Duane's Little Handbook of Advice for Young Biostatisticians on How to Work with Investigators

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FORWARD

Anyone reading this handbook should know that almost none of the ideas presented in it are my original ideas. I learned everything in this handbook from working with other people. During my career I had the good fortune of working with scores of talented statisticians and epidemiologists, and literally with thousands of physicians and scientists. I have tried to learn something from each of them.

To try to individually name all of the people who have helped me in my career is impossible in a *little* handbook. Instead, I would like to emphasize that the Department of Health Sciences Research at the Mayo Clinic was a wonderful place to be a statistician. My colleagues were willing to and liked to help one another. When I had a statistical question, which was often, I knew that, if I tried, I could find a statistical colleague who either knew the answer or who knew how to find it. I was also fortunate to work with many talented epidemiologists who taught me how to approach clinical problems from a perspective that you will not find in most statistics textbooks. The vast majority of the advice that I present in this handbook has been taken from these colleagues.

Finally, I need to thank the physicians that I was privileged to work with at Mayo. Everyday I looked forward to learning something new from one or more of these dedicated physicians. Most of them were a pleasure to work with. *Some* of them were more difficult to deal with. I hope that the lessons that I learned working with these physicians will be helpful to the biostatisticians who read this handbook.

INTRODUCTION

This handbook is intended to provide young biostatisticians with a set of guidelines about how to effectively work with investigators. Not all of these guidelines will work well in every consulting situation. You may find that you may develop better ways for you to deal with some situations than those which are given here. The advice given here should, however, help you to at least formulate for yourself how you should conduct your own consultations.

CHAPTER 1: An Introduction to Ethics

Who do you work for?: Ultimately, you work for the patients whose diagnosis and treatment will be influenced by the results of the studies which you conducted with medical investigators. It is highly likely that at some point you will be pressured by an investigator to produce a specific result. In other situations you may be pressured to present an analysis prematurely in order to meet an artificial deadline like an abstract or meeting deadline. How you deal with these and other situations may directly affect the welfare of future patients. These issues will be covered in more detail in Chapter 4.

Authorship?: Do not accept authorship if you really did not substantially contribute to a paper. If you feel that you did substantially contribute to a paper and you have not been offered authorship, ask for it. They can only say no. Never accept acknowledgements. "Getting an acknowledgment is like kissing your sibling. It isn't much fun and you can only get in trouble!", Lloyd Fisher, Ph.D.

CHAPTER 2: Teamwork

Rewards: Working with a team should be one of the more rewarding aspects of your career. You, however, have to make an effort for it to be rewarding. The relationship that you build with your team will directly affect your ability to be a good statistician.

Working with your team: Share responsibility and recognition with your team.

1. Include team members in all meetings with investigators and you. Your team will understand the problem and the questions, and they will be much more motivated than if they are just told what to do by you alone. You should have your team members take detailed notes of the meeting, while you concentrate on the big picture. It may cost the investigator more initially to have the team members in the meeting, but they are much less likely to do the wrong thing, and in the long run the study will be more efficient.

2. Make your team members stretch by giving them responsibility. The primary reason for this is that you cannot, and should not attempt to, do everything yourself. In addition the team members will become a better asset to both you and to the investigators. Will Rogers was right when he said: "Even if you are on the right track, you will get run over if you just sit there." Your team members will grow in ability and in confidence if you let them. When a team member has done a good job, let them know. If an investigator appreciates their work, ask the investigator to send them a note about it with a copy to you. If a team member has made an error, or has not lived-up to your expectations, talk to them about it. You should do this in as positive a way as possible. You may find that some of your team members are much harder on themselves than they should be when there has been a problem. Tell them that a particle physicist, Frank Wilczek, once said, "If you don't make mistakes, you're not working hard enough problems, and that's a big mistake." They should learn from their errors, but they should not get hung-up about them. When team members are ready, allow them to meet alone with the investigators.

3. Ask your team members to prepare written documentation about what they have done, and about the results of their analyses. This documentation provides feedback to you and to them, and it provides a record of the team's efforts to the investigator. Ask for periodic updates on all of the team member's projects. It is the only fair way for you to determine which projects should receive higher priority.

4. When possible, see to it that your team members attend the local presentations of the results of the projects that they worked on. They will often be recognized by the investigators, and they will have a better idea about how their work can directly affect patient care. This also emphasizes to the investigator that we have an interest in their research.

5. If you sit on a local specialty research committee, ask a qualified and experienced team member to also attend the meetings. They will gain more appreciation for the clinical specialty, and they may attend the meeting when you cannot.

CHAPTER 3: Consulting with Investigators

Friend or Foe: Why do investigators come to a statistician? Many investigators really do not want to see you. They may be there only because their advisor told them to. They may be there because their abstract or paper was rejected and they want you to perform a resurrection. They may be there because they have planned their study without your help, they have conducted the experiment and collected the data, and now they have no idea what to do with it. In an ideal situation, they are there because they really want your advice before they start their study.

The Fear factor: Fear of consulting with a statistician is common among first time investigators. It is part of your job to alleviate that fear. Why are investigators afraid of working with a statistician? They may relate that they had a "bad experience" in a college statistics course. Many college statistics courses for non-statistics majors are remarkably bad. They may tell you that they previously had a bad experience with a statistician. Some statisticians are good mathematicians, but they communicate poorly, or they may have a personality disorder. To be an effective statistician, you must work on your communication skills! Some investigators do not want to consult with a statistician because they do not want to be told that they are wrong. They may not want to take advice from someone who is not in their profession. They may feel that their training qualifies them to analyze their own data. Finally, some investigators fear that the statistician may in someway prevent them from publishing their study. This is particularly true for fellows who are here for only a short time. Their future careers may depend on their ability to get an article published in an American journal. You must be very vigilant with these individuals. You must be sure that they understand what you ask of them, and you have to keep their advisor up to date on the progress of their study.

Establish a Positive Relationship: Make it clear that you are not a foe. You may not have to be their friend, but you need to emphasize that you and your team are there to help them. Some of the best advice that you may ever give is to tell them that they should not do their study. Their study may not be designed to answer the question that they are posing, or given the available timeframe or number of patients they may not be able to complete their study. In my career, the most prevalent reason for study failure was that the investigator tried to do too much in too little time. You should urge them to move on to another project that has a better chance of success. If their study is feasible, you should emphasize that your statistical advice should help them to conduct a more efficient and focused study. Tell them that your analysis of their data should allow them to arrive at the correct conclusions, and that their chance of publication should be greatly enhanced.

The Initial Consultation: Prior to meeting, ask the investigators to e-mail a draft of their protocol. It should include how novel their idea is, how it will impact their field, and what the literature says about it. When you first meet, ask the investigators to describe in detail the medical condition that they are studying and what they want to accomplish. Most investigators love to talk about their field of interest, and when doing so it puts them at ease. If you do not understand something, ask the investigators to stop and explain it. You cannot efficiently design or analyze a study if you do not understand the clinical condition and the clinical questions. You and your team will waste less time and you will avoid many errors if you understand the clinical nature of the study. A spin-off benefit is that understanding the subject makes your job and your team's job much more interesting and rewarding. You may find that many times the subject is as interesting and challenging as the statistics. Finally, understanding the specialty area will make you a more valuable asset to the physicians and scientists who work with you in the future.

Make sure that you understand how the patients actually got into the study. How were they selected, and what criteria were used in the selection. Often you will find that the study group was highly selected, and inferences from the study may not be applicable to the intended patient population. The selection process may introduce biases that cannot be eliminated by any statistical analysis. With your best efforts you may just more precisely get the wrong answer!

Data and Data Quality: "Garbage in-garbage out" may mean that future patients will receive suboptimal care! Always ask the investigators to go over every variable that they intend to collect. What investigators want to collect and what they should collect often are not the same. You will never know this unless you query the investigators in detail. Examples of the questions that you should ask are:

1. Is the value of the variable collected only once per patient or at multiple points in time?
2. Is the value of the variable a function of time from some starting point like diagnosis or surgery?

If the answer is yes to either of these questions, you should collect dates and you may have to use methods that take time into account like survival methods, the extended Cox model, or other GEE methods.

3. If the variable is categorical, does it take on a single value like status: alive versus dead, or eye color: blue eyes versus brown eyes versus green eyes, or does it have multiple components like symptoms with pain: no versus yes, swelling: no versus yes, and redness: no versus yes?
4. If the variable is continuous or ordinal, what does the distribution look like? Always try to get the investigators to give you some sample data, which you should plot.

You should always design a data form which defines all of the variables that the investigators collect. You should do this even if the investigators have already supplied a

computer file of the data. Many old computer data files are unusable because someone did not document the definitions of the variables.

Finally, you should always ask at least two of the investigators to independently abstract 5 or 10 of the same patient histories. Have them compare their results, and reach a consensus about any disagreement. This is particularly important for a resident or fellow. Their advisor should participate and make sure that the resident or fellow correctly abstracts the data.

Design of Analysis and Analysis: The following suggestion from L. Joseph Melton, III MD is the single best piece of consulting advice that I was given in my entire career. Always ask the investigators to write a draft of both the abstract and of the results section of their paper **before** analyzing the data, and preferably **before** collecting the data. Ask them to write it concisely enough that other physicians (in their right mind) would want to read it. These drafts will focus the investigators on what really should be in the paper. These drafts will also provide you and your team with a starting game plan for the analysis. If the primary investigators are residents or fellows, require that their advisor approves the drafts before you begin the analysis. Residents and fellows are often mistaken about what their advisor really wants them to accomplish, and you will save a lot of unnecessary work by getting them all on the same page before you begin the analysis. Finally, with a resident or fellow, meet periodically with the advisor to insure that the analysis stays on track.

Honesty, Forthrightness, and Errors: Always be honest and forthright with investigators and with your team. If you do not know the answer to a question or you are unsure of the proper analysis, **do not fake it**! If you try to fake it, the investigators and your team will see right through you, and you will lose their respect. Tell them that you are unsure of the proper analysis, but that you will try to find the needed answer, and that you will get back to them. Investigators will appreciate your honesty. However, if you promise to get back to them, do it in a timely manner. Do not let it sit on your desk; your desk doesn't solve problems. Ask your team members or another colleague to help. This is one of the reasons why we have teams.

If you have made an error, tell the investigators about it right away. Just tell them how it happened, but avoid giving an excuse, even if you think that you have a good one. You and your team members should learn from the errors that you make. Do not dwell on the errors that you have caught. You should worry more about those errors that you do not catch! You should periodically step back from the details of the data and the data analysis, and look critically at the results and the conclusions that you have made from the analysis. Ask yourself if they make sense. Most errors are obvious. Sometimes, however, you may catch an error because something just doesn't feel right. You should follow-up on those feelings. It is surprising how often those feelings are correct.

CHAPTER 4: Dealing with Difficulty

Belligerent or Rude Investigators: Always protect your team members. Investigators may be polite to you, but they may be rude or excessively demanding to a team member. Tell such investigators in no uncertain terms that their behavior is unacceptable, and that any issues that they have should be brought to you, not to the team member. If the investigator is a resident or fellow, always notify their advisor in writing. If the problem continues, talk to the Division Chairperson. Try to work out a compromise arrangement. If that is not possible, you may have to tell them that your services are no longer available. Put everything in writing. Give copies to the Division Chairperson, to the investigator, and to the advisor if there is one.

Integrity: Your single most important asset is your integrity. Remember that your decisions do not only affect the production of a medical paper, but they directly affect the quality of life or even the length of the remaining lifetime of our patients. If you sacrifice your integrity to just satisfy an investigator, or to get a paper published, you have let down our patients, our institution, the investigator, and yourself.

Cheating or Cooking the Numbers: It is very hard to detect outright cheating, and it is even harder to prove it. You have to be absolutely sure about it before you confront anyone. Before you confront anyone, ask the investigator to provide copies of the original data. For a history study, get an independent person to review the suspect histories. Perhaps such a procedure should be included in our usual practice. If you are not absolutely sure that you can prove that cheating occurred, do not make a formal accusation. In such instances, make sure that you and your team members are not authors, and that you are not acknowledged in the paper.

Sloppy Data Collection or Study Conduct: Outright cheating is thankfully rare. Sloppy data collection, or study conduct, is, unfortunately, too prevalent. Bad study conduct, therefore, leads to poor patient care much more frequently than does outright cheating. Statisticians need to be vigilant in the design, conduct, and monitoring of clinical studies.

Dropping "Outliers": Investigators may request that you drop a data point because it doesn't fit into the pattern of the other data. This may often occur when the hypothesis test is significant only without the data point. Never drop a data point unless you have reviewed the same variable in all of the patients, and unless you can demonstrate that there was an obvious clerical error, or that some extraneous factor caused that patient's value to be incorrect, while not affecting the other patient values. A good compromise is to present the analysis both with and without the outlier. Let the readers decide which analysis they want to believe. You may call this the "intent-to keep analysis" versus the "per-preconceived notion" analysis.

Searching for Significance: Some investigators may pressure you to try other significance tests to help them achieve significance. Alternatively, they may wish to quote only one of a set of multivariable models. That may be the model in which their main hypothesis achieved statistical significance. You must insist on using the significance test or the model which best fits the data and which satisfies the assumptions of the test or the model. If the significance of a factor is labile, either bootstrap the model, or point out in the paper that the significance is borderline and that the results should be confirmed by further study. For any multivariable analysis don't just believe the model without breaking down the actual data by the factors in the final model. You should graph the results by the combinations of the factors. If you do not see the correct pattern, your model may be wrong.

"*Norman is in Ireland":* For many years the medieval bard duo of "Puke and Snot" performed at the Renaissance Festival outside of the Twin Cities. A favorite sketch of theirs was one where one of them with a sweeping hand gesture to the audience said: "Norman is in Ireland!" The other with ridicule then said: "No, no, it is 'No Man is an Island.'" The moral of this exchange for statisticians is not only to be sure of your quotes, but primarily it is that you should consult with your Division Chairperson and the rest of your colleagues about problems that you are having with investigators in your consulting practice. There is a remote possibility that it is you who is wrong. It is better to find that out from your colleagues before you go toe to toe with an investigator. Your colleagues can be a great resource of experience and wisdom. If the investigator is wrong, as mentioned before, put everything in writing and present it to the investigator. Once again, if the problem cannot be resolved in that manner, in conjunction with the Division Chairperson proceed to negotiate with the investigator's superiors.