A. Specific Aims

Accrual problems, the inability of many research studies to recruit a sufficient number of volunteers in the planned time frame, represents a major hurdle to the conduct of good research and raises troubling issues for researchers, Institution Review Boards (IRBs), and granting agencies.

The goal (long range objective) of this research program is to increase the awareness in the research community that accrual problems are a serious threat to the research endeavor and to understand the factors that cause problems with patient accrual. This will serve as preliminary data in the background and significance section of an NIH R03 or R21 grant to produce quantitative tools for planning and monitoring accrual rates in clinical trials.

Specific Aim #1.

Estimate the proportion of prospective studies in humans approved by the Children's Mercy IRB and completed between January 1, 2001 and December 31, 2005 that have experienced delays in the completion of the studies because of accrual rates problems or which ended without recruiting the original planned number patients.

Specific Aim #2.

Estimate a similar proportion for prospective studies in humans funded internally (KBR grants) that were completed between January 1, 2001 and December 31, 2005.

Specific Aim #3.

In both groups, evaluate the reasons that are offered in interim and final reports in studies with identified accrual problems.

Specific Aim #4.

Identify risk factors associated with individual studies that may be associated with delays in accrual and/or failure to recruit the original planned number of patients.

B. Background and Significance

As the research biostatistician at Children's Mercy, Dr. Simon has supported the development of literally hundreds of clinical trials across just about every branch of pediatric medicine. In his experience and in the experience of many of the people he works with, the greatest practical problem in conducting medical research is slow accrual of patients. Clinical trials invariably have problems recruiting the planned number of patients in a reasonable time frame. According to one source[1], more than 80% of all clinical trials fall short of their accrual goals. The net result is too many research studies that appear with inadequate sample sizes and confidence intervals that are so wide that they are effectively uninterpretable.

The problem of inadequate accrual is a serious issue for Institutional Review Boards (IRBs). If a study has an inadequate accrual rate, that changes the balance of risks and benefits. The patients that are enrolled in the study experience inconvenience and possibly pain, and may even suffer increased risk but do not provide information with

sufficient precision to produce scientifically valid results. It is well understood that IRBs have inadequate tools for gauging the performance of clinical trials.[2] The NIH has recognized this as well and has documented the need for better tools in an Program Announcement[3] which calls in particular for

> *"Development of appropriate outcomes measures and quality indicators for the IRB review process for measurement of adequate protection of human subjects."*

Foundations and government agencies that support medical research directly bear the costs of a study with poor accrual rates. When they invest their limited funds in such a project, this represents money taken away from a different research project that would have met its accrual goals and would have provided scientifically useful output. The amount of research money tied up in these underperforming clinical trials represents a huge lost opportunity cost that dilutes the effectiveness of the agency's grant program.

Clearly, accrual rates are of broad interest to a wide range of parties to the research process. But almost no hard data exists for accrual rates other than the one study cited above. Even simple statistics like how often a research study falls short of its promised sample size are not available.

The goal of this research project is collect some hard data on the extent to which accrual problems occur and examine factors associated with accrual difficulties.

C. Preliminary Studies/Evidence of Capability

Dr. Simon has provided statistical consulting for almost all of the research conducted at Children's Mercy Hospital since 1996 and is in a unique position to understand the barriers to effective research. More research is needed about the research process. The insights produced by this type of research are especially valuable because they have an impact across the board.

Although no decision will be available at the time this KBR grant is due, Dr. Simon has applied for a grant through the Kansas City Area Life Sciences Institute with Dr. Byron Gajewski, "Early Detection of Accrual Problems in Clinical Trials." The work of this KCALSI grant and the work on this KBR grant are sufficiently modular that either effort can continue if the other grant is not funded. Both grants, however, have as their ultimate goal the preparation of data to support an R03 or R21 grant.

The full details of the KCALSI grant are available on Dr. Simon's website[4], and the technical abstract is reproduced below:

> *A key in the success of a clinical trial is the accrual rate--how rapidly are patients being recruited into the clinical trial. Although they are very important, accrual rates are often developed in an ad hoc fashion. If they are monitored at all, accrual rates are examined using only a subjective approach.*
>
> *Our plan is to develop tools for planning a clinical trial through the careful elicitation of a Bayesian prior*

distribution on accrual rates. The prior distribution is a reflection of all sources of uncertainty about the accrual rate and provides a more realistic basis for planning than a single point estimate of accrual.

We also want to develop monitoring tools based on Statistical Process Control Charts. Control charts represent a proven approach for identifying important changes in the accrual process and form the basis of comparing the actual accrual data with the needs of the research project.

In addition, we will evaluate the expected completion date for a clinical trial using Bayesian predictive distributions. The Bayesian predictive distribution shows the range of possible completion dates that is an appropriate mixture of the initial estimates and the observed accrual patterns. As data on accrual accumulates, the predictive distribution will provide increasingly precise estimates of the completion date.

Finally, we want to set up a web server running open source software tools based on the R and BUGS statistical programming languages. The web server will run prototype software that will allow collaborators outside the Kansas City area to examine our work and develop additional methods and approaches.

The work produced from this grant will serve as preliminary data for an R03 or R21 grant from NIH to flesh out our concepts into a fully working system for planning and monitoring accrual rates. If that work is successful, we plan to examine similar approaches for monitoring drop-outs and adverse event rates.

The control charts that will form the basis of the software system for monitoring accrual rates is based on work by Drs. Simon, Cox, and Santos on control charts for monitoring patient safety events. A patent for this system has been applied for and we are currently negotiating with a major health care software company to market and distribute this software. The R03/R21 grant represents an effort to expand the control chart concept to a new market.

Judy Champion is the Administrative Assistant for Dr. Simon. It should be emphasized that the work of Ms. Champion will not be administrative, but rather the abstracting of information from numerous interim and final reports. Ms. Champion already has extensive experience with tracking a research database of over 5,000 articles, books, and websites.

Vidya Sharma has collaborated with Dr. Simon on numerous research studies and has agreed to work with Dr. Simon on the qualitative data analysis.

D. Research Design and Methods

Study design: This research is a descriptive evaluation research studies approved by the CMH IRB and of studies funded by KBR. There will also be a qualitative analysis of the reasons provided in interim and final reports for delays in recruiting a sufficient number of patients. This is a pilot study intended to develop preliminary data for an R03 or R21 grant to develop software for planning and monitoring accrual rates in clinical trials.

Patients/Subjects/Samples: This research study will collect a random sample of 100 prospective studies in humans approved by the CMH IRB and completed between January 2001 and December 2005. The sample will be stratified by year.

The study will also collect a census of all prospective studies in humans supported by KBR and completed between January 2001 and December 2005.

Both randomized and nonrandomized studies are eligible for inclusion in this evaluation. Studies which were not completed during this time frame or which did not produce final reports will be excluded from the study. Retrospective studies and studies not involving human subjects will also be excluded.

Treatment groups: Since this is an observational study, there are no treatment groups. The researchers will identify possible risk factors associated with the research studies that may be associated with accrual problems.

Drugs/devices/experimental interventions: There are no drugs, devices, or experimental interventions planned for this research.

Observation and measurements: For each research study in the sample, the following data will be extracted from the initial research protocol and the final report:

- Planned starting date
- Actual starting date
- Planned ending date
- Actual ending date
- Planned sample size
- Actual sample size

Some of the reports may not specify all of the information required for this research study, but this in and of itself is an interesting statistic for analysis. For example, how many studies were approved by the CMH IRB without the researcher having specified an ending date for the research? This does happen rather frequently, according to some informal interviews that Dr. Simon has conducted, but it represents the equivalent of the IRB signing a blank check.

Study specific variables will also be extracted from these reports:

- External sponsor (yes or no)
- Study coordinator (yes or no)
- Consent required (yes or no)
- Randomized study (yes or no)

Although it will be more difficult to obtain in a quantifiable fashion, we plan to also collect data on how busy the principal investigator was (e.g., how many other projects did this person serve as PI for, and the percentage of release time from clinical duties, if any).

Data analysis: This primary outcome variable is the proportion of all IRB approved studies that either finished later than planned or which finished with fewer patients than originally planned. Secondary outcome variables are

- Average percentage shortfall in those studies with fewer patients than planned.
- Average delay in those studies that ended late.
- Proportion of studies with insufficient information in the original protocol to estimate accrual rates.

An exploratory data analysis will examine the study specific factors to see

if any are associated with delays in completion or shortfalls in sample size. These analyses will use simple graphical and tabular methods with no formal tests of hypotheses.

Another secondary outcome will be the qualitative analysis of the reasons (excuses) provided in the interim and final reports of those studies which accrued patients at a slower rate than planned or which ended with fewer patients than originally planned. A large number of these studies will be expected to offer no reason or excuse.

The quantitative data analysis will be descriptive with 95% confidence intervals presented for any estimates produced. A sample of 100 studies will provide very good precision for estimating the primary outcome variable, the proportion of studies that finished late or with insufficient numbers of patients. For example, if the proportion is estimated to be 30%, then the 95% confidence interval will have a width of plus/minus 9%. If the proportion is 50%, then the confidence interval will have a width of plus/minus 10%.

The estimated number of KBR supported grants that were completed between 2001 and 2005 is estimated to be too small to allow for precise estimates, but these estimates should still be interesting and helpful.

The qualitative data analysis will proceed using an established approach that has been used in numerous research settings.

Among those studies identified as being behind schedule at an interim report, Ms. Champion will identify any text in that report that offers an explanation for the delay or which offers a proposed change to help get the study back on track. She will perform the same task for any study with a final report that ended later than planned or which fell short of the target sample size. She will enter these explanations into a database with a coded link to the original research studies.

Two independent reviewers will meet prior to reading the textual information and will develop a list of categories that could represent a small and manageable set of discrete responses that is expected to capture the full range of textual responses. Two reviewers will then take that list of categories and independently assign individual text items to one or more of these categories. The degree of agreement among the reviewers will be estimated and the reviewers will meet to resolve any discordance between the two classifications.

Study Flow Sheet: Lest this study be accused of falling behind schedule like some of the studies it will be examining, a table showing the time frame for accomplishments of the various tasks is presented here:

Month 1-2: Apply for and receive IRB approval for this study. Because no personal identifiers will be included in this study, it is expected that this study will be classified as exempt by our IRB.

Month 3: Obtain a list of all IRB approved studies that produced a final report between 2001 and 2005. Obtain a similar list for KBR supported grants. Identify any studies in these lists which based on their titles or abstracts clearly do not meet the inclusion criteria.

Month 4: Obtain all reports for a random sample of 100 IRB approved studies from the above list. Create a backup list of 20 additional studies that will be drawn from in case some of the 100 studies are found to be ineligible after a more careful review of the reports. Obtain all reports for all KBR supported studies from the above list.

Months 5-6: Extract and analyze the quantitive data on planned/actual starting dates, ending dates, and sample sizes and study specific characteristics. Enter this data into a database for analysis.

Months 7-8: Extract and analyze the qualitiative data on the reasons/excuses provided for any study ending late or failing to recruit the planned number of patients.

Months 9-12: Perform qualitative analysis described above. Prepare manuscript for publication.

Literature cited

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3. National Institutes of Health "Research On Ethical Issues In Human Subjects Research." Accessed on October 2, 2006. http://grants.nih.gov/grants/guide/pa-files/PA-06-367.html

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