Executive summary

Recent changes in regulatory requirements for diabetes clinical trials – including demands for larger sample sizes and evaluation of cardiovascular risk – have added significantly to recruitment and retention challenges.

Today, more than 180 drugs are being developed for diabetes and related conditions, resulting in high levels of competition for patients. This crowded marketplace is further complicated by patients with complex medical conditions. By their own admission, diabetes patients struggle with compliance, which greatly increases the risk of drop-out and loss to follow-up – and ultimately missing data. This white paper outlines four best practices to increase probability of success: 1) Understanding patient motivators at each stage of the diabetes journey; 2) Designing the protocol and informed consent form to be patient-centered and “fit for purpose;” 3) Setting expectations for 100% retention; and 4) Using “site intelligence” to provide sites with preferred recruitment and retention tools.
# Table of contents

Executive summary 1
Background 3
**Improving probability of success** 4
  - Understanding patient motivators 4
  - Keeping the protocol and informed consent form patient-centered 5
  - Setting expectations for 100% retention 5
  - Using “site intelligence” to provide sites with preferred tools 6
Conclusion 8
References 9
About the authors 10
Background

It is no secret that new diabetes drugs face an uphill battle in reaching the market. Regulatory authorities have increased requirements to approve new therapies in this area, demanding larger sample sizes and evaluation of cardiovascular risk – a process involving recruitment of higher-risk patients, longer trials and near-total retention in endpoint-driven, intent-to-treat (ITT) study designs.

The number of subjects needed to complete a diabetes trial has increased sharply since the U.S. Food and Drug Administration (FDA) issued regulatory guidance on evaluating cardiovascular risk in diabetes trials in 2008, and more participants with renal impairment must now be included. This is illustrated by a comparison between phase 3 trials carried out for Januvia® (sitagliptin), which was approved in 2006 and included 1,538 patients and Invokana™ (canagliflozin), which was approved seven years later and required more than 5,000 additional patients. With more than 180 drugs currently in development for diabetes and related conditions, larger and longer trials have only increased competition for patients.¹

Enrolling trials in a crowded marketplace is a challenge that is confounded by patients who have complex medical conditions and are typically noncompliant. According to various online patient surveys conducted by Quintiles in the United States and the United Kingdom, patients often take more than five medications per day to treat their diabetes and common comorbidities, including hypertension, high cholesterol levels and obesity, which further shrinks the pool of eligible patients. By their own admission, patients struggle with compliance, which greatly increases the risk of drop out and loss to follow-up, and ultimately missing data. In recent trials evaluating cardiovascular outcomes, inadequate retention has led to non-approval as illustrated in statements below made by the FDA.

Thomas Marciniak, FDA Cardiovascular and Renal Drug Products Division
Medical Team Leader:

“While I am sympathetic to the difficulties of performing outcome trials in the modern era of increased patient awareness of medical treatments and mounting privacy concerns, if this trend [of high loss to follow-up rates] continues we will not be able to interpret cardiovascular outcome trial results. This problem is the number one study conduct problem today threatening the integrity of cardiovascular outcome trials.”³

Briefing materials for the Cardio-Renal Drugs Advisory Committee’s July 28, 2010, review of ticagrelor

“The rates of patients with unknown vital status greatly exceed the reported differences in mortality rates. We cannot have confidence that the claimed mortality benefits are real.”⁴

Briefing materials for the Cardio-Renal Drugs Advisory Committee’s May 23, 2012, review of rivaroxaban

Regulatory demands have heightened the awareness of early withdrawals and the statistical impact of missing data throughout the research and scientific community. While the FDA acknowledges that retention is a major challenge, its position is that to truly prove a positive hypothesis, all patients must be accounted for and all outcomes collected.

Quintiles is tracking more than 257,000 members of online patient communities, including ClinicalResearch.com, a clinical trial matching service, and MediGuard.org, a medication monitoring web site. Through online surveys, companies can gain valuable patient insights regarding protocol design.

ClinicalResearch.com

MediGuard.org
Improving probability of success

This white paper outlines four “best practices” to increase probability of success. Recruiting the “right” patients within an intense study environment and reducing the risk of dropout and lost to follow-up takes proactive, common-sense planning that starts at protocol design.

- Understand patient motivators at each stage of the diabetes journey;
- Design the protocol and informed consent form to be patient-centered and “fit for purpose”;
- Set expectations for 100% retention; and
- Use “site intelligence” to provide sites with preferred recruitment and retention tools.

Understand patient motivators at each stage of the diabetes journey

Surveys suggest that patients are generally satisfied with their diabetes medication and are motivated to participate in clinical trials by access to comprehensive physical evaluations, medication and supplies, diet and exercise education at no cost, as well as altruism. However, the needs of these patients evolve as their disease progresses, comorbidities develop and they require more care and treatment. To design a protocol that will attract participation, we must first understand what motivates patients at each stage of the diabetes journey.

- **When beginning monotherapy**, patients benefit from education and support to learn to live with their disease. The cost of metformin, a first-line treatment and standard of care, is relatively low in developed countries so access to marketed medication may not motivate patients as much as access to specialized care and counseling.
- **When adding therapy**, access becomes a key motivator because newer medications are more expensive and may require patients to either pay out of pocket or pay high co-pays.
- **Transitioning to insulin** can be intimidating. At this stage, patients need support to learn how to self-inject, monitor glucose levels and understand how activity level and nutrition can affect the amount of insulin they need. Those already on stable insulin therapies and doses may be reluctant to switch to alternative regimens unless it offers better control than their current therapy.
- **Patients with early-stage nephropathy or neuropathy** often lack concern because their symptoms are minimal. Education is needed about early intervention to slow progression and to “stay the course” once enrolled in a study because there may be no tangible benefits.
- **Patients needed to complete cardiovascular outcomes trials** have complex healthcare needs. They are likely to be motivated by access to specialized care and medications (including background medications) over an extended period of time. Equally, they can become easily de-motivated to continue their participation because it is often unlikely that their conditions improve.

Generally, what motivates a diabetes patient to join a study is likely to remain their primary motivation to stay in the study. For example, it may be straightforward to attract and maintain the motivation of a diabetic who is failing on metformin by providing free add-on therapy and additional high-quality treatment in a three- to six-month efficacy study. However, engaging and maintaining the motivation of a chronically sick patient, with multiple comorbidities, over a four- to five-year outcomes trial is much more challenging. A trusting relationship between an investigator and the patient is fundamental to recruitment and retention, but in studies with complex patients and longer timelines, we may need to support our sites with additional tools to maintain motivation and processes to closely manage retention.
It is important to note that these characteristics have been generalized to illustrate evolution of the diabetes patient and the need to fully understand the patient population. Actual quality, availability and cost of healthcare and diabetes medications vary significantly across the globe. These differences should be identified during feasibility studies to assess the potential impact on recruitment and retention at the country level.

Keep the protocol and informed consent form patient-centered and “fit for purpose”
Reducing barriers to enrollment and the likelihood of dropout requires that our patients’ needs and motivations remain the focal point. Whenever possible, the protocol should be designed with consideration for what patients will tolerate beyond the standard of care. A fit-for-purpose protocol utilizes a reasonable frequency of fasted blood tests, fair clinical site visit schedule, minimal pharmacokinetic or genomic sampling, and relatively few cognitive/psychometric tests. It should be “smart” with its handling of withdrawals, allowing multiple, temporary breaks from medication and, if treatment is withdrawn, proposing a clear, low-burden assessment strategy. From a retention perspective, the protocol should consider all treatment withdrawals as temporary – allowing restarts – and should clearly differentiate between withdrawal from the investigational product, refusal for further study assessments and withdrawal of consent.

Because every protocol has a unique set of challenges, it is important to proactively address those that may become barriers to enrollment and retention. The informed consent form (ICF) should be designed to help sites overcome barriers with education to facilitate understanding of the study design, emphasize their responsibilities as a patient, and explain follow-up processes to protect their safety.

The ICF should respect patient rights while emphasizing the following points.

- Commitment to participate and maintain compliance
- Importance of completing the study for patient safety and study outcomes
- Clear differentiation between discontinuation of treatment and withdrawal from the study
- Consent for contact with family members or doctors in the event of lost contact
- Consent for third-party, direct-to-patient contact in the event of lost contact

To streamline the consenting process and reduce the risk of error, check boxes and signatures should be kept to a minimum and “opt in” should be the default rather than agreement being optional.

Set expectations for 100% retention
Investigator meetings provide the ideal opportunity to set expectations among investigators, site staff and clinical research associates (CRA) that outcomes must be collected for all participants. To achieve this goal, the agenda must focus on the regulatory requirements for complete data collection, site responsibilities, tools to assist and processes to closely monitor and respond to retention issues.

Some best practices are outlined below.

- Convey clear and consistent messaging. An enrolled patient who does not complete follow-up is a greater threat to the integrity of an outcomes study than a patient never enrolled. Patients that become lost to follow-up can jeopardize their own safety and that of other study participants and future patients treated with the investigational product. Enrolling the right patients who will be compliant and complete the study is ultimately each site’s responsibility.

- Clearly outline expectations for patient retention, including:
  - Definitions of “retention” from the protocol and ICF;
  - What to do and how to report study drug interruptions, withdrawal of consents and lost to follow-up via process diagrams;

Because every protocol has a unique set of challenges, it is important to proactively address those that may become barriers to enrollment and retention.

As a measure of the success of these approaches, three recent Quintiles outcomes studies have delivered impressive and improving results for patient retention.

- Cardiovascular MACE Endpoint Study (closed in 2013) involved more than 20,000 patients, with only a single patient lost to follow up
- A Venous Thrombo-Emboli Endpoint Study (closed in 2013) involved more than 8,000 patients, with only 0.13% LTFU and 0.81% withdrawn consent
- An ACS MACE Endpoint Study (closed 2012) involved more than 9,000 patients with a study duration of 30 months, and collected data on 99.8% of all patients
– Instructions for identifying patients who are at risk to being lost; and
– Detailed instructions for how to track all patients through a clinical study.

• Allow time for breakout sessions with roundtable discussions facilitated by the local CRAs to discuss protocol challenges and practice with recruitment and retention tools, including the ICF.

• Train investigators to use the ICF to gain commitment from their patients. The consenting process should reinforce trust between investigators and patients through education about the study and expectations for compliance and completion. This is the time to identify and address individual barriers to enrollment, such as lack of transportation, inability to take off from work to attend appointments, or need for childcare. These issues may ultimately become reasons for noncompliance and dropout and should be addressed with retention tools during consent.

Use “site intelligence” to provide sites with preferred recruitment and retention tools
Site toolkits should be developed to support enrollment of the right patients, as well as reduce the risk of delays and non-compliance. Preferences for recruitment tools vary by region and country based on what is allowed by the regulatory authorities and what is culturally acceptable or preferable to investigators and their patients.

Anticipate the need to supplement recruitment to prevent enrollment delays
Less than 50% of sites globally claim to have adequate patient numbers to enroll diabetes trials, according to a 2012 Quintiles survey. If timelines are critical, study teams need to anticipate if sites will be able to meet enrollment targets with patients from their own databases. If not, plan in advance with approved recruitment tools to supplement recruitment via physician referrals, advertising and/or patient advocacy groups to prevent costly delays. Identify countries where recruitment can be supplemented via site-driven activities and/or central campaigns. This requires that regulatory authorities allow direct-to-patient outreach and this practice is culturally appropriate to both physicians and patients.

Having site intelligence allows us to answer these questions and provide them with appropriate tools that complement local recruitment practices. Figure 1, below, shows preferences at the regional level regarding the most effective methods to supplement recruitment.

Figure 1 Most effective recruitment methods: Quintiles diabetes trial sites

<table>
<thead>
<tr>
<th>Region</th>
<th>Adequate Patient Numbers</th>
<th>Physician Referrals</th>
<th>Advertising</th>
<th>Patient advocacy groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe/Middle East/Africa</td>
<td>60%</td>
<td>40%</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>USA/Canada</td>
<td>80%</td>
<td>60%</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>60%</td>
<td>40%</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>Latin America</td>
<td>80%</td>
<td>60%</td>
<td>40%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Provide tools that complement local recruitment practices
Across regions, investigators report that educational brochures and consent tools are most effective, while posters and other promotional tools are needed to raise awareness in the United States. Site intelligence from over 2,000 diabetes investigators regarding the “most effective recruitment tools” (shown in Figure 2) provides valuable insight into the development of localized toolkits that complement physicians’ recruitment practices.

Help sites keep their patients compliant and committed to the study
Patient retention tools are widely used by across regions, with contact and reminder services and patient education being the most popular among diabetes investigators.

Figure 2 Most effective recruitment tools: Quintiles diabetes trial sites

<table>
<thead>
<tr>
<th>Tool</th>
<th>Europe/Middle East/Africa</th>
<th>USA/Canada</th>
<th>Asia Pacific</th>
<th>Latin America</th>
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</thead>
<tbody>
<tr>
<td>Letter/postcard</td>
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<td>Email</td>
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<td>Educational brochure</td>
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<td>ICF tool</td>
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<tr>
<td>Poster/flyer</td>
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<tr>
<td>Posting on clinic website</td>
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<tr>
<td>Social media</td>
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<tr>
<td>Not allowed</td>
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<tr>
<td>Not needed</td>
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Figure 3 Most effective retention tools: Quintiles diabetes trial sites

<table>
<thead>
<tr>
<th>Tool</th>
<th>Europe/Middle East/Africa</th>
<th>USA/Canada</th>
<th>Asia Pacific</th>
<th>Latin America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact &amp; reminder services</td>
<td></td>
<td></td>
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<tr>
<td>Patient education</td>
<td></td>
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<tr>
<td>Travel &amp; meal vouchers</td>
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<tr>
<td>Appreciation items</td>
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<tr>
<td>Not allowed</td>
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0% 20% 40% 60% 80% 100%
Patient education is designed to facilitate protocol compliance and may include:

- Study guides with pictorial visit schedules to help patients plan for study visits and remind them to fast and/or to bring unused medication or glucometer devices;
- Visit reminder cards to keep in their wallets; and
- “Healthy living” tip cards or wall calendars to reinforce the long-term benefits of diabetes management and promote healthy lifestyle changes.

To supplement retention efforts by site staff, an innovative communications program that operates in the background through email and SMS text messages may be considered to reinforce compliance and retention. Depending on the demographics of the patient population and duration of the study, a communication programs may include:

- Health-minded messages about diabetes and/or important study information, as well as the final results for “study alumni” (once publicly available);
- Smartphone app enabling patients to keep study information easily accessible; and
- Study community to promote a sense of belonging, keep the study top of mind and build a sense of responsibility and feeling of contribution.

Conclusion

For recruitment and retention in diabetes clinical trials, one size clearly does not fit all. And waiting until there is a problem can have costly consequences. Every protocol has a unique patient population and set of challenges and requires a unique strategy to address them.

Consider use of best practices developed over the course of more than 20 diabetes trials to increase the probability of success.

- Understand patient motivators at each stage of the diabetes journey.
- Design the protocol and informed consent form to be patient-centered and “fit for purpose.”
- Set expectations for 100% retention.
- Use site intelligence to provide sites with preferred recruitment and retention tools.
References


About the authors

**Erica Caveney, M.D.**  
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Erica Caveney, M.D., is vice president and head of the Diabetes Center of Excellence. In this role, she is responsible for the strategy, innovation, design, and implementation of the company’s diabetes work. Dr. Caveney previously managed the cardiovascular and metabolic physician staff. She also served as medical advisor for Phase II – IV endocrinology and diabetes clinical trials and led Quintiles’ Cardiovascular Outcome Center of Excellence. Previously, Dr. Caveney was on the faculty of the Duke University Medical Center in the Endocrinology, Metabolism, and Nutrition division, where she specialized in Type I and Type II diabetes management.

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**Tracy Stewart, MBA**  
**Director, Global Biosimilars Unit, Quintiles**  
In her earlier roles at Quintiles, Tracy specialized in the development of patient recruitment and retention strategies to support the delivery of clinical trials across a full range of therapeutic areas. As a member of Quintiles Diabetes Center of Excellence, she had a particular focus on refining “best practices” in recruitment and retention within this indication. Tracy has been with Quintiles for more than four years and is currently with the Global Biosimilar Unit in a similar capacity. Prior to joining Quintiles, she spent eight years of her career in medical education and four years in hospital administration. Tracy has a master’s degree in business administration from the University of Houston and a bachelor’s degree in graphic design from North Carolina State University.
About the authors

Scott Oakes, Ph.D., PMP  
Director, Clinical Project Management, Quintiles  
Scott has 15 years experience in research and development within the pharmaceutical industry, including eight years managing global diabetes trials within Quintiles Cardiovascular & Metabolic Therapeutic Area. Currently managing a global cardiovascular outcomes mega-trial in diabetic patients, Scott is aware of pressures associated with the timely recruitment of huge patient numbers and considers that the most significant critical success factor for the trial is the need to ensure that 100% of patients are accounted for at study completion, with all potential endpoints collected and adjudicated.

Kimberly Powers  
Sr. Client Engagement Manager, Health Engagement & Communications, Quintiles  
Kimberly joined Quintiles in 2008. In her current role, she is the global recruitment and retention lead for a cardiovascular outcome mega-trial in diabetes. Kimberly works closely with sponsors and clinical project management teams to develop tailored recruitment and retention strategies and leads the implementation by liaising closely with sites and clinical monitors.