

# The heart of cardiac safety monitoring

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**C**oncern over cardiac safety is the most common factor blocking compounds in development from gaining regulatory approval. Those same worries are also often at the forefront when a drug, already available commercially, encounters safety issues and is withdrawn from the market.

The challenge for many researchers in the life sciences industry is how can cardiovascular monitoring measures in clinical trials be improved to better understand the cardiac safety of a drug before approval. Scientists such as Joy Olbertz of MDS Pharma Services are working on new methods in cardiac monitoring to produce some answers. Since 2005, Dr. Olbertz has served as global QT project coordinator at MDS (mdsps.com), which provides services in preclinical and Phase I-IV development for pharmaceutical and biotech companies. She has worked with several teams in launching the MDS Cardiac Safety Center of Excellence, a joint initiative of MDS Phase I and centralized cardiac services. The goal of the cardiac safety center, according to Dr. Olbertz, is to deliver quality electrocardiogram, or ECG, data and appropriate expertise to clients in a timely manner.

Dr. Olbertz says MDS' cardiac safety center was created after it became clear that the International Conference on Harmonization, or ICH, guidance for E14 — titled "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" — would forever change cardiac monitoring in clinical trials. ICH E14, formalized in 2005, marked the first globally harmonized regulatory guidance for assessment of cardiac safety during clinical drug development.

"ICH E14 was produced in response to growing concerns about the cardiac safety of marketed drugs," Dr. Olbertz says. "In fact, the majority of drugs withdrawn from the market in the last decade have been withdrawn due to cardiac safety concerns. ICH E14 describes several additional cardiac monitoring measures now required during drug development. In particular, ICH E14 describes the requirement for a Thorough QT (TQT) trial."

This process, according to Dr. Olbertz, has had a significant impact on Phase I research and has become a critical component of FDA and EMEA submissions. Implementation of the TQT trial increases cardiac monitoring in Phase I studies from one to five electrocardiograms per patient per day to 30 to 40 electrocardiograms per day.

"Cardiac monitoring has not only increased to meet demands for TQT trials, but sponsors request increased monitoring in many other Phase I trials as well in an effort to assess the cardiac safety risk of a drug earlier in development," says Dr. Olbertz.

With an increased cardiac focus from sponsors, CROs such as MDS are faced with additional challenges in complying with ICH E14. One of those, according to Dr. Olbertz, stems from the inherent variability of the QT measurement and the fact that a relatively small change in QT interval duration can have a significant impact on drug development. She says taking

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into account the variability of the QT measurement is important when designing and conducting a Thorough QT trial. In many cases, a large number of participants — usually more than 200 — are enrolled to better the chances of a successful trial.

Helping MDS' efforts in this area, Dr. Olbertz, who obtained a Pharm.D. and Ph.D. from Idaho State University, uses her training as a Lean Sigma green belt to assist clients in meeting the challenges set out in ICH E14.

"The initial focus of my Lean Sigma process improvement project was to improve MDS sites' abilities to produce high-quality ECG data when working with large groups of participants," Dr. Olbertz says. "During this project, every aspect of conduct was reviewed from storage of ECG supplies to minimizing environmental stimuli that may impact data quality. In evaluating clinical conduct of TQT, not only ECGs, but other conduct events such as dosing, vital signs, and blood draws had to be considered. Participant and staff move-



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ments were scrutinized to minimize unnecessary movements between and during all conduct events."

During the MDS project spearheaded by Dr. Olbertz, her team wanted to not only increase the patient group size but also maximize ECG data quality. As a result, major revisions were instituted to MDS' ECG data collection training plans. With ICH E14 raising the expectations for ECG data quality, all related training plans at MDS were modified to ensure those standards were met in all trials.

According to Dr. Olbertz, several error-proofing measures were also put in to place to ensure that increasing the number of participants did not also increase the number of errors. For example, additional methods of participant identification were employed so that conduct associates could easily verify the identity of each participant. To track data quality, an ECG error score was developed that reflects both the number of errors and the severity of errors generated. ECG tracing quality was verified by the involved cardiac core labs in order to ensure quality QT measurements could be obtained from ECG data collected.

Dr. Olbertz says the MDS team has observed up to a 38% reduction in ECG error scores on subsequent trials and positive ECG quality reviews from the involved cardiac core labs. She cited one example in which a lab indicated that out of 19,400 electrocardiograms collected in one trial, only nine were of questionable quality.