PharmaSUG China 2021 - Paper 30

Visualization to detect risks of clinical data in Risk-Based Quality Management

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1. ABSTRACT

As clinical studies are becoming increasingly complex, particularly with complicated design, large team across the globe and diverse data sources, it is highly recommended to apply the Risk-Based Monitoring (RBM)/Risk-Based Quality Management (RBQM) approach for ensuring subject rights and data quality by regulatory authorities, including FDA, EMA and NMPA. By using visualization techniques, study teams can easily identify the areas of highest risks in operational compliance and subject's data and take actions to mitigate the risks before they become imminent.

In order to meet the demands of risk reviewers from various corporate levels and different types of clinical data, multiple visualization techniques are used in the development of our Tigermed RBQM system. In this paper, we will introduce the techniques applied to provide holistic view and detailed view on data risks.

2. INTRODUCTION OF RBQM

Risk-Base Monitoring (RBM) is an adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest need which have the most potential to impact subject safety and data quality. Risk-Based Quality Management (RBQM) is a system for managing quality throughout a clinical trial. It will outline how sponsors and contract research organizations (CROs) can harness the power of risk-based trial management, making clinical trials better, faster, and cheaper for the industry and safer for patients.

Clinical monitoring is an important measure to improve the quality data. There are many ways to achieve this, including 100% Source Data Verification (SDV). However, some studies show that a high proportion SDV does not necessarily mean good data quality. The centralized monitoring mainly refers to the timely evaluation of project data (EDC data, operation data, etc.) by the sponsor or all functional departments on behalf of the sponsor in a remote way. Centralized monitoring can help reduce the frequency of on-site monitoring and assist in concentrate more on preventing quality issues from occurring than on only fixing problems. RBQM utilized a combination of monitoring and statistical assessments to guide on-site monitoring to increase efficiencies, safety and quality and make data-driven decisions.

As the first step in the implementation of RBQM, representatives of all functional departments (including operations, medical, statistics, dada management, drug safety, etc.) should be organized to conduct a full and comprehensive risk assessment of study at the start-up stage, and guide the formulation of the quality management plan and strategy of the study. This evaluation step can be conducted with Risk Assessment & Categorization Tool (RACT).

In this paper, we use Tigermed RBQM platform as the example of risk visualization to develop a KRI analysis tool. It provided graphical analysis to track changes in site overall risk over the study of a clinical trial, enabling PM/CRAs to follow up on the results of possible risk mitigation actions.

3. KEY RISK INDICATOR

Key Risk Indictor (KRI) is a measure used in management of the possibility of future adverse impact. They are designed to detect potential compliance issues during clinical development before they become problems.

Aligned with the TransCelerate RBM guidance, key risk indicators are generally categorized into one of the following eight options:

1. CRA/On-site Workload
2. Data Quality

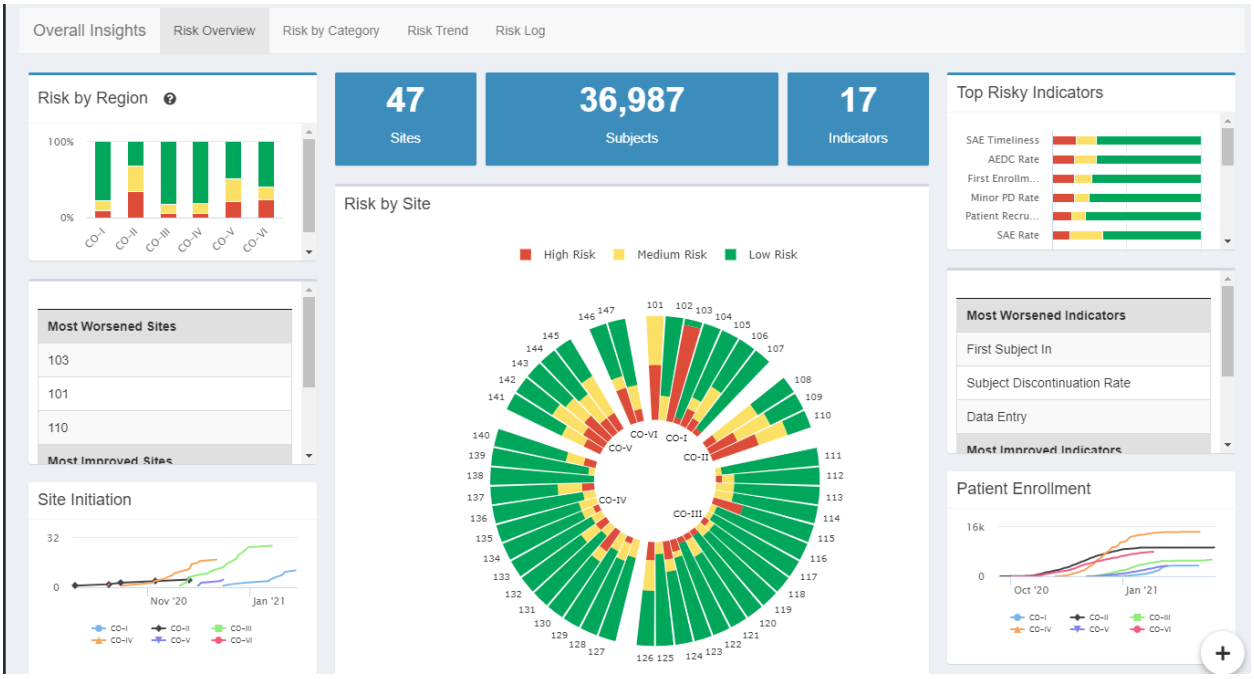
3. Essential Documents
4. Investigational Product
5. Issue Management
6. Safety
7. Staffing, Facilities and Supplies
8. Subject Recruitment and Discontinuation

4. VISULIZATION TO DETECT RISKS

Project Management

The platform supports an interactive data-analysis-based visualization platform that makes it easy to interpret and evaluate trials data from multiple sites, enabling project teams to quickly and effectively insight and identify problems.

Figure 1: Dashboard of Risk Overview



The risk distribution is mainly by sites and regions. The overall risk level of the study should consider three aspects of risk, probability, detectability and impact, and also rate then on a number of degree scales. The color-coded based on the changed in KRI. Red means “High Risk”; Yellow means “Medium Risk”; Green means “Low Risk”.

On the top of the dashboard, the overall of the risk overview include **Sites, Subjects and Indictors**. On the left of the dashboard, the line graph shows how many sites in six regions (CO-I, CO-II, CO-III, CO-IV, CO-V, and CO-VI). On the center of the dashboard, the circular stacked plot presents a plot showing KRI risk classification (high risk, low risk, and medium risk) base on sites and regions. On the right of the dashboard, the line graph shows how many patients enrolled in six regions. The top risk indicators ranking is based on the high risk. (Figure 1)

The risk dashboard allows the project leader to directly and clearly see the risks situation and some important and basic data of the whole trial, so as to have a better grasp of the overall situation of the whole experiment.

Site Management

Basically, a CRA only responsible for one or two sites. The CRA conducts regular site visits to ensure proper progress and record keeping on the part of the clinical site. They needs know about site’s

performance, like why the site identified as high or medium risk, and when the site has a high risk, what CRA should do to prevent it from becoming a problem.

Figure 2: Threshold based on Ordinal Data – SDV Rate

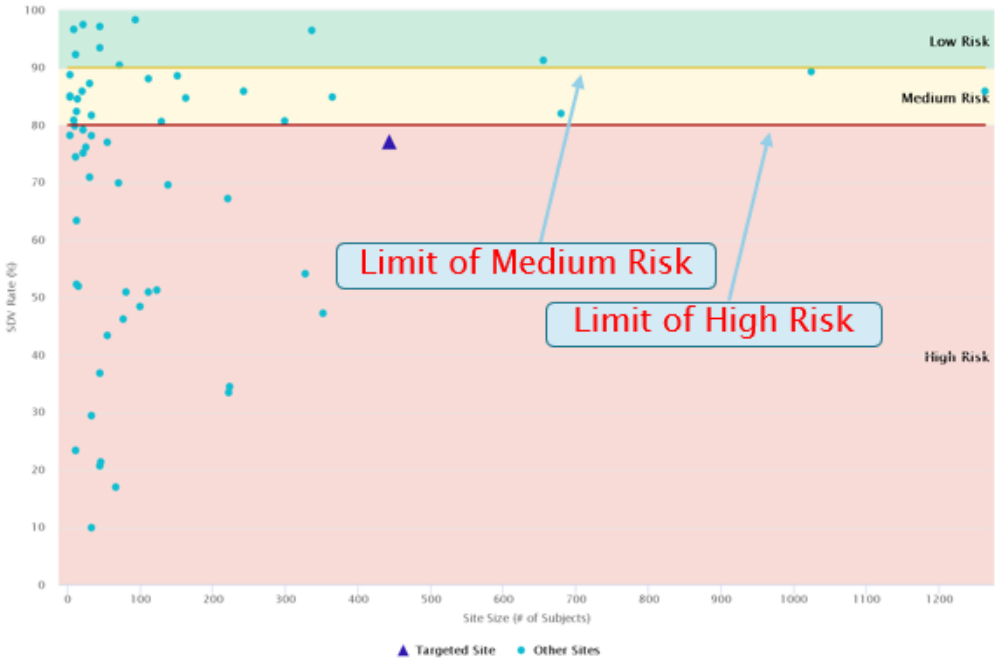
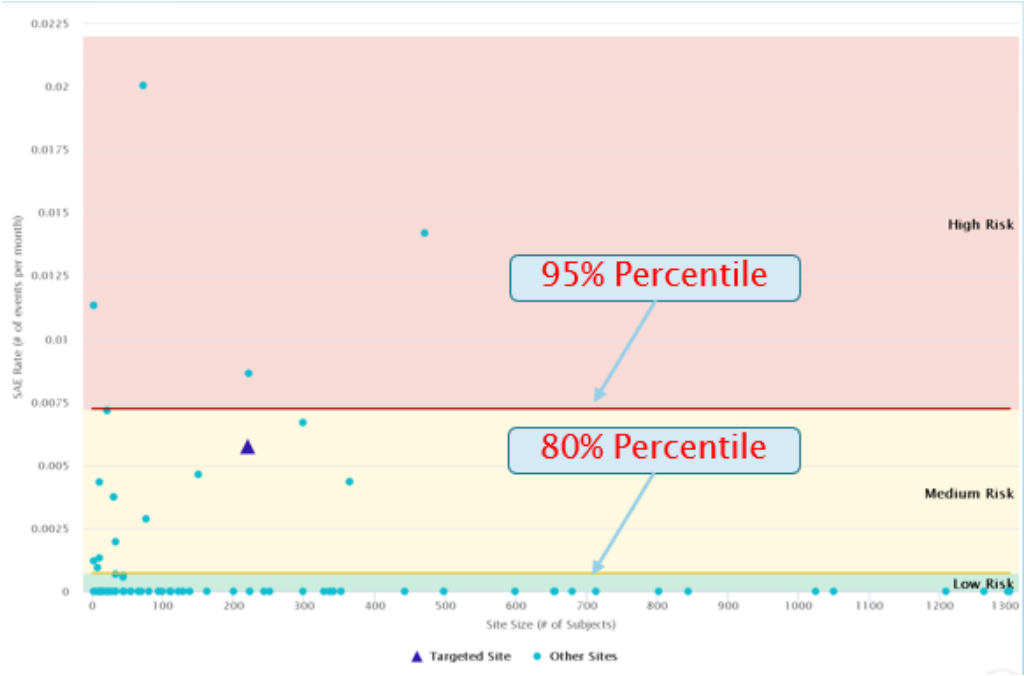


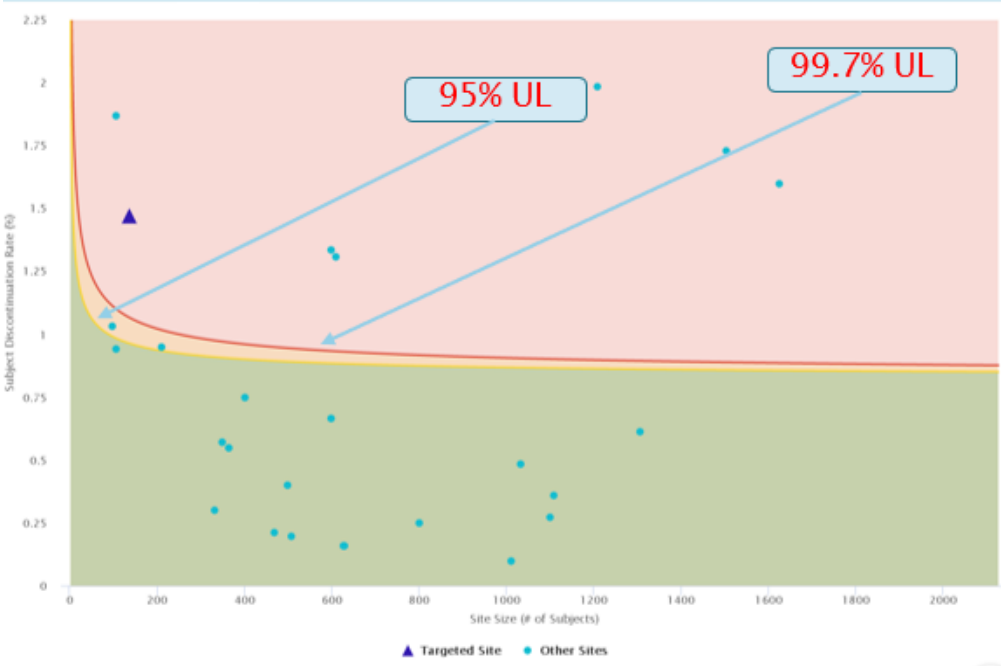
Figure 2 shows the risk thresholds based on ordinal data, with 90% as the limit of high risk (red) and 80% as the limit of medium risk (yellow) for the SDV rates. The higher the SDV rate, the lower the risk. In other words, the lower the SDV rate, the higher the risk.

Figure 3: Threshold based on Percentile – SAE Rate



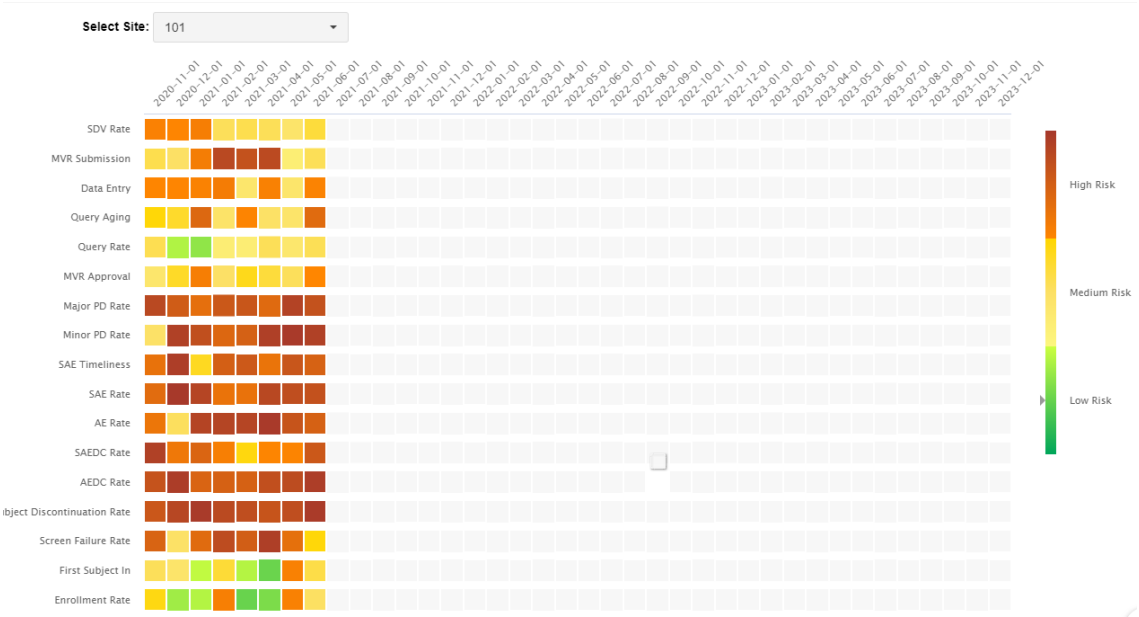
The Figure 3 presents the monitoring rules based on the percentile approach. The limits of high risk and medium risk are set as 95% (red) and 80% (yellow) percentile. Many of the sites are classified with very low SAE rates.

Figure 4: Threshold based on CI of Binominal Distribution – Subject Discontinuation Rate



The Figure 4 shows the risk thresholds based on 95% (yellow) and 99.7% (red) confidence intervals for the binary event of interest (early discontinuation from the trial) when considering the number of subjects of each site. The risk thresholds were increasingly tighter as the number of patients per site increased. The early discontinuation rates were within 95% confidence intervals at most of sites. Most of sites in the lower risk level, and target site is in the higher risk level.

Figure 5: Risk Trend – Risk Distribution by KRIs and by Analysis Points



The Heat Map is color-coded to provide an easy, visual representation of how risks affect each KRI. The darker the red, the higher the risk score is compared to the benchmark. The lower the green, the lower the risk score is in comparison. (Figure 5)

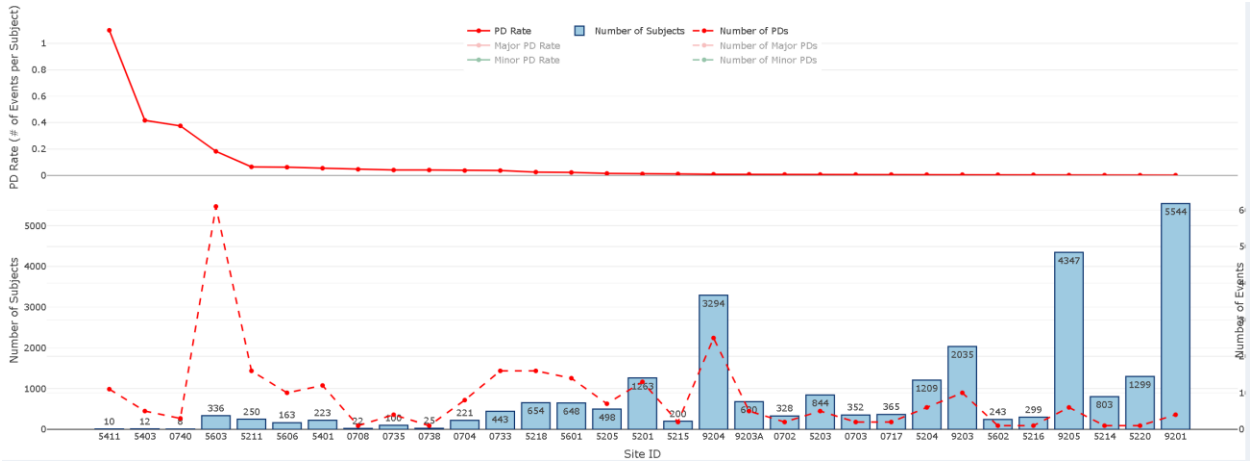
Medical Monitoring

Previously medical monitoring may have needed to be monitored through different platforms because the data came from different sources. Now, through the RBQM platform, all the collected data can be integrated together, and the unified system can be used for monitoring, which brings great convenience to medical monitors.

Monitoring in the following options:

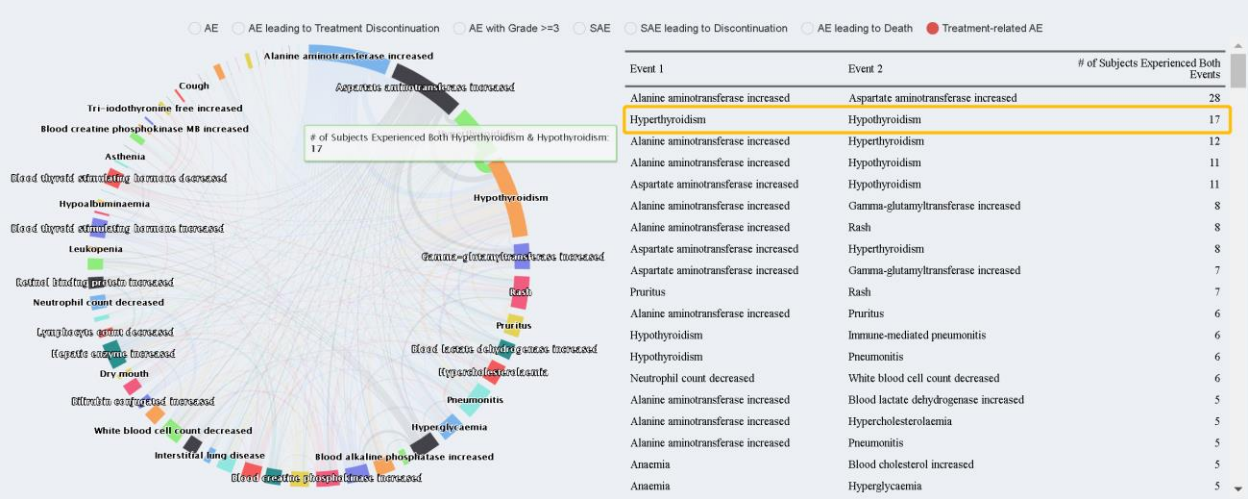
1. Subject Eligibility
2. Critical Endpoints
3. Protocol Deviation
4. Adverse Event
5. Central Labs
6. Patient Profiles

Figure 6: Example of traditional visualization– PD Rate



On the bottom of plot, the bar chart shows the number of subjects in each site, and the line graph shows the number of PD in each site. On the top of plot, the line graph shows the PD rate (number of events per subjects).

Figure 7: Example of exploring visualization – AE chord



Event 1	Event 2	# of Subjects Experienced Both Events
Alanine aminotransferase increased	Aspartate aminotransferase increased	28
Hyperthyroidism	Hypothyroidism	17
Alanine aminotransferase increased	Hyperthyroidism	12
Alanine aminotransferase increased	Hypothyroidism	11
Aspartate aminotransferase increased	Hypothyroidism	11
Alanine aminotransferase increased	Gamma-glutamyltransferase increased	8
Alanine aminotransferase increased	Rash	8
Aspartate aminotransferase increased	Hyperthyroidism	8
Aspartate aminotransferase increased	Gamma-glutamyltransferase increased	7
Pruritus	Rash	7
Alanine aminotransferase increased	Pruritus	6
Hypothyroidism	Immune-mediated pneumonitis	6
Hypothyroidism	Pneumonitis	6
Neutrophil count decreased	White blood cell count decreased	6
Alanine aminotransferase increased	Blood lactate dehydrogenase increased	5
Alanine aminotransferase increased	Hypercholesterolaemia	5
Alanine aminotransferase increased	Pneumonitis	5
Anaemia	Blood cholesterol increased	5
Anaemia	Hyperglycaemia	5

A chord diagram represents flows or connections between several entities (called nodes). In the left of chord diagram shows the connection between each AE event in different colors. In the right of example is how many subjects experienced in both events. (Figure 7)

Centralized Statistical Monitoring

Centralized Statistical Monitoring (CSM) is a statistical approach to central monitoring in clinical trials. CSM ensures the ability to determine data quality and ensure that monitoring efforts focus on sites with statistically atypical data. CSM offers the potential to determine where issues might lie in clinical data during study conduct and before significant problems occur, consequently, helping to avoid and shocks and surprises at the points of regulatory submission. In addition, a CSM approach can be useful in detecting faulty equipment errors, negligence of fraud, protocol deviations and unexpected patterns which then identifies the sited that need further investigation.

In order to apply CSM, we usually use univariate or multivariate statistical techniques. Once subjective data fraud appears, it will have a subversive effect on the credibility of the clinical trial. In addition, systematic data errors will affect the trial results, so we should pay attention to them. However, random data errors are less common and distributed randomly among random sets, so they have little influence on clinical trials' results.

Listing some detect systematic data error ways are below:

1. Digit Preference
2. Too few or too many outliers
3. Too little or too much variance
4. Data too skewed
5. Too weak or too strong correlation
6. Invented patterns

5. CONCLUSION

RBQM is a professional strategy and system application that can improve overall performance of clinical trial and reduce or limit potential risks. In this paper, we take advantage of a platform provided by Tigermed RBQM and analysis KRIs. Visualization plays a very important role in RBQM application. Specifically, it incorporated a dashboard concept to enable users to start from summary of study with regard to risk at site level or region level, and allow for data exploration.

Building a good data product, from product designer's view, the first step is to pinpoint users' need and determine how your unique capabilities will solve the key problem for that need. In the development

stage, the product needs easy and repeatable, also meet the demands of users from various corporate levels.

6. REFERENCES

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7. CONTACT INFORMATION

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