Ensuring the highest possible data retention rates in clinical outcome trials

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Executive summary

In clinical trials, maintaining acceptable data retention rates is a challenging task, especially in long-term follow-up studies. The U.S. Food and Drug Administration (FDA) has declined certain drug applications for approval largely due to concerns over missing follow-up efficacy and safety data and methodological issues with the trials in the drugs’ clinical development programs. This emphasizes the critical importance of a robust process for obtaining data retention and survival status information for all patients enrolled in an investigational trial.

With key milestones on the line, Quintiles and Duke Clinical Research Institute, jointly with the sponsor project team for the TRILOGY Acute Coronary Syndromes (ACS) clinical trial, developed and implemented a robust data retention process to ensure maximum control of subject retention during the study. At study completion, TRILOGY ACS had a subject lost-to-follow-up (LTFU) rate of only 0.2%.

This concept was later validated and even improved in at least two other Quintiles managed large outcome trials. This trial can therefore be used as a guide for future studies to increase overall subject safety, survival outcomes, and ensure data integrity.
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Introduction

To protect the scientific integrity and validity of endpoint trials, a robust data retention plan is of paramount importance to maintain acceptable data retention and survival rates. This white paper considers the TRILOGY Acute Coronary Syndromes (ACS) clinical trial as a case study. At study completion, TRILOGY ACS had a subject lost-to-follow-up (LTFU) rate of only 0.2%. This paper reviews the need for and the methodology used in the study to achieve these bar-raising metrics, and hopes to aid other investigations maintain similarly high data retention and survival rates.

Understanding the FDA guidance on data retention when subjects are withdrawn from FDA-regulated clinical trials

U.S. Food and Drug Administration (FDA) law and regulations recognize that a complete and accurate benefit-to-risk profile of an investigational product depends upon the data from every subject’s experience in the clinical trial. For example, if a subject’s data could be withdrawn from a study, a sponsor would not have access to data on adverse events (AEs) experienced by the subject. The sponsor would be unable to evaluate whether changes to the protocol or the informed consent documents are needed to ensure the rights, safety, and welfare of other trial subjects. The agency needs all such data to be able to determine the safety and effectiveness of the drug (or device). The fact of being administered an investigational product cannot be taken back. Also, if a subject were able to control the use (inclusion and exclusion) of his or her data, and particularly if the clinical investigation were not blinded, the potential for bias would be immense.

It should be appreciated that FDA’s response applies to the most potentially difficult situation, that is, studies involving an exception from the informed consent requirements in which subjects, due to a life threatening medical condition, are unable to provide informed consent to participate in the study. Subjects may subsequently withdraw from such studies, but the data collected up to withdrawal may not be removed (revoke consent by the subject).

Study validity

The validity of a clinical study would also be compromised by the exclusion of data collected during the study. There is a long-standing concern with the removal of data, particularly when removal is non-random (e.g., one therapy being associated with more nuisance bleeding, leading the patient to withdraw consent from participation in the trial), a situation called “informative censoring.” FDA has long advised that “intent-to-treat” analyses (analyzing data related to all subjects the investigators intended to treat) should be employed, and a variety of approaches for interpretation and imputation of missing data have been developed to maintain study validity. Complete removal of data, possibly in a non-random or informative way, raises great concerns about the validity of the study.

Study reliability

There is particular concern with a study’s reliability when subjects withdraw their data in a non-random way because they are unhappy with their experience, either because they failed to obtain a desired effect or suffered an AE. Loss of these subjects’ data could greatly distort effectiveness results and could hide important safety information (e.g., toxicity) related to a poorly tolerated treatment. Allowing subjects to withdraw data could even provide an opportunity for unscrupulous parties to “improve” study results by selectively encouraging certain subjects to withdraw from a study.

The reporting, extent, and handling of loss to follow-up and its potential impact on the estimates of the effect of treatment in randomized controlled trials has been assessed in the LOST-IT trial, and plausible assumptions regarding outcomes of subjects LTFU could change the interpretation of results of randomized controlled trials published in top-tier medical journals.
The need for a robust subject retention plan therefore seems clear. The methodology and elements of the LTFU strategy discussed in this paper are specific to TRILOGY ACS, but the principle can be used as a primary tool to help sponsors when developing a protocol, considerations when educating sites, and the overall study benefits and outcomes. The scientific design of the LTFU plan in combination with operational implementation (i.e., detailed subject tracking) will result in the best possible data and optimize subject survival status and safety. TRILOGY ACS used this holistic approach to address the current challenges of study retention and obtaining survival status data prior to study completion for almost all subjects.

TRILOGY ACS: A case study

TRILOGY ACS, a double-blind, controlled, randomized clinical trial involving over 9,000 subjects with acute coronary syndromes treated with medical management, was important as it considered a population that had not been studied before. This population of subjects has the highest risk of adverse outcomes compared with subjects undergoing coronary percutaneous intervention (PCI). TRILOGY ACS provided important information of how to optimally medically manage the ACS subject. From June 27, 2008, through September 12, 2011, TRILOGY ACS enrolled 9,326 subjects at 966 sites in 52 countries.

The primary efficacy endpoint was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among subjects under the age of 75 years. Suspected ischemic and bleeding endpoints were evaluated by an independent cardiovascular adjudication committee (ICAC) whose members were unaware of study-group assignments, using the Clinical Events Committee adjudication process established at DCRI. Quire uncommonly in cardiovascular endpoint trials, suspected new, non-benign neoplasm endpoints were adjudicated by an independent oncology adjudication committee (IOAC), also at DCRI. Due to the study complexity and high risk for subject LTFU, it was evident that a robust data retention process needed to be developed early in the project planning process to ensure maximum control of patient retention during the study. As a result, of 9,326 subjects who underwent randomization, 573 did not complete the study; however, data retention/vital status information was collected at 30 months or at the end of the study for all but 18 subjects (0.2%).

At 30 months, there was no significant difference between groups in the rate of the primary endpoint among the primary cohort of subjects under the age of 75 years. At 30 months, the key bleeding endpoints of non-coronary artery bypass graft (CABG)-related severe or life-threatening events (according to the Global Use of Strategies to Open Occluded Coronary Arteries [GUSTO] criteria) and major bleeding (according to the Thrombolysis in Myocardial Infarction [TIMI] Study TIMI criteria) occurred with similar frequency among subjects under the age of 75 years in the two study groups.

Lost-to-follow-up methodology

To control the LTFU in an outcome study, several actions need to be taken. The goal is to obtain follow-up data on all subjects randomized. The steps are discussed here in turn.

1. Protocol – LTFU definitions

The protocol should define all possible situations where subjects discontinued study drug or discontinued from the study. These discontinuations should be divided into various subcategories if possible, prior to starting the trial. It should be made clear how to deal with these various stages of subject withdrawal. In addition, the investigator should be requested to contact the study team or medical helpline prior to (permanently) discontinuing study medication for any subject ensuring patient safety to ensure it is clear what steps need to be taken regarding patient treatment and follow-up and to ensure that the site investigator clearly understands the various definitions, so that withdrawal of consent is minimized. This discussion is best handled by a physician-to-physician dialogue. In order to allow for language barriers
a physician leader was assigned to each country/region to facilitate non-English communication when needed. However, in the majority of cases it was possible to perform this communication in English.

Discontinued subjects can be classified into the two main risk categories:

1. Subjects who discontinue study requirements:
   - Subjects who permanently discontinue study drug prior to completing the trial, but remain in the study to be evaluated regularly for efficacy and safety endpoints.
   - Subjects who discontinue study drug as well as their participation in the study. Only upon completion of the study, these subjects are to be contacted for a final retention/survival status update.
   - Subjects who revoke their consent and further contact is therefore not possible, nor can be collected from that subject after the documented revocation of informed consent. This is also the only group the FDA will accept as a legitimate lost-to-follow-up.

2. Subjects LTFU
   - Subjects considered at risk for potential LTFU. These subjects fail to return in time for a scheduled visit during the course of the study. They will have their retention/survival status collected via the LTFU plan. Examples of this collection would be through family members or through legal public records.

It is crucial that the above mentioned subject discontinuation/LTFU categories are well defined in the protocol to ensure that the data collection process and subject informed consent forms are properly developed.

2. Protocol – Subject completion definitions
In part, the LTFU methodology describes the proactive steps to be taken to ensure each subject is evaluated to determine the correct time point to be discontinued from the study. Clearly defined study design, subject discontinuation status, and case report forms (CRFs) are important to the LTFU development and implementation. It is also essential that withdrawal of consent is properly documented and signed by the patient in the source documentation, and properly documented in the CRF by the site.

It is important to outline in the protocol definitions itemizing the time point at which subjects will complete the study. As a Case Study, consider the time points in TRILOGY ACS:

**Primary endpoint**
- Study will continue until required numbered of subjects have experienced an adjudicated event
- All subjects <75 years of age have completed at least 6 months of follow-up or discontinue before 6 months

**Elderly population**
- At least 2000 subjects >75 years of age have been randomized into the study, with the last subject having either completed at least 3 months of follow up or discontinued before 3 months

**Study duration**
- All subjects will remain on study drug for a maximum of 30 months or until completion of the study, whichever time is earlier

**Study closure**
- A rolling close out will be performed over a 3 month period
3. LTFU plan and implementation
The first step for the Project Team is to develop a robust LTFU tool by taking the protocol LTFU and study completion definitions and developing LTFU strategies, and then to work in partnership with all assigned study team members, including sites, to ensure that all parties understand and comply with those strategies. Those elements include:

- Program management that synchronizes cross-functional collaboration and input between clinical, data management, project management, pharmacovigilance, and statistics;
- Leveraging lessons learned from studies that successfully managed each potential LTFU and discontinued subject on an individual basis, consistently knowing their study status;
- Evaluate each country and its capabilities early on in the trial and take the appropriate steps, thereby allowing enough time to have an impact in locating subjects, and to have an established trial leader in this country that can provide the appropriate guidance.
- Development of mitigation strategies for subject withdrawal/revocation of consent with an aim to be able to collect required study outcome data at the end of the study.

It is important to develop separate customized decision flow charts for subjects that discontinue study drug/discontinue study participation/revoke consent and subjects who are at risk for potential LTFU as LTFU strategies may significantly differ in these patient risk categories.

Additionally, the subject discontinuation and LTFU pathways should be further described so that it is clear where each risk category is referenced in the protocol, what the visit planning and eCRF expectations are, what should be documented in the subject source notes, how to deal with any serious AEs (SAEs) or endpoints, and what the study completion requirements are.

4. Strategies for locating lost subjects
Potentially LTFU Subjects are defined as subjects who have missed one or more scheduled visits for an unknown reason and cannot be contacted by phone or other means. To mitigate any subject lost to follow-up, at the start of the study site personnel should obtain any relevant contact details as well as contact details from relatives/relevant third parties. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit. Study sites need to implement LTFU strategies in parallel, not sequentially, and repeat these at the end of the study or at the subject’s final study completion, whichever comes first.

To mitigate revocation of consent, it is imperative that sites clearly communicate the benefits of subject follow-up prior to a subject’s decision to revoke consent. If somewhere during the study a subject consequently revokes consent, it is recommended to obtain the subject’s decision to revoke consent in writing. If a subject revokes consent, vital status will be collected through public record only. (Some jurisdictions have data protection laws which require study participants’ written withdrawal of consent or authorization to use or disclose their personal information for study purposes. It is generally recognized that any personal information collected from the study participant up to the point of withdrawal in writing can continue to be used for study purposes.)

Many sites have a range of experience and regulatory knowledge with regard to locating subjects once the subject indicates he or she would like to discontinue taking study medication. Many do not know the laws and regulations with regard to LTFU strategies as they are different by country. As expected, some countries are much more stringent than others. Therefore, it is vital to develop the plan early at the onset of the clinical study to ensure proper training and information transfer at the start of the trial. A partnership with an Academic research group that has local clinical trials knowledge can facilitate this process and allows each site investigator to be clear what the expectations are. If needed, location firms can be part of the overall strategy, but the decision needs to be made in a timely manner to maximize results. It should be noted that when using a location firm, this requires Ethics Review Board (ERB)/Institutional Review Board (IRB) review and approval prior to implementation, which has timeline and cost implications. It is therefore important to

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The laws and regulations with regard to LTFU strategies are different by country. As expected, some countries are much more stringent than others.
keep abreast of local laws and practices to ensure the most appropriate strategy can be adopted in each country. Table 1 provides a summary of proven LTFU Strategies.

### Table 1: A summary of proven LTFU strategies

The timing and frequency of each of the strategies should be clearly outlined in the LTFU plan.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone follow-up</td>
<td>Using all available contact numbers provided by the subject.</td>
</tr>
<tr>
<td>Institution resources</td>
<td>Sites to search institution’s medical records for changes of address and phone numbers and institution’s billing department to determine if new contact information is available.</td>
</tr>
<tr>
<td>Sites to search public domain websites</td>
<td>For current information if allowed (e.g., public social networking websites commonly used in each country; use of internet or equivalent (public data source), e.g., free or fee-based resources that a site can use to search for subjects; use of death/obituary roll (public data source).</td>
</tr>
<tr>
<td>Sites to send certified letters to all contacts</td>
<td>Subject can be repeated after a certain time if no response was received.</td>
</tr>
<tr>
<td>Information Resource Firm services</td>
<td>Familiar with healthcare laws can be offered to sites.</td>
</tr>
<tr>
<td>Other known country-specific LTFU strategies</td>
<td>Complying with data privacy regulations.</td>
</tr>
<tr>
<td>Any other general strategies</td>
<td></td>
</tr>
</tbody>
</table>

If the subject is not immediately located when LTFU strategies are implemented, the site should also be advised to repeat the LTFU strategies at the end of the study as it may be possible to find subjects some time later. Adequate source documentation of all LTFU efforts should be ensured in case one needs to refer to previous actions.

5. Site training

Site and Clinical Research Associate (CRA) training should be conducted in conjunction with the academic leadership of the trial upon study initiation, and regular retraining is critical to ensure high-quality execution of the LTFU plan. A good understanding of the ‘how and when’ of each subject’s discontinuation status should be clearly documented at the site and reported in the eCRF. In addition, it is crucial to enforce a proactive role from investigators to minimize LTFU subjects, maintain subject safety, and therefore ensure data integrity.

These steps can help to set a clear expectation to each study site to be inspection-ready upon the submission to regulatory authorities. The development, training, and implementation of a LTFU plan at the start of any clinical trial are keys to its success.

6. Monitoring approach

Clinical Research Associates (CRAs) who are assigned to monitor the trial must be knowledgeable about the different categories of premature study drug discontinuation, and aware of the LTFU processes to be implemented throughout the study and at the end of the study to obtain vital status information. The CRA’s role must be defined in assisting sites to obtain final vital status. Their primary activities should include:

- Confirming that site personnel understand the difference between the protocol specific-patient discontinuation definitions;
- Confirming that the study site has received all communication tools regarding the LTFU plan;
- Performing source data verification (SDV) on the source data for subjects classified as potentially LTFU subjects;
• Confirming the study site is documenting its LTFU strategies and activities when contacting and locating the study subject;

• Following the escalation process when reporting sites are not demonstrating LTFU strategies.

CRAs or study designee will support and oversee sites to confirm all strategies are implemented, and will monitor progress of the sites’ diligent efforts to find potentially LTFU subjects. Monitoring activities related to LTFU should be outlined in the monitoring plan (specifically, what can be performed remotely and what needs to be conducted while on site).

7. LTFU tracking
The study team should develop a global tracker to capture all subjects who have been identified as:

• Potentially LTFU subjects based on missed visits and outstanding data from IVRS;

• All subject discontinuations separated out by risk category.

It should be noted that tracking is only as good as the data received from the study site and data entered within the eCRF.

These data should be carefully maintained throughout the course of the study and should be frequently monitored and analysed, preferably monthly so that trends and any new or re-training needs can quickly be discovered. In addition, frequent follow-up should occur with regard to what LTFU strategies have been implemented and if subject contact and vital status can be obtained.

Managing towards zero LTFU
To manage LTFU to as close to zero as possible, another tool should be developed by the team to control the subject end-date at study completion, i.e., Site Termination Action Roll-off (STAR). The STAR guides each site regarding the subject end-date, clarifying roll-off details for each single subject. STARs should be discussed with sites by the CRAs. STARs should be maintained with scheduled as well as actual subject completion data throughout the backend process to ensure Last Subject Out (LSO) is achieved on time and any LTFU subjects are flagged so that additional LTFU strategies can quickly be deployed.

Data from each STAR should feed into a global subject completion tracker: this is a vital tool to manage and control the complete roll-off process (including confirmation of planned subject visits, actual scheduled visits, and occurred visits (globally, and per region, country, or site) and to flag any unscheduled subjects visit issues for immediate follow-up.

Barriers/key challenges
The TRILOGY ACS study team performed a lesson learned exercise upon completion of the trial. Several barriers when running studies with a LTFU component include:

• Real time follow-up by the study staff;

• Compliance with the LTFU strategies;

• The study sites’ knowledge of available strategies in their respective country;

• The subjects’ understanding of the importance of collecting their vital status at the end of the study.

Proof of concept
Due to robust processes, innovative LTFU tools, and vigilant follow-up, the TRILOGY ACS study team was able to identify, address, and resolve LTFU issues. In a very small portion, the utilization of IRB-approved subject finder vendors brought additional success.
The LTFU management has had a focus on early tracking, identification, and immediate follow-up, a process that minimizes LTFU costs to the client. For 99.8% of the subjects an outcome was obtained. TRILOGY’s LTFU rate was only 0.2% upon study completion.

Based on the successful methodology for managing subject retention developed by the TRILOGY Team, two other notable successes have been achieved. In the largest venous thromboembolism (VTE) study conducted, which compared a new oral anticoagulant against standard-of-care warfarin in over 8,000 subjects, an outcome was obtained for 99.87% of the subjects. This study team used a customized retention methodology focusing on withdrawn patients and assessing options as agreed by subjects to collect final outcome data. The LTFU rate was therefore 0.13% upon study completion (0.81% withdrawn consent subjects). In an atrial fibrillation study comparing a new oral anticoagulant against warfarin, over 20,000 subjects were enrolled worldwide. This study also used similar retention strategies and tailored them to their needs. In their effort to manage LTFU to as close to zero as possible they applied the STAR and global subject completion tracker principle. During this process, the team customized the STAR by developing a specific web-based application to facilitate collection of relevant subject data. Only 0.9% of subjects withdrew and only 1 subject was LTFU. At time of database lock, the outcome data for only 1 subject was missing.

Concluding comments

Section 4.3.4 of the ICH E-6 Good Clinical Practice: Consolidated Guidance reads as follows: “Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject’s rights.”

Given today’s regulatory landscape, the importance of maintaining acceptable data retention rates is to ensure the overall safety and survival status of subjects during the course of a clinical trial. Many outcome studies have not established a systematic approach to implement and follow each subject randomized into a given research study, thereby leaving data gaps, increased study costs, and ultimately failed demonstration of efficacy. The low LTFU status of the outcome studies discussed as a case study in this white paper can be attributed to early planning and implementation of innovative and robust strategies necessary to track and locate study subjects. Implementation of a proven methodology ensures subject safety and the highest chance to perform a robust overall efficacy analysis upon study completion.
References


About the authors

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Kelly has over 23 years of pharmaceutical research and development experience in clinical and project management. Kelly’s expertise includes large trial management, strategic and operational project management and study initiation and implementation. She has an extensive background in trial strategy with financial acumen and extensive cross functional leadership which helps ensure study results.

Kelly is currently the financial and operational risk management lead for project management. This team provides a continuous focus on financial performance and risk management within the Therapeutic Delivery Unit. She has oversight for and develops corrective action plans for key projects at risk, and also leads transition studies for enterprise accounts. She has been part of the data driven trial execution (DTE) team along with process reengineering and organizational change around Business Management Transformation. She is a leader in Project Management and conducted the TRILOGY study.

Prior to joining Quintiles in February 2008, Kelly served as a Senior Director at Omnicare Clinical Research. She has held other project management and clinical positions at Tap Pharmaceuticals and Abbott Laboratories in R&D.

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Irene is based in Amsterdam, Netherlands, and has over 20 years of work experience in Clinical Development in the CRO industry. Irene currently develops business strategies and study delivery models for clinical studies in drugs and devices. In her role she is responsible for the direct operational oversight of multi-national Project Teams, as well as for the design, implementation, and maintenance of operational processes, including consulting with clients in the overall design and management of their global programs. In 2013 Irene led the Quintiles Medical Device Centre of Excellence, a multi-disciplinary therapeutic-focused approach to define business strategy and study delivery models for medical device studies, which since 2014 has been an integrated part of Novella Clinical, Quintiles’ dedicated solution for Medical Device and Diagnostic. Her expertise lies in management principles and also conducted the Trilogy study.

Prior to joining Quintiles, Irene assumed project management and key operational positions at PAREXEL, MIRAI/VERUM and Cardialysis. Irene began her career as a data manager at the Daniel Den Hoed cancer centre.

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Dean has over 15 years of clinical research experience and over 36 years of experience managing complex organizational structures, implementing and overseeing global programs, and administering multi-million dollar budgets. He has held key leadership positions with Quintiles for twelve years in project management, clinical operations and global customer management. Additionally, Dean has three years of experience at a mid-sized CRO in project management and he led the company’s clinical operations department.

Prior to his work in the pharmaceutical industry, Dean served for over 21 years globally in key leadership and management positions within the United States Army. His progressive leadership and management experience in diverse business disciplines allows him to draw on strengths in problem solving, decision-making, organizational effectiveness and customer service solutions.

For the past two years, Dean has served Quintiles as Senior Director and Head of the Delivery Strategy and Budgeting Team, Customer Solutions Management Group, where he has had a positive impact working with proposal developers and operational teams to develop cost efficient and differentiated offerings for new business opportunities. Dean is a mentor and team-builder who fosters creativity in others and considers alternative methods to achieve desired results. He is a team player, who creates and facilitates an environment that supports change. He is known as a results driven strategic and tactical senior management professional.

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