that long acting calcium channel blockers (vs. other antihypertensives) may reduce the risk of diabetic foot ulcer in diabetics with a high degree of variability of their blood pressure.
- A friend at the university has developed a new compound that seems to improve long tern neurological outcomes in mice after carotid occlusion. It has passed preliminary human safety trials and received approval by the FDA for testing in acute stroke patients.
- You wonder whether the use of medical marijuana will improve cancer patients' tolerance of chemotherapy.
- You recently did a colorectal anastomosis in a novel way because the stapler you usually use wasn't available. It worked really well, and you're wondering if it's superior to the standard technique.
- Design a study….

Designing the study: Resources

- If a procedure is required, can you do it? How long will it take?
- If an assay is required, who will do it and what will it cost?
- Do you need help, and can you get the help you need?
- Where will you find the patients?
- Will they consent? Will they drop out if it's prospective?
- How will you get the data?
- Where will you do the procedures?
- Is there adequate surgical space, clinic time, cage space, etc?
- Are all relevant protections in place for patients, animals, investigators?
- Do you have adequate equipment (ventilator, surgical instruments, microscope, catheters, sutures, etc.)?
- Do you have enough time, funding, data to achieve your sample size? Don't compromise!

Getting help

- Lots of people want to help you. They just don't know it yet!
- Premed students need research to enhance their applications
- Med students need to do research to enhance residency apps.
- (Students can be a lot of work to train but they are also fun!)
- Nurses going back to school for Masters/PhD need projects.
- Basic science labs need human-relevant data.
- Animal care facility veterinarians can advise on study design, housing issues, techniques. Talk with them BEFORE you start the study. They will appreciate it.
- Local physicians, surgeons, veterinarians, university faculty may welcome a chance to collaborate
- Other investigators can be valuable collaborators. Even if you haven't done what you want to do, someone else probably has and can help.

IACUC

- All animal projects require IACUC approval
- Use a previous application for a similarly structured study as a model
- Talk with the veterinarian before you submit
- Allow enough time for review and necessary changes
- A sense of humor is an asset in dealing with any bureaucracy!

IRB

- Human studies require IRB approval
- This includes retrospective chart reviews!
- Use a previous application for a similarly structured study as a model
- Talk with an experienced investigator or the IRB coordinator before you submit
- If you will work in multiple institutions or have a university faculty appointment, you must request multiple IRB approvals.
- Allow time for review and necessary changes
- Remember that they are here to safeguard patients, not impede your work!

Common IRB issues

- Patient privacy is important even in chart reviews
- All studies require patient consent or the IRB (not you) to decide that consent can be waived.
- Vulnerable populations require special attention
- Your patients are a potentially vulnerable population if you get the consent
- Patient risks include deviation from standard of care
- Who will pay for experimental treatment/tests?
- How will you deal with potentially clinically relevant findings that are discovered during the research?
- Data management and security
- If the study is not scientifically valid, no risk is justified

Troubleshooting

- Do one or two procedures or chart reviews or mock enrollments and carry the analysis all the way through before you embark on a 200 patient study!
- Develop a data dictionary for human study variables.
- Complex procedures can have a steep learning curve. Allow for this in your IACUC or IRB application and your attitude!
- Make sure your reagents and assays actually work with your samples! Make sure that if you will store patient samples for subsequent assay, the samples will be stable and assays still be valid thereafter. Try this FIRST!
- Successful procedures with poor sample collection, handling, or storage yield poor results!
- Poorly defined inclusion/exclusion criteria will doom a study, as will poorly trained data abstractors.
- When things go wrong, seek help!

Analyzing your results

- Get help from a colleague with a stats background. For human studies in particular, it is a good idea to consult a statistician BEFORE you start the study. Discuss study design, endpoints, sample size, power.
- There are lots of fancy stats packages, but Excel may have what you need and is much easier. If you use Excel, set up a mock data set and try the stats functions before entering real data, because some stats functions only work if the data is organized in a certain way.
- If the study "fails", it may still be publishable! That your hypothesis was wrong may still be new knowledge.
- If the study "succeeds" but $p > 0.05$, redo the sample size calculation with your new information. Is it realistic to keep going and enter more data? (Get help to do this prn)
- Sample size (re)calculation for dummies: Just recopy a fraction of your data, add it back to the original data set, and redo the stats to see if $p<0.05$.

Abstracts

- Relatively easy and fun to write. Students like meetings because they are mini-vacations with free food.
- Pick the meeting based on what is usually accepted there.
- Some smaller meetings have mandatory manuscript submission requirements. Check and decide.
- Presenting without publishing has less impact both on your CV and on the world at large (which is presumably why you started this in the first place).

Writing the abstract: Part One

- Read the instructions!
  - Structured vs. non-structured
  - Word limit vs. character limit (+/- spaces)
  - Do title and authors count in the limit?
- Write what you need to. Cut to size. Don't write to size
- Introduction
  - 1-3 sentences
  - Set the stage: What is the overall question and why is it important?
  - Consider your audience for context)
  - State the hypothesis
- Model/methods statement: How did you test the hypothesis

Writing the abstract: Part Two

- Results
  - Level of detail balances amount of data vs. space limitations
  - Do NOT say "results will be presented"!
  - Try to offer n's and p values for credibility if space permits
- Conclusion
  - 1-2 sentences
  - What is your key take home message (derived from but not your result)?
  - How does this relate back to your hypothesis and then back to your overall research question
  - Why do we care?

From your notebook…..

- 400 patients with colon and pancreatic cancer were randomized to receive either medical marijuana or a placebo BID.
- The groups were similar in age, sex, and pre-chemo performance status, but the control group had 180 colon CA patients and 20 pancreatic CA patients while the experimental group had 190 colon CA and 10 pancreatic CA patients.
- 75% of control colon patients completed chemo. 80% of experimental colon patients completed chemo. 12/20 control pancreatic patients completed chemo while 5 of the experimental pancreatic patients completed chemo. Overall completion was statistically improved in all patients receiving medical marijuana and in the colon patients, while the reduction in pancreatic cancer patient completion did not achieve statistical significance because of low numbers.
- Ratings of well being on a validated survey were higher in all groups than in historical controls, but there was additionally a higher rating in the experimental group taken all together both at the midpoint of the chemo and at the end of the chemo. No difference was found one month later.
- Two patients in the medical marijuana group tested positive for marijuana in a random drug test by his employer and lost his job. Interestingly, one patient in the control group also tested positive for marijuana and lost his job, and he told you later that he figured he was on it anyway so he might as well smoke it also.
- For those patients who went on to surgery, there was no difference in OR time, blood loss, or complication rates. No survival data is available because follow up is too short.
- WRITE A 200 word abstract

DRAFT ABSTRACT

Background: Medical marijuana has been reported to allay nausea and reduce pain in cancer and other patients and is now legal in North Dakota.

Methods: We randomly allocated 400 colon and pancreatic cancer patients to receive medical marijuana or a placebo twice daily, and assessed rates of completion of chemotherapy and patient-reported well being during treatment.

Results: Patients receiving marijuana were more likely to complete chemotherapy overall (78% vs. 73%, $p<0.05$) and in the colon cancer group (80% vs. 75%, $p<0.05$) while pancreatic cancer patients were less likely (50% vs. 60%, n.s.) Furthermore, cancer patients receiving marijuana reported statistically higher well-being scores midway through and at the completion of chemotherapy regardless of the type of cancer.

Conclusions: Medical marijuana may improve the subjective well-being of cancer chemotherapy patients and may improve chemotherapy completion rates. However, the apparent trend toward worsening of completion of chemotherapy for pancreatic cancer patients requires further investigation.

Writing the paper…..

Manuscript writing step by step

- Abstract = meeting abstract or adaptation thereof
- Introduction: 3 paragraphs. First sets up the overall problem or question. Second elaborates your hypothesis. Third explains how you tested it.
- Methods:
- Results.
- Discussion:

DRAFT INTRODUCTION -- FOR COMMENTS?

Medical marijuana is increasingly accepted in the US. It has recently been legalized in several states including North Dakota, Colorado, XX, and XX. There are even states in which recreational use is legal. Recent information suggests that marijuana can be used to control seizures, and it may help with nausea and appetite.

Cancer patients often don't complete their chemotherapy for a variety of reasons. While some non-completion reflects disease progression or ethical discussions, other non-completion reflects inability to tolerate the side effects of chemotherapy. Chemotherapy for pancreatic cancer is often worse than chemotherapy for colon cancer, but both are necessary for patients to tolerate.

We compared 200 patients with colon or pancreatic cancer who received medical marijuana to 200 patients who did not. We studied their rates of completing their chemotherapy and asked them to rate their well-being using a previously validated psychological survey developed at the University of Delaware in 1997 and applied previously to both cancer patients and those undergoing kidney transplants. We also assessed how many went on to surgery after chemotherapy and what happened to them. Finally, we unexpectedly learned that two patients who received medical marijuana lost their jobs because of random drug testing, which requires legal and ethical discussion. This is the first randomized study of marijuana in adjuvant colon cancer chemotherapy.

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Para 1 unfocused. Too much info. What is the question being studied?

Colloq. style. Still giving background. What's the research about? Why discuss panc vs colon chemo?

Still no hypothesis
Why do we care about U Delaware 1997? Too much info.
2 pts lost their jobs is interesting but why here?
Avoid priority claims ("first study")

REDRAFTED INTRODUCTION

Medical marijuana is increasingly accepted in the US. Marijuana has been suggested to have analgesic and anti-emetic properties and to stimulate appetite. Cancer patients undergoing neoadjuvant chemotherapy often suffer from pain, nausea, and anorexia, as well as mood disturbances. Failure to complete chemotherapy for these reasons can substantially impair long term survival.

Although marijuana use has been reported to improve cancer patient well-being, it is difficult to distinguish effects of the marijuana itself from placebo effects. In addition, illegally obtained marijuana may be contaminated by other substances that could have different effects. We hypothesized that prescription-grade medicall marijuana would promote patient well-being and facilitate completion of chemotherapy.

We randomized 400 patients receiving adjuvant chemotherapy for colon or pancreatic cancer to receive either medical marijuana or a placebo. Both patients and care-givers were blinded to patient allocation. We studied their rates of completing chemotherapy and asked them to rate their well-being using a psychological survey previously validated for cancer patients. Although there was a tendency for pancreatic cancer patients to be less likely to complete their chemotherapy after medical marijuana, numbers were unexpectedly small and not well allocated between the two groups in this regard. However, overall, completion rates were higher and self-reported well-being was higher in the medical marijuana group.

Manuscript writing step by step

- Abstract = meeting abstract or adaptation thereof
- Introduction: 3 paragraphs. First sets up the overall problem or question. Second elaborates your hypothesis. Third explains how you tested it.
- Methods: IACUC or IRB approval. Study design. Animals and model description, or Patients (inclusion/exclusion), or Database description. How did you measure/define endpoints? (Assays or measurements) Stats paragraph.
- Results. Narrate the figures.
- Discussion: 5-6 paragraphs
  - 1. Two sentence background. Then: This study shows A, B, and C.
  - 2. A is your topic sentence. How is this credible/not credible/different from the literature/novel/important/problematic? Limitations of this conclusion?
  - 3,4. Same for B and C.
  - 5. 1-2 sentences summarize your conclusions and validate/invalidate the hypothesis. 1-2 sentences describe larger implications for your overall research question.

DISCUSSION PARAGRAPH ONE DRAFT

Many states such as XX, YY, and ZZ have legalized medical or recreational marijuana. It is legal in other countries. The ethical debate about this continues but as physicians we must use whatever tools we have for our patients. Medical marijuana is becoming increasingly acceptable in our society but its utility in cancer chemotherapy patients is still not well understood. We found that patients receiving marijuana were more likely to complete chemotherapy although pancreatic cancer patients exhibited a different trend in subgroup analysis. Patient reported well-being was also improved. We found no difference in the outcomes of surgical procedures in those patients who subsequently went on to surgery. illegal marijuana. This will be important information for physicians considering whether to use marijuana in their cancer patients and for legislators considering whether to support medical marijuana legalization.

CAN YOU HELP REDRAFT THIS?

DISCUSSION PARAGRAPH ONE REDRAFT

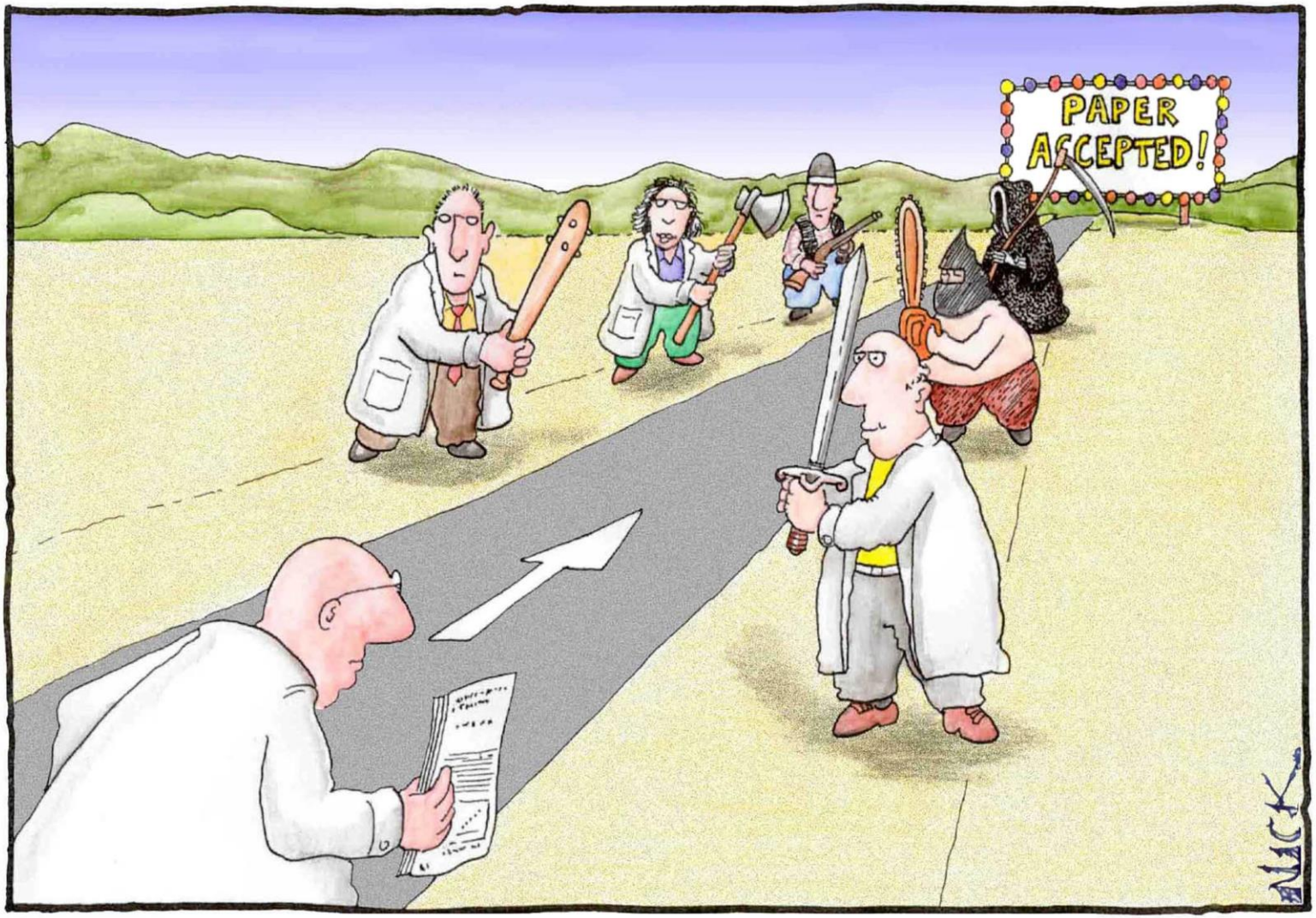
Medical marijuana is becoming increasingly acceptable but its utility in cancer chemotherapy patients is still not well understood. This double blind randomized trial demonstrated that medical marijuana increased chemotherapy completion rates and patient self-reports of well-being in patients receiving neoadjuvant therapy for colon cancer. Well-being was also improved in pancreatic cancer patients, but completion rates tended to decrease. An unexpected adverse event in this trial was the loss of three jobs to random drug testing for marijuana, two in the medical marijuana group and one in a control patient who used illegal marijuana while on protocol.

Journals

- Pick a journal that has published similar stuff.
- Be realistic.
- PubMed listing is important.
- Print vs. on-line, depending on your institution.
- Format to journal style. Consider EndNote or other bibliography manager.
- Number pages
- Follow all formatting and submission instructions
- (Remember Journal of Investigative Surgery!)

Cover letters

- Write a cover letter!
- The editor will not read the paper before sending it for review. Summarize the study in 2-3 sentences.
- Include any required verbiage from instructions for authors.
- Always suggest reviewers in your cover letter. Include contact information. Explain why each reviewer is appropriate. The editor is not obligated to use your reviewers, but might.
- Don't suggest reviewers with obvious conflicts of interest. This will enrage the Editor.
- Don't contact suggested reviewers outside of the process.
- Do consider referencing relevant work by suggested reviewers.
  - Make the editor happy because this may enhance perceived reviewer relevance.
  - Make the reviewer happy because we all like to see ourselves referenced.
- You can also suggest individuals who should NOT review



Most scientists regarded the new streamlined peer-review process as "quite an improvement."

The decision

- Accept, Accept with modification, Revise and Resubmit, Reject
- Few manuscripts are accepted on initial submission.
- If it is accepted, you may have shot too low! Would you really want to publish in a journal that would accept your work?
- Read carefully: Is it really a rejection or an opportunity for resubmission?
- Revise and resubmit without guarantee of acceptance is the most common

Revise and resubmit

- Read the reviews carefully, get angry if you want, then put them aside and come back 24-48 hours later.
- If the "typical blot" doesn't match the graph or figures are poor quality, it's your fault.
- If something wasn't clear, it's your fault.
- If the reviewer didn't understand, it's your fault.
- If the reviewer is just wrong, it's still probably your fault for not laying the right groundwork.
- Avoid arguing with reviewers. You will almost always lose.
- If the reviewer misunderstood, clarify anyway & say you have done so.
- (Avoid the temptation to point out that the reviewer was wrong and you were right!)
- If the reviewer is truly irretrievably wrong, indicate that this is controversial and bolster your argument with references.
- In general, do what they ask you to do.
- It's almost always better to revise and resubmit if possible than to start over with another journal that may ask for the same things or even harder revisions.

Cover letters for resubmissions

- Introduce the mss by explaining that it is a resubmission and indicating in general what you have done to revise. (Shortened and edited for clarity? Expanded the discussion to address reviewers' concerns? Increased the n? Added new experimental data?)
- Write a detailed point by point cover letter, indicating how you have responded to each concern and quoting the relevant change in the manuscript. Cite page and line #'s. Cut and paste the new figures into the cover letter as well if the online submission process allows.
- Make it easy for reviewers to see that you have adequately responded to their concerns.
- The reviewer should ideally not have to look back at the manuscript to judge your revisions. (If they do, they may find something else wrong!)
- Respond to reviewers in the manuscript, not just in your cover letter!
- If something is truly impossible, you can try to respond in the cover letter by showing why it's not possible and acknowledging the reviewer's concern in the discussion somehow.
- End by thanking the reviewers for their careful reading and the editor for allowing resubmission (even if you don't mean it!).

Rejection

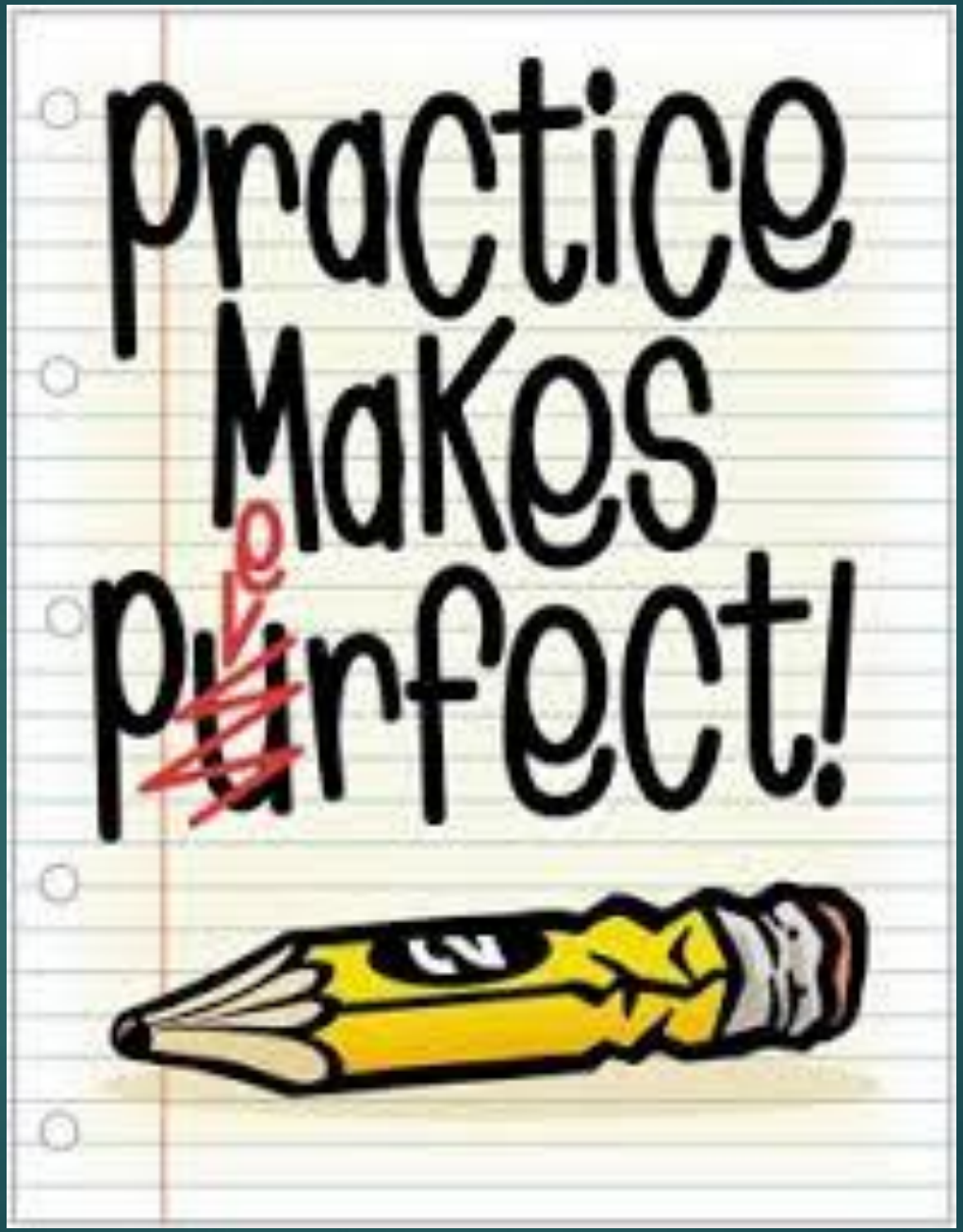
- If true rejection, consider the reviews to see if there are things that can be corrected or criticisms that you can immunize yourself against by adding new data or discussion, refining your hypothesis or conclusions, or even raising the criticism yourself in the discussion and explaining why it doesn't invalidate the work.
- Then submit somewhere else. Do so rapidly. Do not let papers sit or you will lose momentum.
- (Almost) anything can be published somewhere!
- However, if critical flaws in experimental design have been described, it may be better to think about doing new experiments first.

Common reasons for rejection

- Too preliminary. Not enough data. (Look at the journal to understand the amount of data in a typical manuscript.)
- Not sufficiently novel. Doesn't advance the field. Sometimes true. Sometimes represents authors' failure to adequately discuss the literature and demonstrate novelty and importance.
- Study design critically flawed. Lacks appropriate controls. Model inappropriate.
- Data doesn't support interpretation/conclusions
- Data is of unacceptably poor quality (bad blots, stains, etc.)
- Outside the scope of the journal
- Poor organization and writing makes the manuscript unreadable
- Inadequate/inappropriate response to reviewers after revise and resubmit

DaCCoTA
DAKOTA CANCER COLLABORATIVE ON TRANSLATIONAL ACTIVITY

Key Components & Goals


Practice
Makes
Perfect!