# What's the Risk?

**The ability to reliably collect, analyse and store data in compliance with global regulatory standards drives patient safety and decisions regarding efficacy. Only with consistent, high-quality data can the drug development process move forward**

Greg Ambra and Jean Battikha at DZS Clinical Services

Access to high-quality, real time data is the driver behind risk-based monitoring (RBM) – a methodology used to enhance subject safety and data quality, and to deliver significant efficiency benefits. An RBM approach replaces the in-person, 100% source data verification (SDV) process based on the identification of risks and issues. Its use in clinical trials is increasing as sponsors begin to realise the potential to improve the quality of data while, at the same time, reducing total trial costs by an estimated15-20% (1). This approach is also in line with the push from regulatory authorities in the US and EU for targeted monitoring, as it is more effective than spreading resources equally across all sites.

However, managing and analysing all clinical data during the study – to identify potential current issues and future risks – is a complex speciality, which becomes particularly challenging in global, multi-site trials. Large pharmaceutical companies and CROs may have entire departments devoted to this, but that kind of scope and expertise is expensive and, for many small- and mid-sized biopharmaceutical and device organisations developing a product on a budget, it simply may not be an option.

Aligning these smaller teams with affordable and robust technologies, which enable the adoption of a risk-based approach to study monitoring, creates cost efficiencies that can significantly benefit them without compromising data value or patient safety.

## KRIs and CSM

Traditionally, when an RBM programme is implemented, it relies primarily on key risk indicators (KRIs). In this scenario, summary metrics and thresholds are determined prior to the study, which means that KRIs must be programmed, tested and validated in advance, and establishing parameters for each indicator is a process that could cause delays. KRIs can also be restrictive and difficult to use when they are contained in multiple systems – such as the data management system, the trial master file and monitoring reports – because data may not be readily accessible for summary and analysis across a study.

Central statistical monitoring (CSM), on the other hand, processes all of the clinical information gathered in the data management system of a trial. It operates under the principle that all variables have an impact on quality – including clinical, laboratory and treatment data, as well as patient-reported outcomes. In a CSM study, information worth collecting is worth analysing. Adherents of CSM point to its ability to identify issues that may be missed by KRIs.

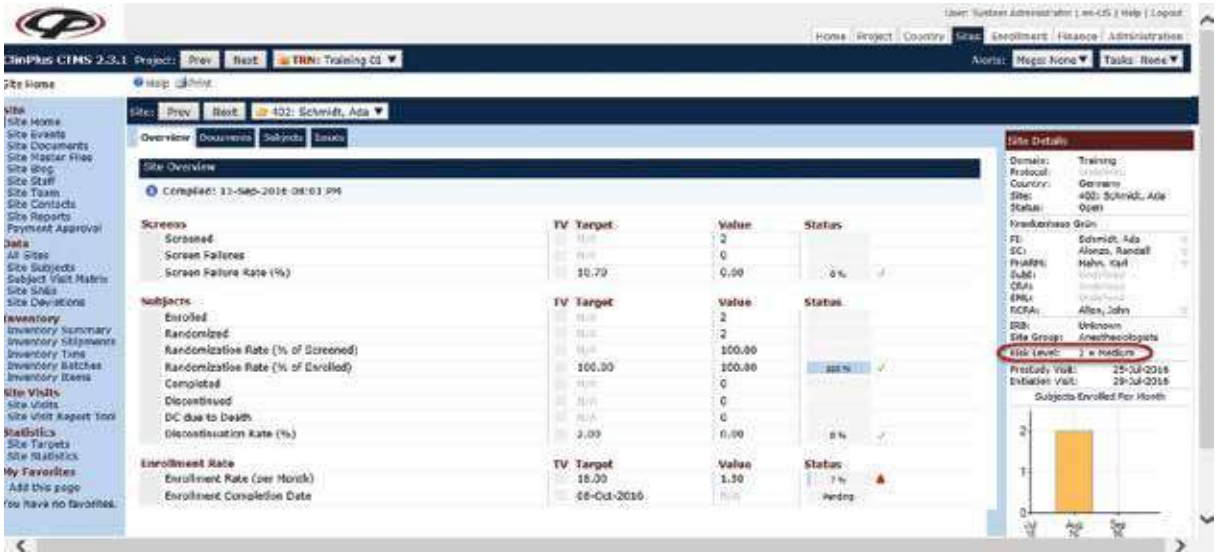
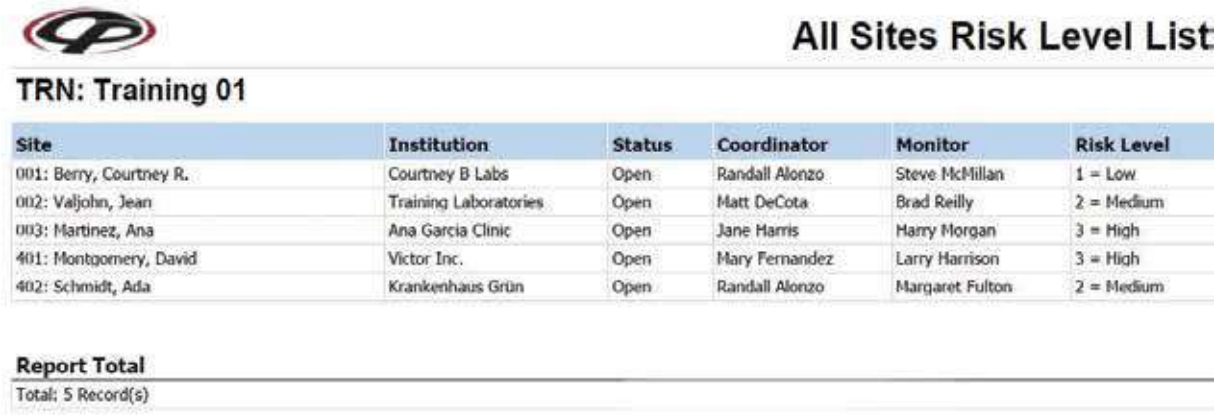



**Figure 1:** Risk appraisal – sponsors get a rapid assessment of study sites on the display of the CTMS.
1 = low (no risks identified, no need for immediate follow-up)
2 = medium (potential areas of risk; no need for immediate follow-up, but should be re-evaluated)
3 = high (risks identified that require immediate attention to determine the cause)



All Sites Risk Level List

TRN: Training 01

| Site | Institution | Status | Coordinator | Monitor | Risk Level |
|---|---|---|---|---|---|
| 001: Berry, Courtney R. | Courtney B Labs | Open | Randall Alonzo | Steve McMillan | 1 = Low |
| 002: Valjohn, Jean | Training Laboratories | Open | Matt DeCota | Brad Reilly | 2 = Medium |
| 003: Martinez, Ana | Ana Garcia Clinic | Open | Jane Harris | Harry Morgan | 3 = High |
| 401: Montgomery, David | Victor Inc. | Open | Mary Fernandez | Larry Harrison | 3 = High |
| 402: Schmidt, Ada | Krankenhaus Grün | Open | Randall Alonzo | Margaret Fulton | 2 = Medium |

Report Total

Total: 5 Record(s)

**Figure 2:** The addition of administrative study data captured systematically with the clinical data in a unified EDC and CTMS platform enables the application of statistical algorithms that can be enhanced to find issues beyond what is captured in the clinical database alone

Although supporters of CSM claim that it minimises the work of defining KRIs and does a better job of obtaining objective data that can be used to optimise monitoring, it can require massive computing power as well as complex programming and analysis, depending on the size and scope of a study. CSM will also almost certainly capture significant amounts of data that are, ultimately, without value.

## Unified Data Systems

Pilot programmes are being developed to maximise the benefits, while minimising the disadvantages of both KRIs and CSM through targeted central statistical monitoring (tCSM).

Some KRIs – such as adverse events (AEs) – are common to virtually every clinical study. However, tCSM utilises a unified eClinical platform that gives sponsors of small- to mid-sized organisations the opportunity to take a more proactive approach to statistically monitor administrative and clinical data, and to effectively identify risks without having to analyse each data variable. By defining many – but not necessarily all – of the KRIs early in the process, sponsors can implement a statistically driven and effective RBM system, including off-site monitoring and a more targeted approach to on-site visits, thereby lowering costs and improving efficiencies.

In line with regulatory requirements, risk assessment must guide trial monitoring plans. These plans should be developed as soon as the needs and risks associated with a study have been reviewed, taking into account the therapeutic area, trial phase and complexity, knowledge of the drugs being used, and so forth.

As part of this plan, standard KRIs can be predefined and designed to reveal deviations and poor performance in the study conduct – for example:

- Planned versus actual recruitment rates*
- Predicted versus actual screen failure rates*
- Planned versus actual missed or late visits or data by site*
- Serious AEs reported by site
- Predicted versus actual early termination rate by site*
- Number of protocol deviations or violations by site*
- Case report form (CRF) submission and completion times against actual patient's progress (for paper-based studies)
- Electronic CRF completion times in relation to visits or expected times (for electronic data capture (EDC) studies)
- Query rates on key safety and efficacy variables
- Time to query resolution versus number of active queries

*Data for these KRIs require information from outside the data management system, but can effectively be analysed through a unified platform

Different from traditional KRIs, these metrics may be statistically analysed to objectively detect potential data risks or issues. Through the use of appropriate technology, these results can be automatically programmed into the display of the clinical trial management system (CTMS) to give study personnel a quick indication of sites or patients needing extra attention. Resulting values can be labelled to indicate actions required, for instance (see Figure 1, see page 17).

By utilising the right technology, information related to site risk can be communicated automatically to site monitors and project managers to ensure the issues are addressed (see Figure 2).

More traditional KRIs that need to be predefined are still useful; they can generally be applied to all studies and, by adding statistical methodology, they can be enhanced. One specific KRI predefined in a recent study demonstrated that select sites had either over- or underreported the number of AEs relative to the study overall. In this example, those sites reporting AEs per 100-person weeks that were less than 15%, or more than 95% of expected, were flagged for follow-up (sites 2, 4, 6-10 and 14-17). In some cases, the AEs could be readily explained, but in instances where the variation could

| | | | | | | Summary statistics: No of AEs per 100-person weeks | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study site** | **No of subjects** | **No of AEs** | **No of days** | **AEs/subjects** | **AEs/week** | **Mean** | **Standard deviation** | **Min** | **15%** | **95%** | **Max** |
| **Site 1** | 18 | 233 | 8,032 | 12.9 | 0.2 | 28 | 34 | 5 | 11 | 72 | 152 |
| **Site 2** | 103 | 1,493 | 34,106 | 14.5 | 0.31 | 129 | 624 | 2 | 10 | 187 | 6,300 |
| **Site 3** | 137 | 1,168 | 20,412 | 8.5 | 0.4 | 126 | 894 | 3 | 17 | 134 | 10,500 |
| **Site 4** | 63 | 398 | 21,757 | 6.3 | 0.13 | 23 | 26 | 1 | 6 | 67 | 140 |
| **Site 5** | 10 | 47 | 885 | 4.7 | 0.37 | 41 | 30 | 5 | 10 | 84 | 86 |
| **Site 6** | 20 | 162 | 2,605 | 8.1 | 0.44 | 188 | 616 | 6 | 24 | 256 | 2,800 |
| **Site 7** | 37 | 193 | 11,652 | 5.2 | 0.12 | 24 | 43 | 1 | 4 | 59 | 263 |
| **Site 8** | 196 | 1,220 | 72,442 | 6.2 | 0.12 | 39 | 252 | 1 | 4 | 79 | 3,500 |
| **Site 9** | 91 | 1,390 | 24,373 | 15.3 | 0.4 | 63 | 53 | 9 | 18 | 172 | 274 |
| **Site 10** | 54 | 887 | 16,681 | 16.4 | 0.37 | 57 | 66 | 4 | 19 | 237 | 294 |
| **Site 11** | 4 | 17 | 258 | 4.3 | 0.46 | 48 | 24 | 23 | 27 | 72 | 74 |
| **Site 12** | 15 | 51 | 1,405 | 3.4 | 0.25 | 29 | 42 | 6 | 8 | 81 | 171 |
| **Site 13** | 71 | 867 | 31,761 | 12.2 | 0.19 | 30 | 36 | 3 | 10 | 86 | 263 |
| **Site 14** | 16 | 137 | 7,555 | 8.6 | 0.13 | 17 | 16 | 2 | 3 | 45 | 60 |
| **Site 15** | 81 | 449 | 32,265 | 5.5 | 0.1 | 3 | 67 | 1 | 3 | 71 | 525 |
| **Site 16** | 25 | 232 | 11,776 | 9.3 | 0.14 | 20 | 18 | 2 | 4 | 47 | 74 |
| **Site 17** | 71 | 1,048 | 19,034 | 14.8 | 0.39 | 69 | 80 | 1 | 17 | 211 | 525 |
| **Total** | **1,012** | **9,992** | **316,999** | **9.9** | **0.2** | **55** | **172** | **1** | **7** | **141** | **10,500** |

not be accounted for, the AE KRI served as a valuable and early indicator that a site needed additional monitoring and further evaluation (see table above).

In addition to statistically analysing predefined KRIs, utilising this approach lends itself to further ad-hoc tCSM as needed throughout the trial. This way, studies have the flexibility to accommodate RBM precepts, as well as adaptive trial designs and personalised medicine. The system also enables researchers to tap into other data sources to address issues and answer questions once a study is under way.

## Conclusion

Clinical trials take place in a highly regulated landscape dominated by patient safety and efficacy concerns that demand both clinical and trial oversight, as well as data that are easily accessible and analysable. Until recently, all development programmes fulfilled this requirement with a regime of frequent on-site monitoring, where clinical research associates physically verified data quality and monitored the trial for noncompliance against formal protocols – including a mechanism of 100% SDV as part of the monitoring process.

However, this procedure is labour-intensive and time-consuming, and it accounts for a significant percentage of the total cost of a clinical study. Moreover, SDV is prone to human error and inaccuracies, and may not catch certain risks like data fraud. In multi-site trials, on-site monitoring will not identify study-wide issues such as statistically significant variability between sites, for instance.

For biopharma companies of all sizes, an approach that utilises a tCSM plan – including KRIs and ad hoc statistics – is more likely to ensure subject protection and overall study quality than site visits and SDV alone. In addition, this approach can be employed to drive a more scientific procedure to RBM that sponsors of small- and mid-sized organisations can manage and feel more confident implementing. Using expert strategy in the integration of a software system to support a specific trial, even a relatively simple EDC and CTMS system can yield dramatic insights and transparency for sponsors, provide unquestioned safety for patients and significantly streamline clinical operations.

### Reference


1. **Visit: www.pwchealth.com/cgi-local/hregister.cgi/reg/pwc-pharmaceutical-development-risk-based-monitoring.pdf**


### *About the authors*


**Greg Ambra** is Vice President of Clinical Operations at DZS Clinical Services. With nearly 20 years of experience in the clinical research industry, he has held strategic leadership positions in various sponsor and CRO companies. Greg has led DZS Clinical Services since 2012, and earned his Master's degree in Medical Sciences from Boston University, US.

As Senior Director of Biostatistics, **Jean Battikha** has worked in the pharma industry as a statistician for nearly 40 years. He has been involved in the design, analysis and reporting of many clinical trials across several therapeutic areas, as well as with many NDA submissions in both the US and EU.

**Email:** info@dzs.com