

Managing clinical trial data-sharing databases: interview with Professor Daniel J. Sargent

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Professor, Daniel J. Sargent

Daniel J. Sargent, Ph.D., is Professor of Oncology, Professor of Biostatistics and Director of Cancer Center Statistics of Mayo Clinic Cancer Center, Rochester, MN, USA. This interview with him was conducted on the 2013 Annual Meeting of American Society of Clinical Oncology on June 3. In this interview, Dr Sargent shared how his team supports clinical trials all over the world, stories on how he started large clinical trial collaborating databases like ACCENT, and what he plans to do in the new column on clinical trial design that he together with Prof. Qian Shi from Mayo Clinic are in the process of establishing in our journal *Chinese Clinical Oncology*.

Dear Prof. Sargent, could you introduce about how does your department, Mayo Clinic Cancer Center Statistics provide support for oncologists and physicians? How do physicians, your statistical team and industry work together?

Prof. Sargent: We have a large team of statisticians at Mayo Clinic, with PhD statisticians, master-level statisticians and bachelor-level statisticians. We work on trials all the way from early phase I to the very large, several thousand patient phase III trials. We get involved very early in trial development, when an investigator who maybe a medical oncologist, radiation oncologist, surgeon or other investigator, is interested in answering a question. They consult with our group very early, and we help advise on the design the trial, for example whether it should be a randomized trial or not, what sample size is required or what end-points would be appropriate for that trial. This is an interactive process, because trials now have many investigators, and we generally need to secure cooperation with the pharmaceutical partner, with regulatory agencies, and with other interested parties. This process can take some time and it generally requires several interactions. Once we agree on the design, we partner with the investigator to write the formal protocol. When the protocol is ongoing, we have responsibility to monitor the data for the safety of the patients, to look for early signals of efficacy, or for lack of activity. Some trials enroll very quickly, while some trials take a long time. Once a trial is enrolled, we have to wait for end-points. We work very hard at data quality, making sure the data is clean and accurate. When it comes to the time of final analysis, that's when the statisticians analyze the data. For statisticians, that's the fun part.

But I often say, if the trial is designed-well, the analyses should also be straightforward. When it is clear in the protocol what the primary hypothesis is, and you have simple randomization, for example, the analyses can be very straightforward. In reality though

almost all trials have complexities. Protocols almost never go exactly as you think, you may have to change an arm, you may have to pause for toxicity assessment, or biomarkers may be developed to redefine patient subgroups. So in the end, there is always a lot of work to do. Further, we always now carefully conduct subgroup analysis, look at secondary end-points, and also consider whether there are biologic correlates with outcomes to find out whether there are biomarkers that could help us further define who the best patients for the treatment may be.

You initiated some clinical trial databases, such as ACCENT, could you introduce those databases, what triggers you to start them and what are the principles of cooperation using the databases?

Prof. Sargent: Every clinic trial is designed to address a single question. But if we can gather the data from many clinical trials, and put the data together, we can ask and answer so many more questions. Many questions relate to subgroups of patients that we don't have enough patients in any one trial to answer that question.

The very first pooled database we put together was to answer a question about the value of the treatment for elderly patients with colon cancer, and elderly patients are relatively rare in clinical trials. So we had to gather data from several trials to get enough elderly patients, in this case, patients over the age of 70, to determine the efficacy. We determined that the adjuvant therapy for stage II and III colon cancer patients was as effective for older patients as for younger patients. We published that in the *New England Journal of Medicine* in 2001. After that, we had seven trials, and the next question was about trial end-points: do we have to wait for overall survival as our primary trial end-point? We wanted to consider whether we could identify an end-point earlier in the patients' course of disease that would provide reliable information. In order to do that, we used those several trials from the elderly analysis, and added additional trials to create the ACCENT database. ACCENT initially included 18 trials, which allow us to look at the relationship between a surrogate endpoint, in this case, disease-free survival, with overall survival, which was the true endpoint. We were able to demonstrate the disease-free survival was an accurate predictor of overall survival, across these 18 trials, and that led to the United States Food and Drug Administration (FDA) acceptance of disease-free survival as an endpoint for stage III colon cancer, which we published in the *Journal of Clinical Oncology* in 2005. This

allows new treatments to get to patients 2 years more quickly than they would have in the past.

Once we had that success, other people became aware of our database, started asking many more questions, and giving us more data. Now we have conducted at least a dozen analyses, some looking at very young patients, for example, patients under the age of 40, who are very rare for colon cancer. We've looked at the effect of race, white Caucasians *vs.* African American. We've looked at many such questions in patients with stage II or III colon cancer. Because of the success, we thought we should do the same thing in patients with stage 4 disease, so we partnered with Dr. Aimery deGramont to create another collaboration to gather data from stage 4 colon cancer patients. We are just launching now a collaboration to collect data in pancreas cancer patients. And we are midway through a similar collaboration in follicular lymphoma, where we now have data from 15 trials and over 5,000 patients.

There are two key principles for using the databases: when someone gives us data, we never use the data for anything that has not been pre-agreed upon, and that makes people trust the process. The second principle is that any person who gives us data can propose a new question to be answered by the database, but each time all the people who gave data have the opportunity to agree to let their data be used for the new analysis or not. This means that contributors have no risk to give us the data, because we never do anything with it that people who provided the data would object to. This has allowed our database to grow very large, and have allowed investigators all around the world to propose new questions that could never be answered any other way. So it has been very successful so far.

You are the President-Elect (2013 Presidential Term) of the Society for Clinical Trials. What does this society do?

Prof. Sargent: The Society of Clinical Trials is an international multidisciplinary society with about one thousand members, including physicians, statisticians, data management, IT, and clinical research professionals. It's everyone involved in clinic trials. Our goal is to advance the science and practice of clinic trials. We have a journal called *Clinic Trials* where we publish statistical methods, new IT approaches, and new data management approaches. We also have an annual meeting gathering all those people together, and have many educational sessions that many physicians attend to learn about fundamentals of clinic trials, how to conduct data safety monitoring boards, about how to engage

with the community to enroll patients onto trials. This is not only about oncology, it spans across all specialties, cardiovascular, diabetes, oncology, everything. So it's a very unique society that it cuts across many different diseases and disciplines.

The Society's primary charge is education, however we also do publish some policy-type statements, but they are not about treatments. For example, there was a recent petition that all trials should be registered in the public domain, with their results and methods reported. We put up a position statement that the Society of Clinical Trial agrees with this petition. But our primary purpose is education, for all people involved in clinical trials to increase the quality of trials to be conducted throughout the world.

There is limited statistical support that physicians in China can receive from their organizations and how very well trained when they were in school. How is the training of clinical trial design carried out in the USA?

Prof. Sargent: Without involvement of statisticians, the conduct of high quality trials would in my opinion very difficult, because statisticians can be aware of many issues that are subtle and can introduce biases. Particularly important is the principle of randomizing patients, because in a non-randomized trial you never can be sure of what subtle biases may be introduced by only enrolling one kind of patients and not enrolling another kind of patients. I am a very big proponent of randomized trials, including randomized phase II trials. I think we have had in oncology a history of single-arm Phase II trials that far too often lead to results that look more promising than they should, because of biases in patient population. Then when we go to confirm the results in Phase III, the trial does not succeed. So we need to do better job in our phase II trials, to reduce the number of Phase III trials that do not succeed.

At the Mayo Clinic, we teach a course in the principles of clinical trials for physicians and scientists. We don't go into the statistics, but we do teach principles of a good trial, what

is required for the design, should the trial be randomized or not, how to carefully specify end-points and patient populations, and how to pre-specify your objectives. These are the kinds of things that physicians can easily understand, and most readily appreciate these principles. But ideally to do the data management and the analysis, if there is an opportunity to have statisticians, those are the kind of things that an MD cannot learn quickly. They absolutely can learn eventually, but it requires years of study of the mathematical foundations to allow them to do that, which is a challenge. I think the best thing to do will be to educate the oncologists or physicians on principles on how to conduct a good study, then work through universities or other mechanisms to develop a greater number of statisticians who can handle the specifics of the data analysis.

You and Prof. Qian Shi are organizing a special column on statistics in oncology clinical trials for Chinese Clinical Oncology, what will you do in this column?

Prof. Sargent: Our goal is to present important principles of statistics in oncology clinic trials in a way that they are readily accessible to physicians. These will not have statistical formulas or mathematics. They will really focus on the principles of clinic trials, why do we do randomization, what's the importance of that, how to select the appropriate endpoints for a clinic trial, what we have to consider in terms of patient populations, why do we enroll one patient population or another, how do we regularly assess end-points, why do we do things like placebo control, blinding, talk about independent review of end-points to assure objectivity and reduce bias. That would be our goal: outline the principles of good clinical trial conduct without getting into the statistical details. That's our goal for the series.

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