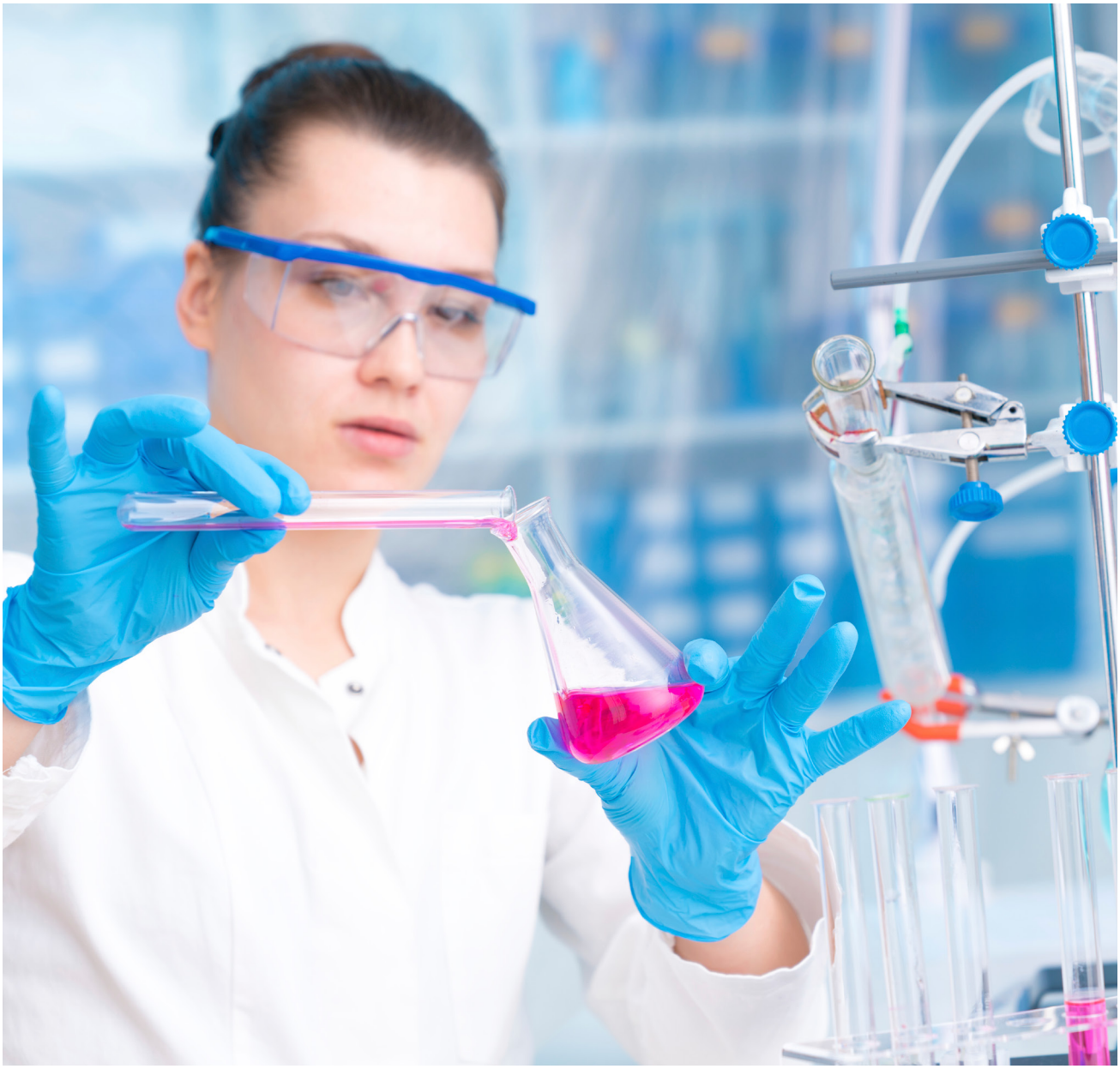
MARSH

Minimising Risk in Clinical Trials



CONTENTS

REGULATORY SPOTLIGHT ON SAFETY AND QUALITY IN CLINICAL TRIALS

Over the past 10 years, regulators globally have been steadily increasing the level of scrutiny of how good clinical practice (GCP) should be implemented to protect patient safety and enhance the quality of trial data and results.

In 2013, the European Medicines Agency (EMA) stated: *"A proportionate approach is required and should be adapted to the risk of the research conducted... Sponsors are expected to cope with this challenge and to move towards a more systematic and risk-based approach."* (1)

This trend has been demonstrated by a 68% increase in the number of GCP inspections requested by the Committee for Medical Products (CHMP) from 72 in 2012 to 121 in 2016. It was also notable that these 121 inspections led to 85 "critical" and 549 "major" findings. Such findings can significantly compromise the prospects of the sponsor safely and effectively achieving their trial objectives.(2)

SPOTLIGHT

MINIMISING RISK IN CLINICAL TRIALS

Top 10 tips from the speakers of a thought leadership event hosted by Marsh in partnership with One Nucleus.

1. Beware of the increase in scrutiny of GCP regulations.
2. Meticulous planning is essential.
3. Engage early with the regulators.
4. Embody quality in every step, go beyond the letter of GCP regulation.
5. Be aware of the key cost drivers and where overruns could occur.
6. Simplify the process to avoid unnecessary errors.
7. Take an "evidence-based" approach when selecting optimal trial locations.
8. Ask difficult questions when choosing your contractual partners.
9. Work collaboratively with your partners, building in regular and effective communication.
10. Periodically re-evaluate strategies and practicalities.

RISK MAPPING IN CLINICAL TRIALS

Marsh recently hosted a thought leadership event in partnership with One Nucleus, an international life science membership organisation.

Speakers collectively presented a 360 degree view of the challenges in planning and conducting a successful clinical trial. Practical guidance and tips were presented from the view points of a sponsor, Contract Research Organisation (CRO), Site management organisation (SMO), and regulatory affairs advisers providing updates on the US and European regulatory landscapes.

The event attracted a diverse audience of sponsors from across the life science spectrum, from start-ups to more mature organisations.

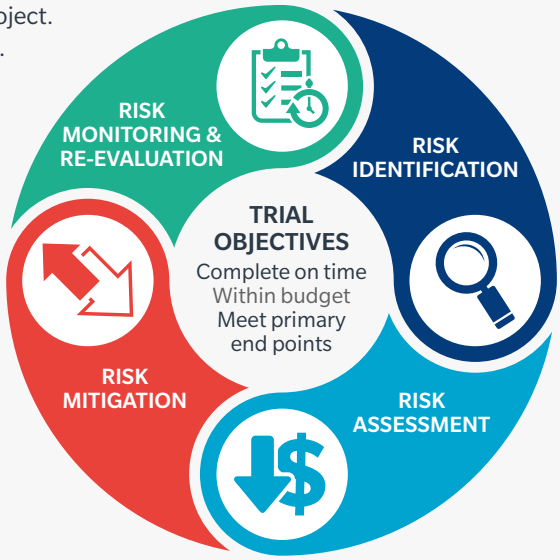
Drawing on many of the themes raised, Marsh presented a "risk management cycle" approach to the challenges faced by a sponsor in the planning and conduct of a clinical trial.

"The top four categories of the critical findings in GCP inspections were in protocol compliance, trial monitoring, data management and the Clinical Study Report (CSR)."

Source: The European Medicines Agency

FIGURE 1 RISK MANAGEMENT CYCLE

- Assess progression of the project.
- Re-evaluate the trial process.
- Validate the risk mapping.



- Create a map of the entire process.
- What happens; if, "when, where, how, and by whom?"

- Remove or reduce.
- Retain within business.
- Transfer to third party.

- What could lead to trial interruption?
- What would the nature of the impact be?
- What would be the financial implications?

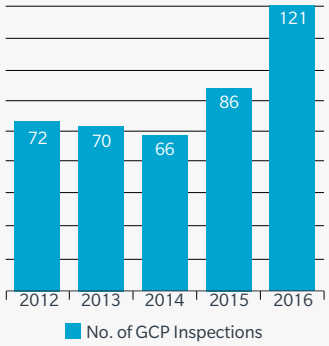
RISK IDENTIFICATION

It is critical to develop a protocol and create a map of the processes; including the manufacturing, packaging, transferring, and storage of trial materials through to the CROs and investigators (SMOs) that recruit and treat research subjects. The clinical trial supply chains are often complex with tight deadlines, so the map should clearly identify what happens, when, where, how, and by whom.

RISK ASSESSMENT

With the outline of the clinical trial map drawn, the next step is to establish what could go wrong and to model the potential time delay and financial impact of each scenario. This should include liabilities to third parties, reduction in the value of physical and intellectual property, interruption to activities, and reputational damage. Examples are highlighted in the table below.

FIGURE 2 INCREASE IN THE NUMBER OF GCP INSPECTIONS



Source: EMA Annual Report 2016

RISK IDENTIFICATION AND RISK ASSESSMENT IN CLINICAL TRIALS

EVENT	NATURE OF IMPACT	FINANCIAL REALISATION
Damage or regulatory shutdown to a facility scheduled to manufacture trial materials.	Trial could be delayed, if there is no alternative supplier.	• Unproductive cash burn for the period of the delay. • Committed costs to SMOs and others must still be paid. • Risk that cash runs out before the end of the trial, additional funds will have to be raised.
GCP breaches and failures to correctly implement the protocol are discovered.	Local ethics committee suspends the trial while failures are investigated and protocol amendments are made.	• Unproductive cash burn for the period of the delay. • Additional expenses incurred to remedy failures.
Suspected Unexpected Adverse Reaction (SUSAR) or Serious Adverse Event (SAE) by patients to the trial drug?	Potential suspension or abandonment of the trial and failure of the products. Potential for significant negative publicity.	• Additional costs and cash burn caused by delays through to the failure of the product to progress if the credibility of the technology is prejudiced.
Closure of trial site due to a force majeure.	Potential suspension of the trial until the site is able to re-open, or the need to find an alternative site.	• Additional costs and cash burn for the duration of delay. • Possible need to produce more trial material.
Injury or death to key personnel.	Might lead to significant delays, depending on the role of the person and the extent to which their knowledge and capabilities are duplicated.	• Cost of recruiting replacements. • Additional costs and cash burn for the period of any delays.
Data management errors are discovered as the unblinding/data validation process commences.	Investigations reveal that it is not possible to credibly re-build the data or to evidence whether the primary endpoints of the trial have been met.	• The only option is to re-start the trial with all of the associated financial costs. • Risk that cash runs out before the end of the trial, additional funds will have to be raised.

"In 2016, the largest number of GCP inspections requested by the CHMP were conducted in the EU/EEA, followed by USA and the Middle East/Asia/Pacific regions."

Source: EMA Annual Report 2016

RISK MITIGATION

Those risks that have the potential to be most damaging can now be prioritised, and steps taken to mitigate the exposure as far as practically possible. Conducted proactively, this allows a preventative and proportionate approach to risk management rather than "fire-fighting".

Clearly, patient safety is at the top of the agenda, and is addressed at every step. GCP regulations exist largely to embody this, but there is a danger in taking a "box-ticking" approach, which can lead to trials that are too complex, with poorly defined responsibilities and ineffective communication and monitoring.

A well-designed protocol, backed by a comprehensive project plan that addresses clearly the practical issues likely to arise, can significantly reduce risk in trial execution.

In addition to maximising patient safety, there are a range of risk mitigation measures that a sponsor can take to maximise the chances of success.

These include the examples shown in the box below:

ACTION	BENEFIT/OUTCOME
Proactive and assertive engagement with partners and regulators.	Greater transparency and improved outcomes in each area, including: • Manufacturing, packaging, shipping, and storage of trial materials. • Reduced risk of harm to research subjects. • Patient recruitment strategies. • Clearly defined responsibilities and balanced indemnity clauses in contracts. • Reduced regulatory uncertainty.
Manufacture increased batches of trial materials.	Replacement of lost or damaged materials without significant delay.
Supply chain contingency planning.	• Resilience will reduce uncertainty. • This can significantly reduce delays in the event of a loss of a supplier.
Conduct an independent mock GCP audit.	Allows plans and systems to be stress tested and practical improvements implemented.
Development of business continuity and public relations strategies.	Creates clear plans for responses to a range of scenarios that can be rapidly implemented if required.

"The overall effectiveness of the organisational quality management system is critical in ensuring successful outcomes."

MARTIN MOXHAM
PRINCIPAL CONSULTANT AT CLINICAL NETWORK SERVICES

RISK MONITORING AND RE-EVALUATION

Risk management should be a continuous cycle. Putting in place risk mitigation plans is not the end of the process, particularly in the dynamic environment of a clinical trial.

Constant monitoring, continuous appraisals, effective communication and, where needed, swift and decisive response to developing situations will maximise the chances of completing a safe and effective trial.

CONCLUSION

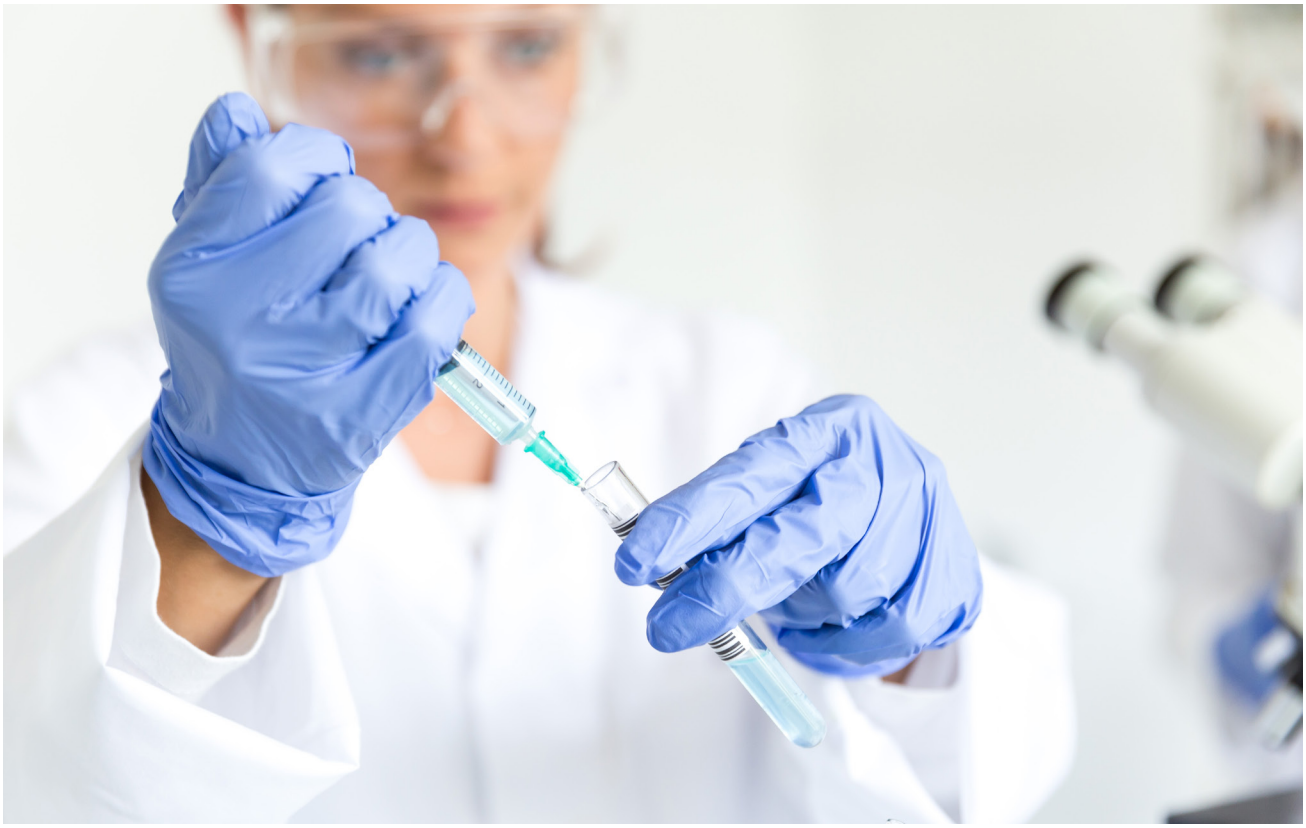
Risk identification and mitigation are the primary defence against trial interruption. There are multiple sources of professional advice and guidance to support this. However, these are not the only safeguard.

Insurance can be a key part of the risk mitigation process. Sponsors should consult their insurance advisers to discuss how best to use insurance as a transfer vehicle for the risks that cannot be mitigated to an acceptable financial level.

The insurance industry has become progressively sophisticated in developing bespoke solutions for the life science industry, and many of the risks identified in this article can effectively be transferred through tailored insurance solutions.

"Robust internal audit programmes help organisations resolve risks before they become issues."

GORDON ELGER
SENIOR ADVISOR,
UL COMPLIANCE
TO PERFORMANCE



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FURTHER READING/REFERENCES

1. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500155491.pdf
2. http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2017/05/WC500227334.pdf
3. http://www.em-toolkit.ac.uk/_db/_documents/EMallRouteMaps_200812031407.pdf

The audience heard presentations, followed by a panel discussion, featuring:

- Aline Charpentier, Business Development Manager, One Nucleus.
- George Morris, COO, ValiRx.
- Peter McLennan, COO, Tailored Clinical Research Solutions.
- Liam Eves, Executive Vice President, hVIVO.
- Martin Moxham, Principal Consultant, Clinical Network Services.
- Gordon Elger, Senior Advisor, UL Compliance to Performance.
- Andrew Tamworth, Senior Vice President, Marsh.
- Joseph Chiesa, Senior Partner, TranScript.
- Dr Julie Simmonds, Director, Equity Research, Panmure Gordon.

Details of the speakers and their presentations can be found on the One Nucleus website (http://www.onenucleus.com/onenucleus-events?id=1090).

For more information, contact the colleagues below or visit our website at: www.marsh.com.

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