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Health Sciences

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WHITE PAPER

Building Risk Assessment and Mitigation into Study Startup

This white paper describes why risk management and assessment are most effective when integrated into clinical trials from the beginning - from the study startup phase - rather than an afterthought addressed once a new product hits the market.

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Executive Summary

Risk-based challenges for study startup, a multi-step process in the initiation of clinical trials, are escalating as studies become more global, and as market pressures to speed new therapies to market intensify.

The growing emphasis on risk-based management, beginning with study startup, is being fueled largely by regulatory agencies, and by an intense desire of the industry to improve study execution. In keeping with the regulatory trend toward identifying and mitigating risk, forward thinking industry leaders have been trading in their Excel spreadsheets in favor of custom-built study startup applications that can automatically trigger workflows as a clinical trial unfolds and provide data analytics. This transition away from Excel and toward technology offers a better risk profile through reporting of real-time data, and better communication with stakeholders.

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Risk Mitigation Pivotal to Starting Clinical Trials

Risk management efforts in drug development have mostly emphasized post-marketing drug safety,[1] but the clinical trials process has its own set of potential risks that can easily derail a company's costly development programs. For study startup, a problematic area of clinical trials, these risks include site selection and patient enrollment issues, budget and contracting delays, logistical problems with timely drug shipments, and regulatory hurdles. Risk-based challenges for this multi-step process are escalating as clinical trials become more global, and as market pressures to speed new therapies to market intensify. As a result, better risk management is critical, and with the advent of purpose-built technologies, it is starting with study startup.

What exactly is risk management? According to the Project Management Institute, risk management is defined as the process of developing options and actions to reduce threats to project objectives.[2] This includes tracking known risks, identifying new ones, performing a risk impact assessment, and evaluating risk process effectiveness throughout the project. Applying this definition to the life sciences sector, the goal is to help stakeholders identify strengths and weaknesses in an upcoming clinical trial, and develop plans for risk mitigation and avoidance. This effort is a key focus of the Metrics Champion Consortium (MCC), an association dedicated to standardizing performance metrics in clinical trials. MCC has developed the Risk Assessment & Mitigation Management Tool, a centralized structure that suggests actions for reducing high priority risks in clinical trials.[3] The associated Risk Management Process quantifies the risk of a potential issue occurring and becoming a serious threat to the well-being of the trial. In addition, to mitigate risks specific to study startup, the MCC member organizations and Oracle Health Sciences are collaborating to define industry benchmark measures for stakeholders looking to accelerate this portion of clinical trials.

Cloud-based technology has emerged as vital to facilitating this critical function, and is replacing the entrenched Excel spreadsheet that has been burdened with tracking risk, a job it was never designed for and cannot perform adequately.

In its place, Oracle Health Sciences has brought to market an end-to-

> **"** Risk-based challenges for study startup are escalating as clinical trials become more global and market pressures to speed new therapies to market intensify."

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end suite of solutions that bring workflow-based processes to study teams (Oracle Health Sciences Activate Cloud Service), help sponsors and contract research organizations (CROs) visualize the data and identify bottlenecks (Oracle Health Sciences Analyze Cloud Service), and provide intelligent site profiling for better site selection (Oracle Health Sciences Select Cloud Service). Using these tools, stakeholders can improve study execution in real time by mitigating challenges that have long plagued study startup.

Drivers of Risk-Based Management

The growing emphasis on risk-based management, beginning with study startup, is being fueled largely by regulatory agencies, and by an intense desire of the industry to improve study execution.[4,5] The regulatory push is coming from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), both of which have released documents on greater acceptance of risk-based methodologies, stating that they should begin from the earliest stages of a clinical trial (Chart1).[6,7] The FDA guidance says that sponsors should be prospective about identifying critical data and processes, and then perform a risk assessment to determine which factors could affect those data.

The EMA Reflection Paper advises establishing priorities and processes during the planning phase to achieve study objectives. Moreover, both regulatory documents comment that in a clinical trial, the degree of risk is predictable, and should be anticipated. This approach aligns with the new Clinical Trials Regulation (CTR) EU No 536/2014, implemented in May 2016, and meant to remove duplication of effort and risk of delays in starting new clinical studies.[8]

In keeping with the regulatory trend toward identifying and mitigating risk, forward thinking industry leaders have been trading in their Excel spreadsheets in favor of custom-built study startup applications that can automatically trigger workflows as a clinical trial unfolds and provide data analytics. This move is part of a larger picture, with research from the Tufts Center for the Study of Drug Development (CSDD) reporting that it takes eight months to move from the pre-visit phase to site initiation.[9] The inefficiencies of Excel contribute to this delay as spreadsheets lack risk- and project management capabilities, house unsecured data, and rely on manual entry of data. This transition away from Excel and toward technology offers a better risk profile through reporting of real-time data, and better communication among stakeholders.[10]

Regulatory Input Encourages Risk Assessment from the Beginning

Food and Drug Administration

Risk-based Monitoring
Sponsors should prospectively identify critical data and processes, then perform a risk assessment to identify and understand the risks that could affect the collection of critical data or the performance of critical processes.

European Medicines Agency
The identification of priorities and potential risks should commence at a very early stage in the preparation of a trial, as part of the basic design process. The concerns with trial and protocol design, design of data collection tools/instruments, the design of the monitoring and data management strategies and plans… Risk assessment and mitigation plans should be appropriately disseminated within the organization.

Chart 1

Source: European Medicines Agency, 2013;
Food and Drug Administration, 2013

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Moving to Purpose-Built Applications

Oracle Health Sciences offers an end-to-end suite of purpose built applications providing an array of information critical to an improved study startup process. This includes highlighting the status of protocol amendments, regulatory documents, and budget and contract documents (goBalto Activate); data visualization and easy identification of bottlenecks (goBalto Analyze); and facilitating the selection, feasibility and activation of performing sites (goBalto Select). These solutions are playing an expanding role as research suggests it is the responsibility of CROs and sponsors to implement state-of-the art technologies to better execute study startup tasks, such as communication among stakeholders, distribution of questionnaires to investigators, and generating reports.[11] These tools help deliver real-time updates while increasing transparency, track study startup milestones in real-time, assign risk triggers with milestone re-projections, and automatically trigger workflows to begin as others are completed. These functions are essential for minimizing risk.

About goBalto Activate

Activate is revolutionizing how stakeholders collect and handle the massive volumes of data generated by study startup activities. It integrates data from other cloud-based solutions, such as electronic data capture (EDC), the clinical trial management system (CTMS), and the electronic trial master file, and offers seamless sharing and visibility of study startup documents in real-time across the globe. This integration is possible through the use of an application program interface, which optimizes the flow of data among various integrated components.

Accessed through a dashboard, goBalto Activate is workflow-based, allowing study teams to discover meaningful patterns in the data for tasks such as status of packages for the institutional review board (IRB), patient enrollment success, and receipt of study drug. Risk can be continuously tracked and mitigation strategies can be adapted much earlier in the decision-making cycle due to multiple features (Chart 2).

A few are profiled here:

- **Manages Alerts**

goBalto Activate features an Activities List, which shows which activities are assigned to which individuals. Stakeholders can filter alerts so team members will only see alerts for their specific activities, advising them of the due date, and only when they are the individuals assigned to the site or country associated with those alerts.

Real-time alerts help decision makers intervene immediately or before a major setback has happened, instead of after the fact. This is crucial, since in conventional study startup, intervention typically takes place after an issue has occurred, when it is too late to proactively avoid the problem.

Key Benefits of goBalto Activate

- **Manages alerts**
- **Manages study team members**
- **Manages milestones**
- **Views of global study status**
- **Can access study data anytime, anywhere**
- **Drives data-based business decisions**
- **Improves collaboration with sites**
- **Exchanges documents securely**
- **Consolidates information in one place**
- **Predicts study progress more accurately**
- **Avoids redundant processes**

Chart 2

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- **Manages Study Team Members**

goBalto Activate allows stakeholders to assign team members to more than one study and to the role each team member is to play within each study. This permits members to view information only for those involved with a particular study, clearly defining what is expected of each member. For example, one individual might be given the role of managing all regulatory documents for an array of studies. That person can receive alerts, notifying them that certain documents need attention. This approach may increase the likelihood of compliance, and lower the risk that specific timelines for regulatory submissions will be missed or that documents will be improperly completed.

- **Manages Milestones**

Stakeholders can configure goBalto Activate to track certain country and site milestones, which appear at the top of each country and site details page. This ensures that members of the study team see and track the same milestones. There are three types of dates for each milestone (Figure 1):

- Baseline - The date projected for completion of the milestone. Once entered, this date cannot be changed.

- Planned - A re-projected date for the milestone. The reason for the change appears on the Timeline Change History and Critical Path Tracking reports.

- Actual - Shows when the milestone was actually completed and goBalto Activate automatically enters the date on the study timeline. During configuration, the study team specifies which activity triggers completion of the milestone.
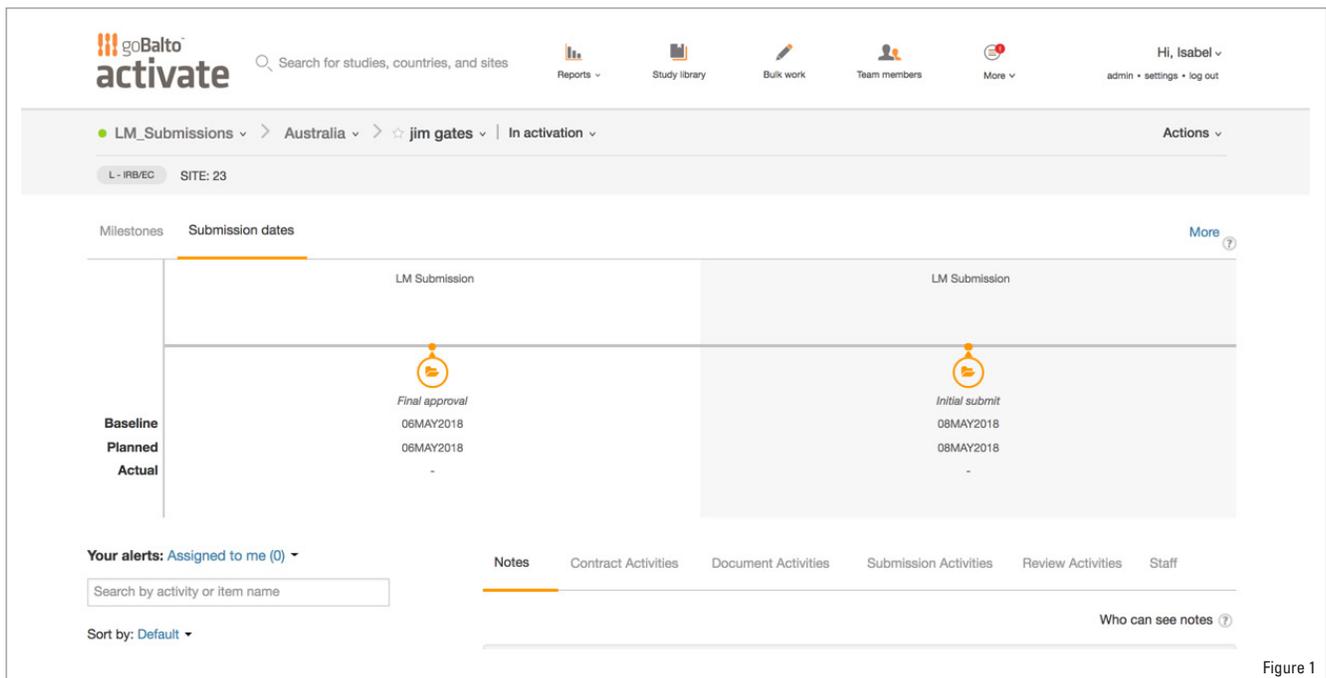
> **"** Real-time alerts help decision makers intervene immediatlely or before a major setback has happened, instead of after the fact."

Figure 1

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This level of careful management of milestone serves to reduce the risk that milestones will not be met in a timely manner as there is transparency and communication among stakeholders to plan and set the necessary milestone dates.

Overall, to minimize risk and for purposes of compliance, goBalto Activate's smart workflows standardize processes and guide study teams to complete and track the specific documents and tasks required for any site, country, or study based on regulatory requirements and a company's standard operating procedures (SOPs).

This degree of functionality allows the project management team to drive discussions and decision-making on bottlenecks impacting site activation. Significantly, time is not wasted charting data and compiling status updates, a practice that is typical with older methods, such as Excel.

About goBalto Analyze

goBalto Analyze is a reporting tool that creates reports using data analytics to aid stakeholders in visualizing study status of multiple studies as part of a risk-based study startup strategy. This functionality uses data from goBalto Activate and goBalto Select and is accessed through a dashboard. goBalto Analyze helps identify bottlenecks across protocols by evaluating completion of documents on the critical path, such as site contracts or an informed consent form, tracks cycle times across individual sites (Chart 3), and shows sites activated per study (Figure 2). If a report signals a trend toward longer completion time for contracts, for example, the CRO can act quickly to steer lagging sites back on track, or consider adding new sites. This data-driven approach enables stakeholders to be proactive in identifying and resolving risk in real-time by instantly viewing status, and quantifying the clinical research team's performance. This capability is a significant improvement over the time-consuming method of assembling data manually from multiple systems or spreadsheets, rendering those data too old to reliably convey study startup status.

Standard reports supplemented with ad hoc reports can be shared with team members via a simple click and an e-mail address to authorize those team members to see a dashboard of the reports.

Key Benefits of goBalto Analyze

- **Helps identify bottlenecks**
- **Track real-time metrics such as cycle time, and key performance indicators, keeping study startup on track and within budget**
- **Proactively supports risk identification by creating data visualizations across multiple trials and a partners**
- **Easily shares standard and ad hoc reports among team members, replacing manual preparation of routine reports**
- **Provides actionable status information**
- **Quantifies the clinical research team's performance**
- **Expedites collaboration with global study teams**
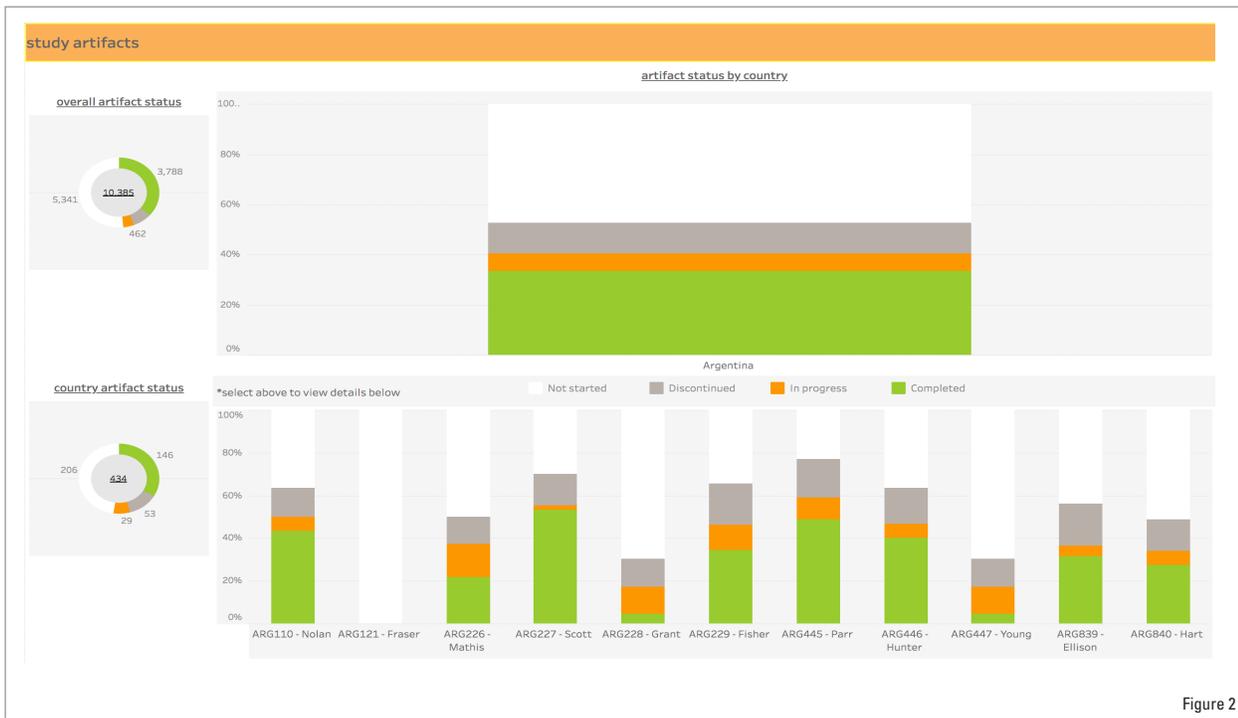- **Encourages high transparency partnerships**

Chart 3

study artifacts

overall artifact status

artifact status by country

country artifact status

*select above to view details below

Not started   Discontinued   In progress   Completed

Argentina

ARG110 - Nolan   ARG121 - Fraser   ARG226 - Mathis   ARG227 - Scott   ARG228 - Grant   ARG229 - Fisher   ARG445 - Parr   ARG446 - Hunter   ARG447 - Young   ARG839 - Ellison   ARG840 - Hart

Figure 2

About goBalto Select

Poorly performing investigative sites have long been an intractable challenge for the clinical trials industry. Half of sites under-enroll, 11% of sites fail to enroll a single patient, and a mere 13% exceed their enrollment target.[12] Phase II-IV study timelines are often extended to almost twice their original length to achieve enrollment goals. These statistics have remain unchanged over the years, as nearly 50% of clinical trials are behind schedule, with slow patient enrollment generally cited as the top reason.[13]

Much of this scenario reflects the fact that site selection remains a manual process, lacking in verification, and resulting in the selection of too many non-enrolling and under-enrolling sites. The growing impact of cloud-based technology notwithstanding, challenges associated with disparate data sets from multiple systems, such as EDC and the CTMS, and a lack of institutional memory continue to plague successful site selection. Beth Harper, President of Clinical Performance Partners, comments on this continual reliance on manual methods. "Despite the plethora of data and information available to us, evidence-based site selection processes still seem to elude us as an industry. Perhaps it is a matter of information overload or inability to integrate the data from multiple sources, but in my experience, teams continue to rely on archaic tools and subjective criteria for selecting sites, only to find a significant number of sites failing to enroll," she remarks.

Given this reality, sponsors and CROs are embracing goBalto Select, a workspace that uses a data-driven approach to intelligent site selection (Chart 4).

Key Benefits of goBalto Select

- **Automates site identification, feasibility and selection processes**

- **Reduces site selection risks**

- **Profiles patient populations to design and tune protocols**

- **Analyzes patient-to-site proximity and select most appropriate sites**

- **Provides built-in reports into start-up time, patient retention, and quality**

- **Expedites collaboration with global study teams**

- **Drives data-based business decisions and customizes data presentation**

- **Enables access to site selection data anytime, anywhere**

Chart 4

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This purpose-built tool facilitates site selection by using an algorithm to weigh data sources so a complete target site profile can be created (Figure 3). The weighted score is tailored to the study protocol and organizational priorities, and is composed of study fit (i.e., site feasibility), site performance (i.e., study startup metrics), and experience (i.e., site, investigator).

This technology mitigates risk factors for recruitment and retention by finding the optimum alignment of top-performing sites with substantial patient databases, and quickly assessing which sites have performed best in similar studies. To aid in this effort, goBalto Select has built-in reports that give insight into start-up time, patient retention, and quality.
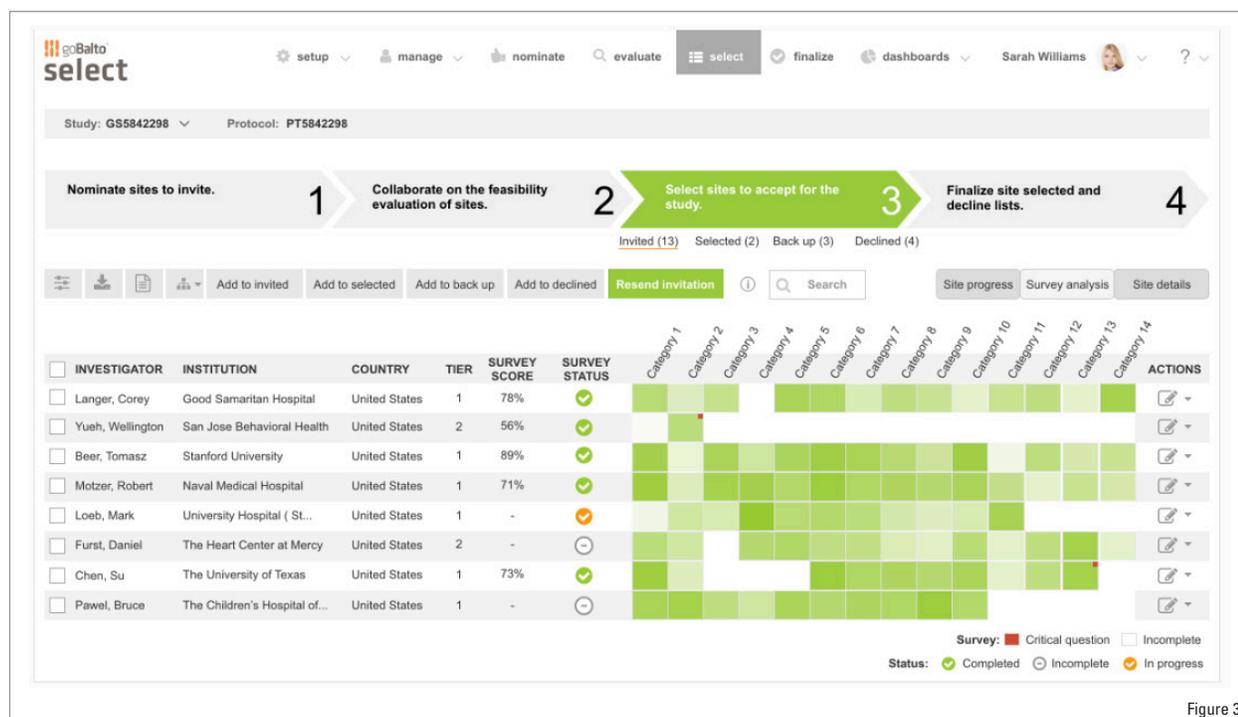

Figure 3

Better Risk Management for Study Startup

There are multiple steps tied to study startup, and without tools designed for risk management planning, each has potential for causing delays, and possibly jeopardizing the study. To mitigate this situation, an end-to-end suite of purpose-built study startup solutions from site feasibility assessment and selection through to activation provides real-time management capabilities and transparency. Contributing to this effort are data-driven analytics, which are a critical improvement over traditional manual processes for making better and faster decisions. Stakeholders can view elements in real time related to site performance, such as site selection, patient enrollment and retention, and critical cycle-time metrics, and take as-needed corrective action. This degree of process improvement is **key to keeping studies on track and within budget, and ultimately speeding new therapies to patients.**

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