PCMG workshop

Risk-based outsourcing and procurement management

24 October 2019; Millennium Hotel, Knightsbridge, London
Sponsored by Premier Research

This was a fascinating and highly informative exploration of various elements of risk management in outsourcing and with outstanding experts in their respective fields. In particular, the workshop explored:

- Risk based quality management (RBQM) – a new philosophy being driven by FDA
- The implementation of risk-based monitoring
- A mechanistic approach to risk identification and mitigation from a global pharmaceutical company
- A discussion of the challenges of working in high risk countries using the model of anti-malarial clinical trials

The workshop was chaired by PCMG Committee members Olena Goloborodko of Celgene Ltd and Laura Lulli of GSK Vaccines.

Speakers and chairs: (L to R) Michael Arlotto, Sandra Johnson, Helen Wood, Laura Lulli, Susan Romberg, Andy Lawton, Olena Goloborodko

An interesting feature of the usual introductions was the discussion of what is a "fourth party" service provider? For avoidance of doubt the third party is the CRO and the fourth party are CRO subcontractors. In principle, there are also fifth and sixth parties as the service providers for a clinical trial form a "spiders web" model with the sponsor in the middle and a wide network of contractors and sub-contractors, who themselves have sub-contractors who are critical to their service delivery. Each sponsor company has to take a view on where to draw the boundaries of governance when faced with this spider web. It was also acknowledged that the decision of what is a critical risk and what is a non-critical risk is a subjective decision to be made by each Sponsor and this should be documented in their Quality Management System (QMS).

Mike Arlotto (founder of Remarque Systems) grabbed the attention with a stark example of how risk analysis can bring benefits. Abraham Wald, a Hungarian statistician, analysed the bullet holes in RAF bombers returning to base after a flying sortie to identify where extra armour needed to be added for critical protection. The initial thinking was to protect the areas with bullet holes but Abraham Wald recognized that the areas where the bullets were hitting were not critical to the health of the aircraft, as they returned safely to base. The armour needed to be placed in the areas where there were no bullet holes, since these were the places where a direct hit resulted in the loss of the plane.

Michael continued with a review of risk-based regulations, summarized as:

- Dec 2012: OECD Recommendation on the Governance of Clinical Trials
- Mar 2013: FDA Guidance: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring
- Nov 2013: EU GCP IWG Reflection paper on risk-based quality management in CTs
- Apr 2014: regulation (EU) No. 536/2014
- Apr 2017: Risk proportionate approaches in clinical trials –EU recommendations
- Jun 2017: ICH E6 (R2) becomes effective in the EU
- Mar 2019: FDA Draft Guidance: A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers.

Risk-based approaches to clinical trial conduct are of increasing interest to the regulators as they seek to reduce the burden on pharmaceutical companies whilst continuing to improve quality standards. This is an ongoing evolution with increasing regulatory interest on risk mitigation. ICH GCP E6 R2 was amended to encourage the implementation and improvement of more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure subject safety and data integrity.

The regulatory authorities are particularly focused on risk assessment as a proactive element of protocol development. The process will be familiar to many – define the critical risks, prioritise according to likelihood and impact, focus on high impact, high likelihood risks, identify the critical data processes and how you will eliminate, mitigate or manage

these risks. To this process the FDA have added proactive documentation of your risk management strategy.

David Burrow an FDA inspector has introduced the broader concept of risk-based quality management (RBQM), extending risk-based monitoring to all aspects of protocol planning and design. The risk mitigation plan should be documented as a pre-specified proactive plan, based on appropriate assessments and with mitigation, escalation, and remediation strategies. For example, the modern methods of trial conduct mean that data can be monitored on site, remotely or in a centralized way and the methods for risk-based tracking will be different for each strategy, but the principles will be the same.

FDA assessor Camelia Mihaescu has stated that the monitoring plan should include a consideration of all three monitoring methods (on site, remote, centralized), even if doing 100% SDV on site. The plans themselves should be documented, reviewed and adapted as necessary as the project progresses so they remain current, relevant and demonstrate evolving diligence. Lessons learned can be applied across programs to encourage a consistent approach and inspire best practice.

There are commercial tools available, for example Transcelerates' "RACT" system for risk identification, prioritization and mitigation. This is a proactive, data-driven process based on evidence-based considerations and with qualified decisions.

RBQM needs people, processes and technology and the monitors require additional competencies to perform the risk assessments well. In answer to a question from the floor, Susan Romberg stated that Premier Research have modified their recruitment processes to look for people with appropriate competencies in areas of risk identification and mitigation.

Remarque Systems aggregate data from different sources into one database, integrating the data into a single format to allow predictive modelling and recommendations to reduce risk. Visualisation of the patient journey can be achieved through analysis of real time data at the site level, the country level and the program level. Remarque Systems can develop bespoke dashboard systems to see the big picture and analyse complex data in different formats to provide critical insight. Clustering of data according to different algorithms allows for rapid and evolutionary analysis of complex data on an ongoing basis – in other words the application of artificial intelligence (AI). One can drill into the data outliers and focus on these for checking, rather than doing a full 100% check. This is an evolving process as data is analysed, according to a pre-defined and documented plan.

A panel discussion allowed the audience to question an expert panel on RBQM and the practical implementation of RBQM into the process of delivering outsourced clinical trials. AL commented that SDV could potentially by reduced from 100% to 5% with an appropriate RBM plan. The FDA was criticized for being vague and leaving the implementation up to the pharmaceutical companies. One comment was that monitors are nervous about doing anything less than 100% SDV on critical data. Susan Romberg commented that Premier Research were reviewing job competencies for monitors and were now recruiting people who could demonstrate risk identification from a field of data and risk mitigation skills. The analogy was made with good ice hockey players (who go to where the puck is) versus great

ice hockey players (who go to where the puck will be). The point was made that site staff should be involved in risk identification and mitigation as they are responsible for quality too. This should be documented in the RBQM plan. Risk and the CRO ability to proactively mitigate risk should be a key consideration when selecting your CRO partner.

Helen Wood works on risk due diligence within the quality and risk management group within GSK, with particular concern for third party resourcing. She advocated agile, proportionate risk-based management with the freedom to allow for evolution over time. The GSK approach involves a structured, process-driven system which is applicable globally with expertise available to confirm appropriate, proportionate and defendable risk management in line with legal, regulatory and industry standards. The process is diligent, defendable and documented and allows for local control and global consistency.

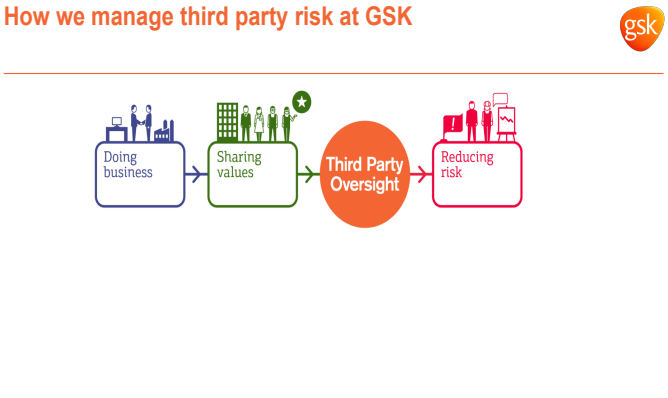
GSK define three key categories of risk:

- Activity-based risk ie what GSK is doing with third parties. Key source of risk, especially when you are transferring value to a third party. GSK use commodity codes for every activity and assign risks in discussion with subject matter experts (SMEs) for that activity / commodity code

- Location-based risk – different legislation in different countries, for example employment laws, sustainability laws, not always easily categorized as high or low risk. And a corruption perception index, which defines perceived likelihood of corruption in every country of the world

- Financial risk – GSK use internal and external cost comparison measures, but there are other risks eg in factoring in the relative value of money around the world. Clinical operations is high spend and therefore potentially high risk

GSK manages third party risks by having a robust "third party oversight" program.
They chose third parties with a similar culture but she acknowledged that they were not always able to eliminate risks.



Areas of risk associated with any third party was summarized in the following slide:

Risks associated with working with Third Parties

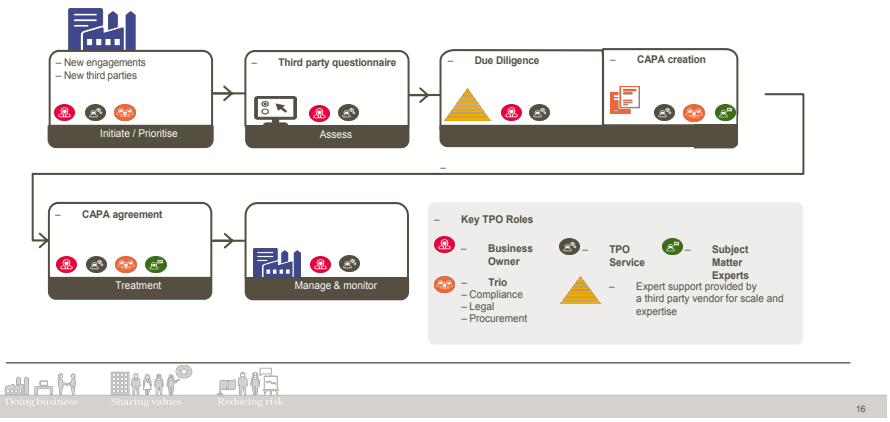
Risk areas assessed by Third Party Oversight (TPO) programme

- ABAC
- Access & Benefit Sharing
- Animal Welfare
- Conflict Minerals
- Competition Law
- Contingent Workers
- Data Integrity
- Environment & Community Health & Safety
- Labour Rights
- Environment, Health & Safety R&D
- GxP – GCP, GCLP, GMP, GLP
- Human Biological Samples
- Human Safety Information
- Inappropriate Promotion
- Information Risk & Operational Technology
- Privacy
- Crisis & Continuity Management
- Suppliers Who Are Also Customers
- Sanctions

Risk Due Diligence Programmes - Helen Wood 14

GSK initially screen potential third parties with an electronic survey, similar to an RFI but focused on risk mitigation. Then they exercise due diligence on the risk assessment through a third-party oversight team, who will organize external expert assessments as necessary.

Third Party Oversight Process



Proportionality is very important when leveraging external assessment and feedback. GSK implements 360º feedback on how easy the process is for third parties. There is constant evolution of their risk database, with real time review allowing identification of risk engagement types which might progress to defining contract terms and/or control and oversight requirements which are automatically indicated to manage this type of risk.

In summary, Helen felt that risk due diligence has a valuable role to play in third party risk management. She feels there will always be a number of potential risks in any third-party

engagement, that there are many benefits to having a systemic process and that proportionality is key to having an effective risk due diligence program.

In response to questions, Helen stated that the design element of third-party risk mitigation sits within the GSK global compliance team and that information risk is a particular concern. And the responsibility for validating third party suppliers is centrally coordinated and the database is available as a central resource for GSK staff worldwide.

Helen recommended that companies start planning due diligence and risk mitigation as early as possible when thinking of engaging with third parties. The most frequent risk mitigation is through specific contractual clauses and in addition there are certain third parties they will not work with because they are deemed to be risky in themselves.

Sandra Johnson is the Director of Outsourcing and Relationship Management at MMV, a not-for-profit organization funded by governments, NGOs and charities with a goal to identify, develop and deliver anti-malarial medication. MMV conducts clinical trials through third parties in remote and undeveloped areas of the world, where risk identification and mitigation planning is much more fundamental to the conduct of a project than in Western locations. Sandra gave a number of surprising and amusing examples of things that go wrong and which we take for granted as being low risk in the West.

Sandra described barriers to GCP compliance: the lack of financial and human capacity; ethical and regulatory obstacles (such as delays in approvals, unskilled authorities, complex and/or strict systems) and complex protocol designs driven by committees and competing priorities (time and prioritization). She categorized the main risks into five groups:

1. Insufficient lead time
2. Misrepresentation of the facts
3. Unethical practice and confidentiality breach
4. External factors
5. Inappropriate strategy/evaluation criteria

Common risks she sees are securing and protecting supplies, providing robust training and oversight processes to meet required standards, defining strategies for clinical laboratories (local versus international versus build your own locally), finding local couriers who will reliably and securely transfer documentation and materials according to GDP and the challenge of finding experienced and talented Senior CRAs and experienced clinical trial sites.

Faithful representation of the facts is sometimes a challenge. In some countries the PI submits dossiers to the regulatory authorities and the ethical committees (as they consider the PI to be the expert). The site evaluation visit is usually a face-to-face meeting and thorough, to identify and mitigate risks early. Financial auditors are sometimes required by some donors / funding groups to ensure prudence and the absence of fraud.

External factors can be major risks in less stable countries. War is not uncommon, giving rise to all sorts of risks which are not always easy to plan for. Earthquake and natural disasters do not happen frequently, but when they do the infrastructure is often insufficient

to react effectively. And there can be health concerns over and above the trial, for example the Ebola outbreak in the Democratic Republic of Congo.

Sandra emphasized the value of having a "safe haven" for the laboratory analyses within the country conducting the study to try and protect the integrity of key efficacy and safety data. Similarly, she advocated the benefits of using in-house monitoring staff and co-monitoring visits with your CRO to ensure they are monitoring to the required standards. She recommended having a clear process in place for CRO selection and that the CRO selection be done early as possible to allow more planning time and so as not to compromise submission dates. Along with thorough due diligence, Sandra advocated having appropriate financial controls in place with clear payment plans, a thorough plan for frequent monitoring at the study sites, including detailed issue escalation plans. Nevertheless, Sandra still described each working day as "daily chaos".

Alan Lawton is the CEO of Risk Based Approaches Ltd, a consultancy he set up after a long and successful career in pharmaceutical companies, latterly Boehringer Ingelheim. He is committed to quality by design and quoted ICH E8 R1 – 3.1 "quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, audit and inspection". Andy's perspective is that our industry plans and trains, but does not look at reasons for failure and introduce change accordingly.

Quality tolerance limits accept that random errors occur and makes the distinction between random errors and systematic errors, which are to be eliminated. He advocated analysis, identification of source and change to reduce incidence of error, then repeat the cycle on a continuous process until systemic errors are minimised. The tolerance will vary, but the process drives continuous improvement, reduces burden, improves knowledge management, allows trial simulations (for PLO comparator) and allows merging of disparate data sources.

During an excellent interactive session, the audience and presenters were split into 3 groups to consider different aspects of **fourth party oversight** and risk, as follows:

Group 1 – How do we ensure the quality of 4th party contractors?

Real 4th parties should be identified (in scope/out of scope) and the most critical ones among those should be more closely monitored (i.e. subcontractors managing endpoints, GxP and data integrity aspects).
The third-party vendor qualification and management plan should be reviewed by the sponsor and sponsor presence at subcontractor audits by the third party could be requested for those critical third parties.
Sponsor should have visibility on contracts, audit reports and qualification reports: full vs partial access to these should be depending on the 4th party criticality
The quality agreement with the 3rd party should specify how and when 4th party issues should be disclosed with the sponsor
The group concluded that quality and legal inputs were essential to ensure risks were appropriately identified and addressed, where possible, in legal agreements, where applicable.

Group 2 – what risks will Brexit provide and how will they be mitigated?

This was a light-hearted discussion with a serious underlying message, that Brexit will result in challenging risks, some of which might not be known until after the UK leaves the EU. The group advocated a thorough risk assessment, with prioritization of mitigation measures defined according to probability and impact. They also made the point that every company will have a different risk perspective, depending on their own circumstances and their exposure to UK and EU transactions.

Group 3 – QBD tolerance limits

Areas where tolerance limits can be defined and outcomes measured against target include, (but are not limited to) manufacture of investigational medicinal product, protocol violations, the trial master file, number of subjects lost to follow up, subject drop out rates and amount of medical review required during a study. SDV and TMF are internal quality processes / documents with tolerance limits documented and shared with regulators.

In response to questions, Andy stated that quality tolerance limits should be documented within the protocol or, if not practical, then in the trial master file. He suggested starting with just 5 QTLs to begin with and growing to 15-20 when you get comfortable and depending on regulatory sentiment and appetite.

During the closing session, Olena Goloborodko considered tools for risk identification and categorization. She mentioned the Kraljic Matrix / supply positioning and encouraged people to really get under the skin of their vendors to understand the risks. The matrix has 2 dimensions (market complexity / risk and profit impact / value). She advocated a standard approach to risk mitigation (Identification, ranking and mitigation) with methods such as a continuity plan, vendor due diligence and a robust contract that addresses risks.

Attentive attendees during the presentations

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