Optimal Data Analysis in Medical Device Trials

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Introduction

The United States is the acknowledged world leader in medical devices and diagnostic products. As the largest medical device market in the world, representing around $110 billion, The U.S. market is expected to reach $133 billion by 2016. In 2012, the U.S held about 38 percent of the global medical device market.

The more than 6,500 medical device companies in the U.S., mostly small and medium size enterprises, are highly regarded for their innovation and advanced technology. However, while the market is expanding, the U.S. lead is narrowing, partly due to the more stringent regulatory environment. The number of device approvals by the U.S. Food and Drug Administration (FDA) has increased by 52 percent over the past decade.

With increasingly more rigorous regulatory requirements for medical devices and diagnostics and a rapidly growing marketplace, the industry needs more efficient ways to manage the growing amount of data amassed in clinical trials. Greater adoption of more-advanced data management technology will improve trial efficiency and foster improved collaboration between device researchers and the medical community to speed new products to market.

This paper explains the differences in medical devices and drugs in terms of clinical development, the regulatory pathway, and procedures for analyzing medical device data. The paper also covers challenges for medical device development and data analysis, and includes a case study of how a medical device company resolved its data management issues.
Differences in Biopharmaceutical Products and Medical Devices

The FDA defines a medical device as an instrument, apparatus, implant, machine, contrivance, in vitro reagent, or other similar or related article which is:

- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.⁴

Unlike drugs, medical devices are generally based on biomedical engineering, comprise a wide cross-section of technologies, and typically have a short product life cycle, often only a few years, due to a high rate of innovation. Whereas drugs are generally discovered, devices are invented, and can be changed during clinical development. Once on the market, a newer, improved version may already be in development.
Clinical Development and Regulatory Pathway

Medical devices also differ from pharmaceutical products in their clinical development and regulatory guidelines.

Not all devices require a clinical trial for approval -- the determination depends on the device classification and risk level. The FDA categorizes medical devices into three classes based on the risk to the user, the intended use of the device and indications for use -- broadly, the level of control necessary to ensure safety and effectiveness.

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Examples</th>
<th>Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Minimal Risk</td>
<td>Crutches, elastic bandages, tongue depressors</td>
<td>No clinical trial required</td>
</tr>
<tr>
<td>Class II</td>
<td>Intermediate Risk</td>
<td>Sutures, inflatable blood pressure cuffs, infusion pumps</td>
<td>May require clinical trial</td>
</tr>
<tr>
<td>Class III</td>
<td>Substantial Risk</td>
<td>Implantable pacemakers, replacement heart valves, blood vessel stents</td>
<td>Requires clinical trial Pre-market approval needed</td>
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</table>

The U.S. medical device industry is highly regulated, with regulations growing increasingly stringent. Medical devices are approved through the Premarket Approval (PMA) application process (for higher-risk products), and a single confirmatory study is often sufficient for approval. They are submitted for approval to the Center for Devices and Radiologic Health (CDRH) or Center for
Biologics Evaluation and Research (CBER) of the FDA. If a device needs a confirmatory study to support a PMA, it relies on historical controls showing the device is safe and effective.

In general, Class I and II devices can be approved by a 510(k) submission, while a Class III device requires a PMA submission, the most stringent type of device marketing application for medical devices. IDE (Investigational Device Exemption) approval allows a device to be used in support of a 510(k) or PMA submission. A 510(k) submission usually compares a new device with a predicate device (legally marketed device) to demonstrate substantial equivalence. PMA submissions are used to demonstrate to the FDA that a new or modified device is safe and effective. Many Class II and most Class III devices require Premarket Notification 510(k), comprising submission of clinical data to support claims.

Although there are no consistent data standards or requirements for medical device submissions and paper is the primary means of submissions, the CDRH announced in October 2012 that electronic standards such as those developed by the Clinical Data Interchange Standards Consortium (CDISC) will soon be required. Sponsors will then have 24 months to comply with the standards, and develop the expertise and infrastructure to utilize the standards to more fully understand and characterize the efficacy and safety of a medical product. The CDISC standards can yield a significant return on investment, and can potentially:

- Reduce the time/cost of study start-up by 70-90%
- Reduce the time/cost of study conduct by 40%
- Reduce the time/cost of analysis and reporting by 50%
- Reduce overall time/cost by 60%
Device and diagnostic trials tend to have fewer sites and subjects than drug trials, and are generally much shorter and less costly, requiring fewer resources. Only larger device companies need significant resources to manage large clinical programs. Many U.S. device trials have a data safety management board (DSMB) and clinical events committees (CECs) similar to drug trial oversight groups. Device sponsors also follow ISO requirements.

Medical device clinical trials focus on prototype development, using feasibility, pilot and pivotal study models. Pilot studies may involve a smaller number of patients with the disease being studied, while pivotal studies include a larger sample size of patients with the disease. Often pilot study data are eventually combined with pivotal study data for analysis. Preclinical and pilot studies focus on data such as how a user, perhaps a surgeon, works with the device as well as the device performance. Designs can be refined or improved as development progresses.

Single-blind trials are possible for some device types, but double-blind trials are uncommon and head-to-head trials with competitors are difficult. Premarket trials for device safety are simpler and compliance is easier to measure compared to drug trials. To determine the safety of leads, single-arm trials with objective performance criteria are used. Post-market device trials are important in providing clinical evidence for physicians, payers and patients.⁶
Two types of studies for medical devices and diagnostics are reproducibility and clinical utility. Reproducibility studies aim to demonstrate the accuracy and precision of a device. For example, a researcher may want to determine how well the assay performs at multiple testing sites with multiple lab operators testing multiple lots of the assay. Statistical measures such as coefficient of variation and precision analyses can be used to determine reproducibility.\(^7\)

The purpose of a clinical utility study is to demonstrate the real-life use of a device in clinical practice. A diagnostic assay may be used to screen subjects for a certain condition in a clinical trial or to monitor subjects given either a therapeutic or placebo. Typical analyses might include measures of sensitivity, specificity, positive and negative predictive value.\(^7\)
A primary concern when conducting a medical device clinical trial is missing data caused by patients who withdraw before study completion for various reasons. Missing data can result in biased treatment comparisons and cause complication in the statistical analysis of clinical data, impacting the interpretation of study results.

Tipping-point analysis is a common method used to handle missing data in device clinical trials and assess its impact.

Tipping points are outcomes that result in a change of study conclusion. The outcomes can be conveyed to clinical reviewers to determine if they are implausibly unfavorable. The analysis aids clinical reviewers in judging the treatment effect in the study. A tipping-point analysis replaces the missing value with some values so that the resulting p value of the hypothesis is equal to or larger than a pre-specified significance level. These outcomes, or tipping points, may convey some questionably poor outcomes.
Bayesian Statistics

Bayesian statistics is an approach for learning from evidence as it accumulates, formally combining prior information with current information on a point of interest. Inferences about safety and effectiveness are being updated each time new data become available.\(^9\)

The Bayesian method may make the clinical trial more efficient and possibly more ethical. Data collected on clinical trials of earlier versions of a medical device can provide valuable information about a new version, and may result in smaller, shorter, less burdensome trials. However, this requires collecting information from preceding related trials or eliciting information from experts and a great deal of communication between the sponsor and regulatory agency.\(^10\)

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Adaptive Design

Adaptive designs use accumulating data from a trial to modify aspects of the study according to a pre-specified plan without undermining the validity and integrity of the trial. The most common adjustment is stopping the trial early. Other applications are the ability to change the sample size, study duration, endpoint selection, patient population, number of treatments and interim analysis. These designs require extensive pre-planning and adequate technology for design, implementation and intensive computing.
Benefits of Improved Technology

As with drug development, improving efficiency and keeping development costs low are critical in the development of medical devices and diagnostics. Particularly for Class 3 and many Class 2 devices, clinical development is the most costly aspect of getting products to market. And with a short lifecycle for devices and diagnostics, speed to market is important for a favorable return on investment.

Since clinical trial managers work closely with medical professionals for the development devices and diagnostics, particularly Class 3 devices, real-time access to data is essential for effective collaboration and decision-making. Fast access to clean trial data is also needed for adaptive and Bayesian clinical trials. Supported by adequate information technology, adaptive trials are efficient, repeatable processes.

Advanced data management technology streamlines the work of clinical researchers by tracking all the clinical and operational data for each participant in a single integrated system. This can significantly improve clinical trial performance and speed, and reduce costs.
However, many device sponsors continue to utilize traditional practices, such as Excel spreadsheets. They are slow to fully embrace a technology-powered data management approach. In traditional data management systems, data from many different repositories are stored in disparate silos, making the system extremely complex. Users receive disconnected reports that do not provide a comprehensive, holistic view of trial events, trends and problem areas. Data-system users need a more effective, efficient solution -- an integrated technology system that provides real-time data, an audit trail, continuous data analysis, and an overall view of progress.

Efficiently gaining critical insights for the management of product development, quickly identifying issues and communicating alerts are essential for clinical and operational effectiveness, desirable outcomes, and favorably competing in today’s marketplace. Sponsors and contract research organizations (CROs) must harness the most current, least complex technologies to achieve the efficiency, accuracy, data integrity, and streamlined development they need to operate effectively and remain competitive. Both CROs and sponsors will significantly benefit from real-time, multi-data-source access to trial data in any system -- a single, on-demand source that provides full auditability. Data scientists must be empowered with a self-service data discovery analytics environment that brings together data from all data sources, with no need for data aggregation.

For both sponsors and CROs, building an analytics-focused culture supported by integrated cloud technology is the solution that simplifies a company’s infrastructure, workflows, and process; improves productivity and decision-making; and facilitates collaboration, data visibility, and improved communication. Cloud technology enables the production of reports for clinical study teams based on real-time data from multiple data sources.
Case History: Transforming Clinical Data Management in the Cloud

**Issue.** The clinical systems and programming group at a leading multi-billion dollar global medical device company struggled to produce reports for clinical data users. Reports with Medidata Rave were not flexible enough to filter enrollment information. Reports on risk scores by site, clinical events committee (CEC) adjudication data, data cleaning and enrollment progress were difficult to assemble. Data review and report generation were not real-time and SAS was unusable by those without SAS experience. Data from their system had to be extracted, re-formatted and built from scratch each time a new request was received. The technology team was burdened by report generation.

**Solution.** When the company deployed Comprehend’s next generation clinical trials reporting solution, they were able to quickly obtain insights regarding clinical trial enrollment, data cleaning, and CEC adjudication data. With the cloud-based, software-as-a-service (SaaS) technology, data from multiple sources are combined in the cloud and key insights identified quickly for team review. The data sources still include Medidata Rave for EDC data, and CEC adjudication data is tied to adverse event data in the original system.

The company now has clear visibility into the mean STS by site, and can see the CEC adjudication status, count of CEC events by endpoint, and average days between procedures and events. The data cleaning status is transparent, showing the number of days queries remained open.
Enrollment visibility is greatly enhanced with a clear picture into overall cumulative enrollment and enrollment by site, assignment, approach and cadence. The technology enables easy production of reports based on real-time data from multiple data sources. Information is provided to the study teams on data cleaning status, data management processes, key milestones achieved during studies, and information for the safety team to track adverse events. Information is also provided to the finance team to ensure proper payments to clinical sites.

The system quickly produces easy-to-view reports on demand, allowing users to get a base dashboard and view data on their own terms. End users can manipulate the data on demand, rather than request multiple reports to be run, saving valuable time and resources.

The new system eliminated the need to manually combine data from multiple sources and install a costly, complex clinical data warehouse. Since the system is SaaS-based, no capital expense or on-site installation was required and set-up was fast.

**Conclusion**

The medical device and diagnostic industry is rapidly growing and becoming increasingly important in the healthcare field. While the regulatory environment is becoming more stringent, the device industry will be fueled by scientific progress, advances in technology and engineering, along with improved, more streamlined methods for conducting clinical trials. To enable the efficient management of medical device clinical trial data and speed health-enhancing products to market, sponsors need improved technology that harnesses the power of real-time data and insights.
References


