The Role of Continuous Physiologic Monitoring in Preclinical Medical Device Studies

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NAMSA Whitepaper Issue 03/2014
Introduction

Preclinical studies are conducted to develop and assess new medical device technologies. Regulatory bodies like the FDA may require such testing in order to initially assess the potential safety and efficacy of new devices. The data obtained from preclinical studies is extensive and includes scientific and medical observations as well as the collection and assessment of relevant physiologic data. These data may be collected at selected time intervals or continuously to provide added insight, such as trends and time course, to a physiologic response. Data collected from continuous monitoring tends to be less biased and offers less methodologic “noise” because often the sensors utilized are implanted and the test subjects have accommodated to their placement. Sampling methodologies for intermittent testing, on the other hand, often require device and test subject handling, which can introduce stress, unwanted physiologic responses, and signal noise.

Sensor technologies today allow for continuous monitoring of a vast array of physiologic parameters. Importantly, software, database, and data management technologies have been developed to collect and process the large amounts of resulting data, which provide valuable feedback for researchers and engineers involved with developing medical technologies. These software and data management tools have been developed according to Good Laboratory Practice quality standards and as such provide data suitable for regulatory review.

The safety of medical products should be paramount in any determination of whether a product is to be marketed. The FDA is charged with evaluating safety and effectiveness as part of its mission to ensure public health and safety while fostering access to new and innovative therapies. The current FDA climate requires significant data and scientific evidence to support approval for commercialization of new device on the US market.

The enhanced insights that continuous monitoring offers for evaluating pathophysiologic responses to medical interventions offers the potential to speed development of new therapies and provide patients with greatly needed medical innovations.

Objectives of Medical Device Preclinical Studies

Safety Studies are conducted to assess the biologic safety and clinical performance of medical devices, including their configurations and materials. Medical device safety evaluations are typically focused on achieving the following objectives:

1. Identify undesirable physiologic responses to an investigational medical device that may have relevance to its safety in humans.
2. Evaluate the incidence and characteristics of adverse events relating to an investigational medical device.
3. Describe the local and systemic gross histologic and toxicologic responses to an investigational medical device use.
4. Monitor and describe activities of daily living and the impact of investigational medical devices on these activities.
To accomplish these objectives, medical device safety studies typically focus on the physiologic response to device functionality and the response of vital organ systems such as the central nervous system (CNS), cardiovascular system, and respiratory system.

Robust data and acquisition methodology can increase the quality of data submitted for regulatory review. Telemetry is often the preferred method for acquiring data from research test subjects for safety studies. Proven health benefits and high-quality data make wireless telemetry the first choice among researchers for chronic physiologic monitoring in a variety of test subjects.

**Telemetry**

Telemetry uses wireless technology to sense and acquire physiologic parameters. Sensor implants are designed to monitor and collect data from conscious, freely moving laboratory test subjects, providing stress-free data collection while eliminating the risk of percutaneous infections.

Data Sciences International (DSI) offers several products to help researchers monitor one or more physiologic signals from a single test subject. Several different product combinations exist that can measure different parameters, including pressure, biopotentials, temperature, and test subject activity. Table 1 outlines the different signal types available for each of the physiologic parameters. DSI devices are capable of measuring multiple parameters simultaneously.

**Table 1. Physiologic Signals and Types**

<table>
<thead>
<tr>
<th>PHYSIOLOGIC SIGNAL</th>
<th>SIGNAL TYPES</th>
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<tbody>
<tr>
<td>Pressure</td>
<td>Arterial, left ventricular, ocular, uterine, penile, bladder, pleural</td>
</tr>
<tr>
<td>Biopotential</td>
<td>Electrocardiogram (ECG), electroencephalogram (EEG), electromyogram (EMG)</td>
</tr>
<tr>
<td>Temperature</td>
<td>Body temperature</td>
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<tr>
<td>Activity</td>
<td>Activity</td>
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**Body System Telemetry**

_Central Nervous System Studies_

CNS studies evaluate effect on:
- Motor activity and behavior
- Coordination and sensory/motor reflex responses
- Body temperature

Neuroscience explores how the nervous system develops, is organized, and functions to generate behavior. Tools can be used to explore the anatomy, physiology, biochemistry, and/or molecular biology of nerves and nervous tissue.

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Nerve cells, or neurons, are organized into neural circuits that receive, process, and transmit electrical (and chemical) signals. Electrophysiologic recordings can monitor the electrical activity of these circuits by placing electrodes near or within the nerve cells of interest. These recordings include:

- Individual neuron action potentials (spikes)
- Low-frequency field potential (LFP)
- Electroencephalogram (EEG), or brain waves
- Electromyogram (EMG), or muscle activity
- Electrooculogram (EOG), or eye movements
- Peripheral sympathetic nerve activity (SNA)
- Activity/sedation
- Behavior

By monitoring the electrical activity of neural circuits, we can obtain a great deal of information that helps us learn more about nervous system function, which can provide information to help prevent or cure numerous neurologic and psychiatric disorders, including sleep conditions, seizures or epilepsy, traumatic brain injury, behavior disorders, neurodegenerative diseases, and more.

**Cardiovascular Studies**
Cardiovascular studies evaluate effect on:

- Blood pressure
- Heart rate
- Electrocardiogram (ECG)

Cardiovascular functionality can be affected by many conditions and diseases (eg, arrhythmias, high blood pressure, etc), and monitoring cardiovascular parameters such as hemodynamics and biopotentials can give researchers valuable information to help them evaluate potential therapeutic compounds that may address, prevent, or cure cardiovascular diseases.

**Respiratory Studies**
Respiratory studies evaluate effect on:

- Respiratory rate
- Respiratory volume (tidal volume)

The physiologic respiration process is defined as the inhalation and exhalation of gases such as oxygen (O2) and carbon dioxide (CO2) between internal and external environments. In most species, energy is obtained by metabolizing compounds such as carbohydrates and fats through a process that requires respiration. Studying respiration, or the means for the body to exchange gasses such as O2 and CO2 between the atmosphere and the blood, is an important part of metabolic function and can be achieved with a variety of different methods.

Studying the toxicological effects of a compound on a research subject is also critical data for regulatory review and can be assessed using telemetry.
Repeat dose toxicology studies are typically conducted to characterize the structural (physical/pathology-related) effects of a test article following repeated administration. Such studies are intended to identify target organs, exposure/response relationships, and potential reversibility of toxic effects. This information is required as part of the safety assessment supporting the conduct of human clinical trials.

Data Assessment and Combined Studies
In recent years, many researchers have chosen to include 24-hour continuous assessment of functional effects in these studies as a means of providing an improved risk assessment. The functional endpoints most commonly included are those typically collected as part of the core battery of Safety Pharmacology studies (ICH S7A, S7B); especially the cardiovascular endpoints available from ECG and blood pressure measurements.

One advantage of 24-hour continuous assessment of functional endpoints in repeat-dose toxicology studies is the ability to collect better data—data from conscious, free-roaming test subjects that is not confounded by anesthesia or response to human factors. In this manner, the data more closely represent the clinical situation.

Additional advantages of this continuous approach include the ability to provide a more comprehensive assessment of the cumulative effect of a test article on functional endpoints (something not currently required by guidelines) and the opportunity to use test subjects more efficiently, thus supporting the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) initiative.

A final advantage of this approach is that it is sometimes possible to omit the need for a separate safety pharmacology study. This advantage is most commonly specific to the development of new biological entities since they do not allow for a traditional Latin Square safety pharmacology assessment and instead require a parallel dose design.

In all cases, whenever adding a functional assessment into repeat dose toxicology studies it is recommended that the studies have the sensitivity to detect, or more
importantly rule out, unwanted drug effects. As such, nonclinical studies should be as sensitive as possible within the constraints of protecting the welfare of the test subjects and reasonable drug and medical device development costs.

Combining study methodology or “Integrated testing” is quickly becoming a necessity in resource-strained environments requiring more from less. In support of this growing need, continuous monitoring technologies offer other life sciences companies the ability to provide more seamless, cross-functional solutions. The goal is to facilitate the combination of studies that might otherwise be executed independently, thus saving time and money while increasing overall efficiencies. Current examples include the combination of telemetered physiologic data with automated blood sampling, automated infusion, metabolic monitoring, and behavioral monitoring systems. Combining these endpoints provides a more comprehensive picture of the physiologic response to pharmacologic interventions.

The combined evaluation of physiology and behavior allows for a complete and comprehensive preclinical assessment. The combined solution enables simultaneous assessment of behavior and physiologic analysis in freely moving test subjects. Investigating the relationship between physiological and behavioral data can lead to a better understanding of research results through interactions or responses illustrated by synchronized data.

Conclusions: Benefits of Implantable Telemetry

Implantable telemetry products are designed for monitoring and collecting data from conscious, freely moving test subjects of various sizes. Telemetry provides the following benefits:

- Satisfies core battery requirements for studies on CNS, cardiovascular, and respiratory studies
- Allows test subjects to be chronically instrumented and used sequentially as their own controls, or in several studies
  - Eliminates confounding effects of anesthesia
  - Eliminates movement artifact from struggling
  - Stress-free data
- Eliminates exit site infections
- Enhances safety for personnel and test subjects
- Supports test subject welfare and reduces the number of subjects required for medical research.
  - Based on design of safety studies – washout period between studies
  - Telemetry can be used chronically and thus test subjects can be used on multiple studies, reducing the overall number of test subjects used in research
  - Decreases costs for many protocols by reducing the number of test subjects required and maintenance costs
  - Reduces stress, discomfort, manipulation, and handling of test subjects

Implantable telemetry enhances research protocols by minimizing stress and increases throughput by reducing overall study costs. Cost reduction is achieved...
by extending test subject usage across protocols, reducing the number of test subjects required, and freeing staff time by minimizing direct subject involvement through automated data acquisition and analysis.

While sensor technology has existed for many years to support continuous physiologic monitoring, only in fairly recent times have the data management and software packages become available to process this vast amount of data and optimize its usefulness for medical technology researchers. These powerful tools provide trend and response information that was previously unobtainable. The data are collected humanely and continuous monitoring minimizes the number of test subjects required to answer medical research questions. Similar technology is increasingly being utilized to manage human medical patients as well.

RESOURCES
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Ted Gorski, NAMSA Founder

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