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Transforming SAE Life-cycle Management in Clinical Trials – Enabling a Streamlined Business Process through Electronic Systems

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Introduction

The process for managing Serious Adverse Event (SAE) reports within clinical trials entailed paper-/fax-based reporting of SAEs, subsequent cycles of paper-/fax-based communication of queries and responses, and manual reconciliation of key data elements to ensure alignment between clinical trial and safety regulatory reporting streams. With the goal of streamlining these processes, in 2009 Amgen embarked on implementing a "best in class", fully electronic SAE life-cycle management platform between our clinical trials database (CTDB) and safety system. At the outset of this effort, key stakeholders from Safety, Clinical Data Management (CDM), Clinical Study Management, and Information Systems (IS) outlined the following key objectives:

- Eliminate manual data reconciliation between the CTDB and safety database
- Significantly reduce the number of manual safety queries and subsequent follow-up cycles
- Optimise safety case processing productivity
- Enhance risk management through improved data quality, standardisation, and synchronicity
- Significantly reduce duplicate data entry, both at the investigator site and sponsor company

Characteristics of a Streamlined Process

In 2009, Amgen's previous technology investments and business relationships provided the proper environment for capitalising on this effort. Amgen had established an electronic data capture (EDC) system (a fully electronic CTDB) as its primary CTDB with many years of practical experience, and had already set the strategy for solely utilising this platform for all clinical trials. Vendor commitment was also a crucial component to the viability of this effort. But perhaps the most important component was the cross-functional, executive sponsorship established at the inception, coupled with talented, committed professionals in key positions who set the vision and drove the change.

While leveraging technology and standards was at the heart of our strategy, it was very evident that if we were to meet our objectives, transformational process changes must accompany technological enhancements. At a basic level, the concepts were logical. Since over 90 % of data required or meaningful for safety reporting (e.g. SAE, subject, investigation product, medical history, concomitant medications) is captured in the EDC, the strategy entailed extending the adverse event (AE) clinical report form (CRF) to include the additional safety information, package the safety case into E2B (the ICH standard for AE data structure – used to transfer SAE data to regulatory agencies and between companies), and transmit this highly structured data to the safety system. This alone offers significant improvement when compared to a paper-based process. However, when evaluating the SAE life-cycle management process comprehensively, we determined that the following process enhancements would greatly increase the value of this effort:

- Ensure a single, streamlined data entry process (coined eSAE) - critical for site compliance
  - o Leverage the CTDB as the comprehensive source by mapping all applicable safety data
  - o Apply basic data requirements (i.e. minimum data completeness) at the source by systematically ensuring required data is entered prior to transmission
  - o Enable a single, fully electronic process for transitioned studies (studies which started in a paper-based process)
- Ensure all "reconcilable fields" are entered in the EDC and are treated as read-only in the safety system (process-driven synchronisation of reconcilable fields)
- Automate the generation of medically significant safety queries for pre-specified events of interest in the CTDB prior to initial transmission
- Centralise query management by providing safety the ability to query the study sites directly in the CTDB
- Link cases between systems so that follow-up cases will be automatically recognized by the safety system

How Technology Supported the Streamlined Process

Ensure a single, streamlined data entry process – critical for site compliance

Amgen worked closely with a vendor to ensure the tool was equipped with features which enable maximum leverage of clinical data. Firstly, the system provides the capability of mapping various CRF data to E2B tags on a per-study basis. The system manages the hierarchical structure of the E2B standard, allowing for the assignment of a CRF to an E2B node (e.g. adverse event) and also allows for

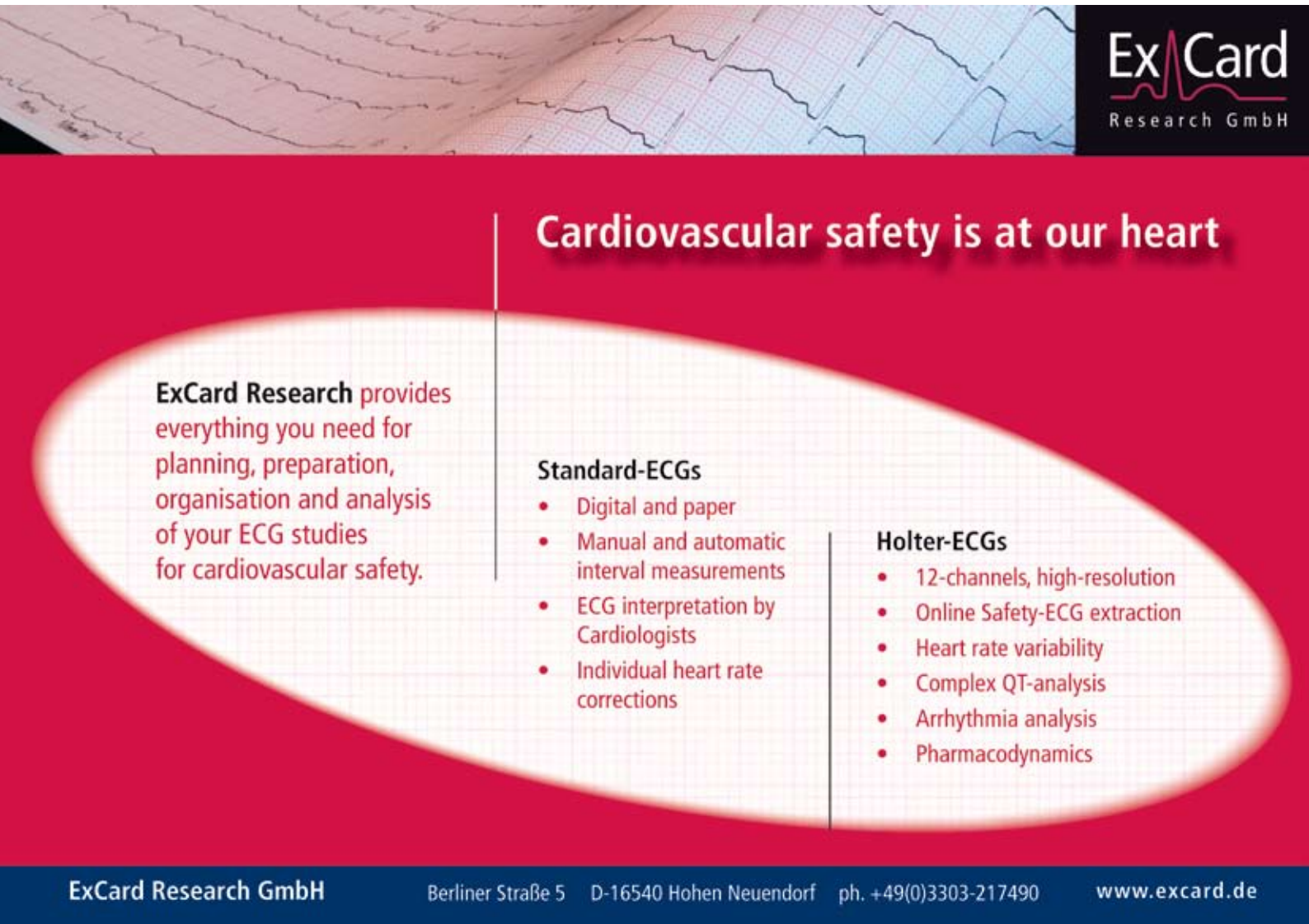
the mapping of multiple CRFs into an E2B node when applicable (e.g. surgical history and radiotherapy history CRFs mapped to medical history in E2B). Secondly, the system provides a translation layer for E2B dictionary terms. This configuration can be used to meet E2B specifications for code lists (e.g. dose units, route of administration) without altering CRF configurations and data management standards (i.e. addition of non-E2B data fields). Lastly, the system provides additional mapping flexibility by enabling extension of the E2B standard. Because of this, we were able to map concepts such as event level seriousness criteria and patient race, which are not currently supported by the E2B standard.

Complementing the data mapping was a substantial effort to build systematic, real-time communication with sites through the EDC. It was recognised early on that driving a fundamental process change across thousands of sites globally is a significant challenge. In combination with an aggressive, comprehensive training strategy, our focus for the eCRF design was to be simple, in-line with established data entry practices, and to provide instructive feedback to sites in real time when required. Through a series of new edit checks and custom functions (programs that run at the time of page save), we used the EDC's querying mechanism to fulfill the following requirements:

- Inform site when SAE transmission is necessary for both initial and follow-up scenarios
- Prohibit transmission of SAE if required fields are not entered
- Raise queries to inform the site which data needs to be entered to fulfill transmission requirements
- Close queries when site performs requested actions
- Enforce various data integrity rules (e.g. ensure a serious criterion is entered only when event is serious)

Eliminating Manual Reconciliation

A key objective of this effort was the elimination of the resource-intensive, manual reconciliation process between CTDB and safety systems. At Amgen, this process entails ensuring alignment of the following key attributes: event seriousness, causality to investigational product (IP), MedDRA-coded event term (at times conceptually in absence of exact match), and patient death flag. In the eSAE process, our strategy entailed ensuring all these fields were entered in the CTDB then treated as read-only in the safety system. For the MedDRA-coded event term, this was a fundamental process change. In the paper process, event terms were coded in batches by the medical coding organization, typically after the corresponding event in the safety system was coded real-time (report by report) by the safety function to meet regulatory reporting timelines. By performing the coding process up front into the initial data entry process, this would ensure process-driven synchronisation and consistency of all fields that were previously reconciled



manually. While the medical coding organisation was amenable in theory to this solution, we were concerned that the operational impact to the change meant not only an increased workload for this function, but also a fundamental shift from a scheduled batch process to an individual event coding paradigm each with its own regulatory reporting timeline. In order to help mitigate this potential resource impact, we devised a two-pronged approach for ensuring up-front coding.

The first prong entailed leveraging the site data entry process. The verbatim term entry field was transformed to a type-forward control (e.g. like Google™) backed with MedDRA low-level terms. This provides the site user the ability to select a term from the list if the user chooses and, like Google™, the user can choose to type anything into the control. This increases data quality (i.e. correct spelling of medical terms) and efficiency (medical terms can be very long) for site staff while providing flexibility to enter the exact term of choice. When the site selects from the list, the term will "self-encode". However, if the site does not select from the list, the medical coding team is notified and codes the term prior to transmission (the second prong). In order to streamline this operation, the vendor delivered functionality called "deep-linking" which is a URL taking a user directly to the specified CRF within the CTDB for action (after user authentication). Using this functionality, the system notifies the medical coding team via email including this deep link. The medical coding team enters the CTDB through the deep link and codes the term within a short amount of time to ensure timely reporting.

Another process enhancement achieved during this effort was the standardisation of capturing SAEs observed while study subjects undergo screening procedures before receiving an investigational medical product in the CTDB. Since regulatory agencies have recently increased focus on screening procedures, our study design lead recognised the opportunity to implement a single, standard process for capturing this information. However, the infrastructure enhancements required to support this process were far from trivial. Firstly, the standard matrix was updated not only to include a screening SAE form, but also enhanced to include supporting CRFs such as Medical History. Once a subject successfully completes screening, the CRF structure is adjusted to support the standard on-study configuration. Lastly, the Integrated Voice Recognition System (IVRS) process was enhanced to transfer subject information at the time of informed consent, as opposed to the previous process of an aggregate transfer at the completion of screening.

Other system functionality designed to facilitate a self-synchronising process include case-linking between systems, enabling systematic follow-up recognition as well as the centralisation of query management in the CTDB which, will be described in more detail below.

Q & A – Electrified and Optimised

Perhaps the most daunting task in enabling a fully electronic SAE life-cycle management process was handling the query and follow-up cycle. Fortunately, the building blocks were in place to achieve this objective. Firstly (and perhaps obviously), we were able to leverage the built-in query management module of the CTDB. Couple this with the aforementioned deep link and ability to extend the E2B standard, and voila – you have a recipe for success. The basic strategy entails:

- Safety staff identifying the need to raise a query (in the safety system)
- Safety staff efficiently entering the CTDB and raising the query
- The site answers the query by changing CRF data
- The site transmits the follow-up
- Safety staff analyse the result, and close the query (or requery as needed)

The infrastructure used to support this process is as follows:

- A deep link to the AE CRF was embedded into an extension tag within the E2B file
- Once the case was transferred, the safety system exposed the deep link as an active URL
- Safety staff member enters the CTDB, raises query on appropriate CRF field
- Site staff member answers query
- The site submits follow-up
- Safety staff utilise the CTDB query governance tools (e.g. query task list, query details report) to identify answered queries, and closes query in the CTDB

An added benefit to this process enhancement was that it enabled greater transparency to raised queries cross-functionally. Through centralisation of query management in the CTDB, it is projected that there will be a significant reduction in query duplication.

Events of interest refer to pre-specified medical concepts that require enhanced surveillance. Our Medical Safety Review Team led a comprehensive, cross-functional effort to standardise the collection of medically relevant information for events of interest. This effort yielded standard query events (SQEs) – a standard set of queries associated to a medical concept. In the paper world, once an event of interest is recognised (after event coding), the SQEs are then faxed to the site which by definition is a process which builds in one or more follow-up cycles. The eSAE process, with in-process event coding, provides a unique opportunity to generate SQEs during initial data entry, providing sites the opportunity to address queries before initial transmission, reducing follow-up cycles. A combination of custom function and SQE to LLT mapping tables was provided by the vendor to enable this functionality.

The combination of SQEs coupled with enforcing data entry requirements in the CTDB (approximately a quarter of queries raised in the paper process are due to missing or unreadable data) is the cornerstone of our strategy for significantly reducing manual queries and subsequent follow-up cycles.

A Technological Spin on "Trust but Verify"

Automation is great…when it works. One challenge to introducing this level of automation is the reduction of the paper trail and corresponding manual touchpoints which, in a sense, provides built-in manual oversight. Electronic efficiency by definition reduces the tangibility of a paper process. Recognising this, the team developed the PROACT active notification system. Because the eSAE process is self-synchronising, it allows PROACT to independently compare data across systems and raise any discrepancies accordingly. When data are discrepant beyond a defined timeframe, PROACT raises the alert by sending a detailed email to the appropriate stakeholders to remediate said discrepancy. As long as the eSAE processes are followed, PROACT will not yield any results. However, it provides the ultimate safety net which is essential for instilling confidence in the self-synchronising process across the enterprise and managing the few manual decision points within the process where discrepancies may arise. PROACT provides active monitoring and alerting for the following scenarios:

- Raise alert to safety if reconcilable fields are changed in the safety system
- Raise alert to site if an SAE is entered, but not transmitted to safety in allotted amount of time
- Raise alert to site if reconcilable field(s) is (are) altered, but not transmitted to safety in allotted amount of time
- Raise alert to medical coding if coding does not occur within timeframe of internal service level agreement (SLA)
- Raise alert to safety if event is found in the safety system, but not in the CTDB
- Raise alert to safety if event has been transmitted from the CTDB, but not yet incorporated into safety system (e.g. follow-up event with "reconcilable" field change not yet accepted and incorporated)
- Raise alert to safety if two cases for the same subject with the same event term occur within 30 days (as the second may be considered a duplicate)

Taking the "Standards" Approach

Process efficiency is not limited to the business process the system supports, but also applies to the operations of the system itself. eSAE has introduced a significant increase in infrastructure including the CRF to E2B mapping module, as well as myriad edit checks and custom functions. A single variation in a field OID could potentially have a large ripple effect, requiring code changes and validation of mapping and within edit checks and custom functions. And since this infrastructure must be equipped with each study start-up cycle, managing study design variability was paramount to ensuring operational viability (i.e. not exploding current study start-up timelines).

The approach was to deliver a common set of CRFs and mappings consistent across all studies. While studies obviously have inherent differences (i.e. investigation products (IPs), varying medical history forms), the goal was to lock down as much as possible (target 80%) which includes all edit check/custom function impact. Therefore, the only study-specific operational impact would be mapping the remaining 20%. Furthermore, as we gain more experience, we project supplemental standards for a given therapeutic area (TA) or IP can be achieved, thus providing a greater reduction in study-specific variability. Amgen has further demonstrated its recognition of the value of standardisation by aggressively engaging in a Clinical Data Interchange Standards Consortium- (CDISC-) based initiative, and the two project teams have worked closely to ensure seamless integration.

Implementing Transformational Change – Iterating Iteratively

Delivering transformational change for such a fundamental, established process required a total team effort. Our operational team was comprised of leaders from a broad spectrum of functions including safety (case management and medical review), clinical data management, CRA liaisons, development operations, biostatistics, clinical quality assurance, training, and IS. With such a large, cross-functional team, consistent communication was critical for realising and refining requirements and ensuring alignment. While iterative development is fairly standard in software development today, the ability to incrementally course-correct was paramount to successfully establishing the new process. The validation plan was comprehensive, including three rounds of integration testing prior to operational qualification (OQ). The strategy also entailed soliciting feedback from all key stakeholders as early as possible, then consistently throughout development including both internal functions as well as external study site staff. Roadshows with mock-ups and prototypes evolved into working sessions within an active development environment. Additionally this strategy delivered major dividends in uncovering requirements that were previously unrecognised. As an example, the need to build a form-based report to send to investigational review boards (IRBs) was realised during a pre-release visit to a site who volunteered to provide feedback. Early engagement enabled the team to address key gaps well before real-world impact.

To our benefit, the iterative approach was a shared philosophy between Amgen and our vendor. Even though there was an eight-hour time difference, the teams worked diligently to maintain communication through countless cycles of requirements-gathering and refinement, development, informal user acceptance test (UAT), and formal validation. Maintaining a high degree of verbal communication between analysts and developers was critical, as it not only ensured in-depth alignment between requirements and design (and ultimately the end product), but it also facilitated vital discussion concerning the use of technology (and sometimes its constraints) to practically meet business needs leading to much of the functionality described above.

The iterative approach was not simply limited to the development cycle. Our implementation approach entailed transitioning twelve diverse studies into production, then evaluating and adjusting before ultimately releasing on an enterprise basis, including all new studies and additional active study transition (i.e. a pilot). This decision truly demonstrated our commitment to the iterative approach as transitioning active studies comes at a comparatively high cost in relation to new study implementation. Firstly, transitioning a study meant applying eSAE infrastructure (mapping, edit checks, custom functions) to established CRFs, which based on their creation adhered to different standards. Secondly, in order to enable a fully electronic process, the team migrated safety-specific SAE data into the CTDB for legacy cases. Lastly, the training and change management component requirements for facilitating a fundamental process and behavioural change on global studies were an immense undertaking. For the twelve "pilot" studies, training was developed and successfully delivered to site staff, CRAs, and functional staff (e.g. safety case management, data managers, etc.) in 35 countries and over 500 sites.

Although the effort was significant, the approach yielded invaluable feedback. Six weeks after the release, sites participated in a survey which provided positive and constructive, actionable feedback as well. During this "hypercare" period, the team was able to make adjustments to both the technology and processes. But equally as important, it afforded us the opportunity to engage in the change management aspects evaluating the success of our training, support infrastructure, and overall site compliance to the new processes.

The Results

Within the first three months having the twelve studies transitioned in production, the system facilitated nearly 1300 transactions equating to approximately 700 distinct SAE cases from 35 different countries. After ten months, the cumulative number of transactions has grown to over 4500. After receiving approval from the senior management to equip all new studies with eSAE (with rare exemptions), the team has successfully implemented the first of many new studies in September of 2011. Furthermore, the team has embarked upon a second wave of high priority transition studies. The core team has primarily remained intact, fostering the transition of responsibility to operational functions concerning the alignment of study start-up activities for safety and CDM. Functional champions have established operational forums to manage change and discuss future strategy. With the combination of new study implementations and transitioned studies, it can be projected that over 90 % of Amgen's study portfolio will be eSAE-enabled by the end of 2012.

With regard to our goals and objectives, while some were qualitative objectives and others were boolean (e.g. did we eliminate manual reconciliation? – which we have, consistent with process adherence), reducing the number of manual queries is a quantifiable measure which can be

tracked. Overall, investigators have received 39 % fewer queries on an eSAE study when compared to a paper study. Furthermore, of the queries received by investigators on eSAE studies, 30 % of these were system auto-generated SQEs. Therefore in total, safety is manually posting 57 % fewer queries in eSAE in comparison to paper studies, which exceeded our expectation.

While we at Amgen are very excited about the value that eSAE has provided and will continue to provide, there certainly were a number of noteworthy challenges the team was and is required to overcome. While this in itself could be a separate publication, listed below are some of the most significant.

- **Study transitioning** – while strategic study transitioning has increased our ability to remove paper studies and manual reconciliation processes by approximately six years, it was a meticulous, resource-intensive effort which required an extreme level of coordination across multiple functions
- **Ensuring operational efficiency while increasing infrastructure** – there is an inherent upfront cost to incorporate eSAE into existing study start-up timelines, given the increased infrastructure and configuration. To minimise this cost and ensure that study start-up timelines are not negatively impacted, the team has increased focus on standardisation (i.e. reuse of standard CRFs and mapping), aggressive training on new applications and tools to all appropriate staff, and clear functional governance of eSAE components as well as cross-functional impact awareness.
- **Managing study variation** – most supporting this industry can attest that no two studies are the same. However, some study types have required significant

analysis on how best to handle (or potentially not handle) within the eSAE process.
  - o Observational studies – managing the difference in the sponsor's safety reporting responsibilities in contrast to clinical trials
  - o Roll-over studies – oftentimes, elements needed by safety (e.g. medical history) are not included
  - o First-in-human (FIH) and early development studies – given that SAEs are often rarely reported, there is a significant question concerning cost-benefit for these studies
- **Managing change while changing** - even though we have greatly increased our overall transition timeline through the efforts outlined above, Amgen still must actively manage multiple processes (eSAE and paper) for a couple of years. This is most challenging to central functions such as safety who work across studies, molecules, and even therapeutic areas. Some of the practical challenges include:
  - o Developing and maintaining two distinct operational processes including documentation, training, etc. regarding safety case management
  - o Ensuring efficient identification within the safety system of which process to adhere to
  - o For eSAE, globally aligning all stakeholders, including business partners, to a single process
  - o Working out the details – a big challenge to a first-in-industry paradigm is that there are not any reference points or resources with experience. An example where the team has had to provide specific focus is driving the paradigm shift where specific eCRFs within the CTDB are actually the "source document" for the safety case.
- **More tightly coupling processes between safety, CDM, and development** – while the eSAE process offers significant efficiencies, it also requires greater alignment between functions and in a few cases, blurs lines of accountability. Below are a few examples:
  - o Aligning data conventions between CDM and safety (especially concerning event capture conventions)
  - o Providing safety staff appropriate level of training for querying in CTDB and leveraging CDM query conventions
  - o Clearly outlining ownership, responsibility, and cross-functional interaction for governing safety queries in the CTDB
  - o Providing cross-functional, systematic communication/escalation channels between safety, CDM, and development.

In today's environment, streamlining core operations may be more important than ever to ensure we can deliver vital, novel therapies to patients throughout the world. At Amgen, the eSAE initiative represents a big step in the right direction. The approach of process-focused system delivery coupled with consistent, iterative communication with a broad set of stakeholders has enabled us to deliver an innovative solution which enables Amgen to manage the SAE life-cycle responsibly - not only significantly increasing efficiency, but also improving quality and availability of this critical information. And ultimately, it is the patients we serve who will reap the benefits of what we have learned for many years to come.

Marty Markley has over fifteen years experience delivering innovative solutions across various functions supporting drug discovery, development, and life science industries. While at Amgen, Marty has led efforts to improve efficiency, data quality and standardisation, and decision-making capabilities within clinical and post-market drug safety, clinical data management, risk evaluation and mitigation strategy (REMS), analytical chemistry, and drug discovery. He can be reached at **Email: mmarkley@amgen.com**

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