

When Should a Patient Registry End? Draft White Paper for AHRQ Patient Registries Handbook II

Authors:

Kenneth J. Rothman, DrPH (lead author)
RTI Health Solutions

Joanna Haas, MD, MS
Genzyme Corporation

EXECUTIVE SUMMARY

The authors consider issues relating to stopping a patient registry study, discuss decision criteria, and suggest some guidelines. Although the specific approach will vary from study to study, the issues to consider are more general. The emphasis is on registries designed to assess safety or effectiveness outcomes.

Stopping an Experiment

The principles regarding rules for stopping a study mostly stem from the need to consider stopping an experiment. Experiments differ from registries in crucial ways, but it is worth examining why and how experiments are stopped. This important decision is typically made by an advisory group, such as a Data Safety and Monitoring Committee. In a biomedical experiment, the investigator has a greater ethical obligation than in a non-experimental study to safeguard the well-being of study participants, because the investigator is administering an intervention to study participants that is expected to affect the probability that study participants will experience specific health outcomes. Many investigators agree that if the principle of “ equipoise ” with regard to the benefits or harm of the intervention becomes untenable as study results accumulate, the study should be stopped. To address statistical concerns that can arise from repeated analyses of accumulating data, many experiments are planned with a specified number of interim analyses, and the interpretation of study results takes into account the number of such analyses.

Stopping a Fixed Length Non-experimental Study

Ethical concerns are the primary motivation for stopping an experiment. In non-experimental studies, ethical concerns relate to data privacy, intrusive questioning, or excessive inducements for participation, rather than the direct care or life activities of the participants. Although it is theoretically reasonable that an investigator could choose to stop a non-experimental study for ethical reasons, those reasons would presumably relate to ethical problems that were discovered in the course of the study. Unlike the experimental setting, the investigator in a non-experimental study is not administering the exposure to any of the study subjects, and thus has no responsibility to the study subjects regarding their exposure.

As a result, interim findings do not often dictate an early conclusion to the study; especially given that the desired precision of the effect estimate is unlikely to have been reached.

Stopping an Open-ended Study

For registries focused on safety or effectiveness outcomes, there is little reason to support a registry continuing indefinitely. To guide the choice of when to conclude an open-ended registry, it is helpful to formulate a specific goal that permits a satisfactory conclusion to data collection and include this goal in the registry protocol or charter. The goal might be framed in terms of a minimum number of specific adverse events of some type, or to continue data collection until the upper bound of a confidence interval for the rate or risk of the key outcome falls below some threshold, or the lower bound falls above a threshold. Other reasons to consider stopping are low patient accrual, or incomplete or poor quality information.

Changes to the research questions of interest may also affect the choice to stop or continue a registry. When questions change or evolve, the choice of stopping or continuing the registry depends on whether it can adapt to address the changing goal or goals. Funding or staffing considerations may also affect the decision of whether to continue an existing registry.

Conclusion

It is advisable that patient registries set reasonable and specific goals at the outset of the project for the amount of information to collect and to cast these in specific terms regarding data quality, study enrollment, and precision of the desired estimates of measures that the registry is intended to describe. Open-ended registries may then measure their progress against these goals to assess whether and when to stop the project. When planning a new registry, investigators may wish to set stopping rules based on when the goals have been met, or conversely appear unlikely to be met even with continued enrollment.

Additional considerations might include the existence of grave safety concerns that require further monitoring, a shift in focus toward longer-term follow-up, or the emergence of new questions regarding the disease or product. If new questions arise, they may be addressed through a change in the registries mandate and design.

KEY POINTS

- Experimental studies may be stopped for ethical reasons, such as when equipoise becomes untenable. The decision to stop non-experimental studies, such as registries, is more complex and may be made due to ethical reasons, achievement of goals, lack of relevance, or cost.

Reasons for stopping a registry

- The registry has fulfilled its original purpose.
- The registry is unable to fulfill its purpose.
- The registry is no longer relevant.
- Funding, staffing, and other support will cease to be available.

Reasons for continuing a registry

- The potential safety concerns are so grave that they must continue to be monitored.
- Essential long-term follow-up can only be secured in the context of the registry.
- The purpose of the registry has changed and the registry can be amended to provide relevant information for an altered mandate.

INTRODUCTION

Once a registry is in place, how long should it continue? What are reasonable decision criteria for stopping data collection? In this chapter, we consider the issues relating to stopping a patient registry study and suggest some guidelines. Although the specific answers to the above questions will vary from study to study, the types of considerations may be more general. The discussion here is focused on registries intended to assess specific safety or effectiveness outcomes rather than those intended to assess health care operations, such as continuous quality improvement.

STOPPING AN EXPERIMENT

The principles regarding rules for stopping a study mostly stem from the need to consider stopping an experiment. Because experiments differ from registries in crucial ways, we should distinguish between the issues involved in stopping an experimental study and stopping a non-experimental study. In an experiment, the patient's treatment is determined by the study protocol, which typically involves random assignment to a treatment regimen. In a non-experimental study, patients are treated according to the treatment protocol devised by their own physician, typically uninfluenced by the study. In a randomized trial of a new therapeutic agent or a field trial for a vaccine, the size of the study population is ordinarily set in the study protocol, based on assumptions about the expected or hypothesized results and the study size needed to reach a reasonable scientific conclusion. Ordinarily this planned study size is based on power calculations, which require as input the criteria for statistical significance, the effect size anticipated, the baseline occurrence rate of the study outcome, and the relative size of the study arms. Because of inherent problems in relying on statistical significance for

inference,^{1,2} the study size may (preferably) be planned around estimation of effect and the desired level of precision. In a study intended to provide some reassurance about the safety of an agent, the study size may be planned to provide a specific probability that the upper confidence bound of a conventional confidence interval measuring an adverse effect would be less than some specified value, given a postulated value for the effect itself (such as no effect). In the latter situation, if no effect is anticipated, a power calculation is not only unreasonable, but is not even possible, whereas planning a study on the basis of precision of estimation is always possible and always reasonable.

Stopping an experiment earlier than planned is an important decision that is typically made by an advisory group, such as a Data Safety and Monitoring Committee, that is constituted to monitor study results and make decisions about early stopping. In a biomedical experiment, the investigator has a greater ethical obligation than in a non-experimental study to safeguard the well-being of study participants, because the investigator is administering an intervention to study participants that is expected to affect the probability that study participants will experience one or more specific health outcomes. A widely accepted (but unfortunately not universally accepted) ethical precept regarding human biomedical experimentation is equipoise.³ Equipoise requires that at the outset of the study, the investigator has a neutral outlook regarding which of the study groups would fare better. A strict interpretation of equipoise requires each of the study investigators to be in a state of equipoise. An alternative view, referred to as “clinical equipoise,” is that equipoise can be achieved at the group level, with the enthusiasm of some investigators for the prospects of the study intervention balanced by the skepticism of others.⁴ Whichever interpretation of equipoise is adopted, most investigators agree that if equipoise becomes untenable as study results accumulate, the study should be stopped to avoid depriving some study participants of a potential benefit, relative to what other participants receive.

For an advisory board to decide to stop a study early there must be solid evidence of a difference between the groups before the planned study endpoint is reached. Such stopping decisions are usually based on ethical concerns, as scientific considerations would seldom dictate an early stop to a study that had been planned to reach a specific size. Advisory boards must base stopping decisions on analyses of accumulating study data, which are usually formally presented at regular meetings of the review board. Statistical concerns have been raised about biases that can arise from repeated analyses of accumulating data.⁵ To offset these concerns, many experiments are planned with only a limited number of interim analyses, and the interpretation of study results takes into account the number of interim analyses.

STOPPING A FIXED LENGTH NON-EXPERIMENTAL STUDY

Like experiments, most non-experimental studies also have a fixed time for their conduct and a planned size that reflects goals analogous to those in experimental studies. Nevertheless, the ethical concerns that motivate stopping an experiment before its planned completion do not have a direct counterpart in non-experimental studies. Non-experimental studies do have ethical concerns, but they relate, for example, to data privacy, intrusive questioning, or excessive inducements for participation, rather than to concerns about intervention in the lives of the participants. Although it is theoretically reasonable that an investigator could choose to stop a non-experimental study for ethical reasons, those reasons

would presumably relate to ethical problems that were discovered in the course of the study but were presumably unrecognized at the outset, rather than to an early conclusion regarding the study goal. The investigator in a non-experimental study could learn, from an interim analysis, that the association between the exposure and the outcome under study was much stronger than anticipated. Unlike the experimental setting, however, the investigator in a non-experimental study is not administering the exposure to any of the study subjects, and thus has no responsibility to the study subjects regarding their exposure.

The discovery of an ethical problem during the conduct of a non-experimental study is therefore possible, but extremely rare. Because the findings from an interim analysis should not lead to discontinuation of a non-experimental study, there is consequently little motivation to conduct interim analyses for non-experimental studies that have been planned with a fixed size and period of execution. If there is some considerable time value to the findings, such as to inform regulatory action, it might be worthwhile to conduct an interim analysis in a non-experimental study to get an early appraisal of study findings. Unless there is an appropriate outlet for releasing interim findings, however, it is possible that early findings will not circulate beyond the circle of investigators. In most circumstances, such analyses are hard to justify in light of the fact that they are based on less data than was judged appropriate when the study was planned, and thus the originally planned analysis based on all the collected data will still need to be conducted. Unless there is a clear public health case to publicize interim results, journal policies that require that published data have not been previously published may inhibit any release of preliminary findings to news media or to journals in the form of preliminary findings.

STOPPING AN OPEN-ENDED STUDY

Although patient registries may be undertaken with a fixed length or size, or both, based on study goals relating to specific safety or efficacy hypotheses, many such studies are begun as open-ended enterprises, without a planned stopping point. For example, patient registries may be undertaken to monitor the safety of patients receiving a novel therapy, without specific hypotheses. The Antiepileptic Drug Pregnancy Registry, established in 1997, is an example of an open-ended registry that focuses on a set of specific endpoints (congenital malformations) among a subset of patients (pregnant women) taking a class of medications (antiepileptic drugs).⁶ It has no fixed stopping point.

Measuring the frequency of rare endpoints demands large study sizes. Therefore, a monitoring system that includes rare endpoints may have to run for a long while before the accumulated data will be informative for low frequency events. On the other hand, the lower the frequency of an adverse event, even one with serious consequences, the smaller the public health problem that a relative excess of such events would represent.

Traditional surveillance systems are intended to continue indefinitely because they are intended to monitor changes in event frequency over time. Thus, surveillance systems for epidemic infectious diseases provide early warning about outbreaks and help direct efforts to contain such outbreaks. In contrast, a patient registry is not a true surveillance system, since most are not intended to provide an early warning of a change in outcome frequency. Rather, most patient registries are intended to

compile data on outcomes associated with novel treatments, to supplement the sparse data usually available at the time that these treatments are considered for approval by regulatory agencies. For example, a patient registry might be mandated by the regulatory agency as a condition of approval, to supplement safety information that was submitted during the application process. How long should such a registry continue?

Although we cannot supply a general answer to that question, there is little reason to support a registry continuing indefinitely, unless there is a suspicion that the treatment effects will change over time. Otherwise, the time should come when the number of patients studied suffices to answer the questions that motivated the registry. The Acyclovir Pregnancy Registry, which began in 1984, was stopped in 1999. Its advisory committee concluded that “The [Acyclovir Pregnancy] Registry findings to date do not show an increase in the number of birth defects identified among the prospective reports [of exposures to acyclovir] when compared with those expected in the general population. In addition, there is no pattern of defects among prospective or retrospective acyclovir reports. These findings should provide some assurance in counseling women following prenatal exposure [to acyclovir].”⁷ The consensus was that additional information would not add materially to the information that had already been collected, and thus the registry was closed down.

To avoid uncertainty about the fate of an open-ended study, it would be sensible to formulate a specific goal that permits a satisfactory conclusion to data collection. Such a goal might be, for example, the observation of a minimum number of specific adverse events of some type. Even better would be to plan to continue data collection until the upper bound of a confidence interval for the rate or risk of the key outcome falls below some threshold, or the lower bound falls above a threshold. Analogous stopping guidelines could be formulated for registry studies that are designed with a built-in comparison group.

STOPPING DECISIONS AND REGISTRY GOALS

Ideally, stopping decisions ought to evaluate data from a registry against its stated goals. Thus, the registry protocol or charter should include one or more specific and measurable endpoints against which to judge whether the project should continue or stop. Without that guidance, any decision to discontinue a registry may appear arbitrary and will be more readily subject to political considerations.

Registry goals will vary according to the motivation for undertaking the project and the source of funding. Product-specific registries may be created as post-approval regulatory commitments. For products about which there are limited pre-approval safety data, the wish for additional comfort about the product's safety profile can be translated into a measurable goal. Such a goal might be to exclude the occurrence of life threatening or fatal drug-related events at a certain frequency. For example, the goal could be to establish a specified level of confidence that unexplained hepatic necrosis in the three months following drug exposure occurs in less than one patient in 1000. Alternatively, the goal might be to provide a more precise estimate of the frequency of a previously identified risk, such as anaphylaxis. Ideally, this goal should be formulated in specific numeric terms. With specific goals, the registry can have a planned target and will not be open ended.

If a registry study does not have a single or very limited set of primary objectives, a stopping point will be harder to plan and justify. Even so, with measurable goals for some endpoints, it will be possible to determine whether the registry has achieved a core purpose and may lead to a reasonable stopping point. Conversely, a registry that fails to meet measurable goals and appears to be unable to meet them in a reasonable time is also a candidate to be stopped. For example, if the registry faces unexpectedly low patient accrual, it should be stopped, as was done with the Observational Familial Adenomatous Polyposis Registry Study in Patients Receiving Celecoxib.⁸ This study enrolled only 72 patients in four years, out of a planned 200 during five years. Another reason to consider stopping is incomplete or poor quality information. Poor quality data is of particular concern when it concerns sensitive or illegal behavior, such as self-reported information on sexual practices.⁹ Decisions about stopping a registry because of low enrollment or inadequate information are made simpler with clearly stated goals regarding both features of the study. The criteria for useful quantity and quality of information should be specified at the outset. How well the study meets the criteria can be assessed periodically during data collection.

A registry may outlive the question it was created to answer. For example, if use of the product is superseded by another treatment, the questions that drove the creation of the registry may no longer be relevant, in which case it may best be retired. For medical devices, for example, newer technology is continuously replacing the old, although safety issues for older technology may motivate continuing a registry of an outmoded technology. A related issue arises when the question of interest evolves as data collection proceeds. Stopping or continuing the registry depends on whether it can address the changing goal or goals. That in turn depends on whether the governance of the registry provides adequate flexibility to refocus the registry in a new direction.

The decision to stop a registry may also depend on mundane considerations such as cost or staffing. For long-running registries, eventually the value of new information may face diminishing returns. Some registries have central core staff, deeply committed to the registry, who serve as its historical memory. Departure of such individuals can cripple the registry's function and a decision to stop may be appropriate. Similarly, a cohort of engaged investigators may disperse over time or lose interest in the registry. Funding sources may dry up making it impossible for the registry to function at a level that justifies its continued existence.

A thorny question is how a registry can continue with altered ownership or governance. Suppose a registry is formed with multiple stakeholders and one or more withdraws for the reasons described above. For example, when the implantable cardioverter defibrillator (ICD) registry was formed, it came about in response to a Centers for Medicare and Medicaid Services (CMS) Coverage under Evidence Development decision. The Heart Rhythm Society and the American College of Cardiology developed the registry with funding from industry to help institutions meet the need for registry participation for payment purposes and layered quality improvement and research goals onto that mandate.¹⁰ The resulting registry was rapidly integrated into more than two thousand institutions in the U.S. Recently CMS has determined that the current ICD registry is no longer needed for its purposes, so the registry must determine if it will continue on as a quality improvement program and whether to add other

stakeholders and funding sources or participation drivers (such as manufacturers, insurers, or other government agencies such as the Food and Drug Administration).

WHAT HAPPENS WHEN A REGISTRY STOPS?

Stopping a registry might mean ceasing all information collection and issuing a final report. An intermediate decision that falls short of a full stop might involve ceasing to accrue new patients while continuing to collect information on existing participants. This step may be useful if the registry goals are in the process of changing. If a registry is to be stopped, the archiving rules should be checked and followed, so that those who need to consult the data for questions not fully addressed in reports or publications can be answered later, provided that the charter of the registry allows it. Following German reunification in 1990, it was determined that the East German National Cancer Registry, which had received detailed reports on 2 million cancer cases from 1954- 1990, was in violation of West German privacy laws and the data were quarantined. In the more usual case, orderly archiving of the data in anticipation of later access should be part of the close-down procedure, in a manner consistent with the charter under which the data were collected.¹¹

A slightly different scenario is when the registry has a single sponsor whose purposes have been achieved or determined to be unachievable and the sponsor decides to end the registry. Is there an obligation to patients or participating providers to continue the registry because some value (e.g. quality improvement, data for other comparisons) can still be derived? It is difficult to argue that the sponsor has an ongoing financial responsibility once the registry has achieved or failed to achieve its primary purpose, especially if this has been spelled out in the protocol and informed consent. Yet, one can argue that to the extent that it's feasible and affordable to engage other stakeholders in discussions of potential transitioning of the registry to other owners, this approach should be encouraged. Nontrivial issues of data ownership, property, confidentiality and patient privacy would need to be satisfactorily addressed to make such transitions possible and therefore, it is always best to consider this possibility early on in registry planning. Both the National Registry of Myocardial Infarction (NRMI), sponsored by Genentech, Inc. and the OPTIMIZE-HF registry, sponsored by GlaxoSmithKline, successfully completed transitions to other organizations (American College of Cardiology and American Heart Association respectively) when those registries were concluded, providing their participating hospitals in each case with the ability to continue the quality improvement efforts begun under those registries.^{12,13}

There is no clear ethical obligation to participants to continue a registry that has outlived its scientific usefulness. In fact, the prospect of altering the purpose of a registry would be complicated, unless the original registry operators were interested in doing so. For instance, if a registry is to be transferred, then it should be a restricted transfer (presumably a gift) to ensure the permissions, terms, and conditions under which it was compiled continue to be satisfied. The participants should be notified and should determine if they will continue participation and allow their data to be used for this new purpose.

There are a few potential reasons to consider preserving registry data once the registry developers have determined that it should end. One reason is that the data may be capable of producing a recognized

public health benefit that will continue if the registry does. Another situation may be that the registry has historical importance, such as a registry that tracks the outbreak of a novel infectious disease that may provide insight into the transmission of the disease if not now, then sometime in the future. Longitudinal collections of data may also be useful for hypothesis generation.

In creating a registry, the investigators should plan what will happen to data when the registry ends. If a public health benefit might be realized from registry data, then archiving of registry data is a potential answer. Decisions must be made by the registry owners in careful consideration of other stakeholders and potential costs. A central repository of data as a registry of registries might be considered, but such a data asset storage location does not yet exist. Perhaps a public entity such as the Library of Medicine could provide archival services as part of its mission, if a sufficient and recognized public health benefit is considered to exist.

CONCLUSION

Experimental studies, such as clinical trials or field trials, come with a high ethical burden of responsibility, which includes periodically re-evaluating the ethical basis for continuing the trial in the light of interim results. Consequently, trials require interim analyses and data safety monitoring boards, who decide whether the study should be stopped for ethical reasons. In non-experimental studies, there is much less motivation to conduct interim analyses, because there is no ethical motivation to do so. There is also no reason to appoint a data safety monitoring board, although any study could appoint an external advisory board. If non-experimental studies are planned to be of fixed length or fixed study size, they can be conducted as planned without interim analyses, unless the time value of an early, interim analysis is important enough to compensate for the added cost of conducting it and the tentativeness of the findings, which are based on only a subset of the planned study data.

If a patient registry is undertaken as an open-ended project, without a fixed endpoint, it need not continue forever. Unlike true surveillance efforts, patient registries of novel therapies are not intended to monitor for changes in occurrence rates over time. Rather, they are conducted to assemble enough data to evaluate associations that could not be evaluated with the limited data available at the time of new drug approval. Therefore, reasonable goals should be set for the amount of information to collect in such registries, based on specific endpoints of interest. These goals can and should be cast in specific terms regarding data quality, study enrollment, and precision of the estimates of specific measures that the registry is intended to describe.

REFERENCES

¹ Rothman KJ, Greenland S, Lash TL: *Modern Epidemiology*, Third Edition. Lippincott, Williams & Wilkins, New York, 2008.

² Rothman KJ, Johnson ES, Sugano DS: Is flutamide effective in patients with bilateral orchiectomy? Lancet 1999; 353:1184.

³ Freedman B: Equipoise and the ethics of clinical research N Engl J Med. 1987;317:141–145.

⁴ Weijer C, Shapiro SH, Cranley Glass K: For and against: clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial. BMJ. 2000;321:756-758.

⁵ McPherson K: Statistics: the problem of examining accumulating data more than once. N Engl J Med. 1974;290:501-502.

⁶ The antiepileptic drug registry <http://www.aedpregnancyregistry.org/>. Last accessed June 24, 2009.

⁷ Acyclovir Pregnancy Registry and Valacyclovir Pregnancy Registry Interim Report, December 1997. Glaxo Wellcome, RTP, NC 27709; as referenced on Web page titled, "GlaxoSmithKline Pregnancy Registries," <http://pregnancyregistry.gsk.com/acyclovir.html>, last accessed on June 24, 2009.

⁸ <http://clinicaltrials.gov/ct2/show/NCT00151476>. Last accessed June 24, 2009.

⁹ Eng TR, Butler WT: The hidden epidemic: confronting sexually transmitted diseases. Institute of Medicine (U.S.) Committee on Prevention and Control of Sexually Transmitted Diseases, National Academies Press, 1997.

¹⁰ "Medicare to Collect Data on Use of Implantable Defibrillators," Senior Journal. October 27, 2005. <http://seniorjournal.com/NEWS/Medicare/5-10-27DefibrillatorStudy.htm>
Last accessed June 23, 2009.

¹¹ Hildebrand R; Minister for Work, Social Affairs, Health and Women, Brandenburg, Potsdam, 24 November 1997 Cancer Registry of Berlin, Brandenburg, Mecklenburg, Vorpommern, Sachsen-Anhalt and the Free States of Sachsen and Thüringen.

¹² "Optimize-HF selected for heart failure program" http://findarticles.com/p/articles/mi_m0EIN/is_2005_July_26/ai_n14818828/. Last accessed June 4, 2009

¹³ "American College of Cardiology (ACC) creates network" from www.medicalnewstoday.com/articles/55798.php. Last accessed June 4, 2009.