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Evolving Risk-Management Requirements in Early Development

On13 July a workshop was organised with Transcrip on the crucial topic of risk management.
Supervision of early phase studies is critical and is more than ever to 'front of mind' for regulators and investors. Focus on safety in such studies will initiate closer scrutiny of sponsors – particularly small, start-up entities whose infrastructure and personnel may fall short of the oversight requirements of the major regulatory agencies. Outsourcing to a CRO is often a preferred option to ensure studies follow protocols. CROs are well aware of regulatory changes, but sponsors have the ultimate responsibility and should know how to meet regulatory standards.

The event offered a good review and insights to what is changing in this area, and provided guidance as to how small companies can be ready – without breaking the bank.

Slides can be found here.

Below is a summary of the vibrant Q&A session that was held after the talks.

Q: Can risk actually be avoided?

The answer is no but as Mark Watling of Transcrip pointed out:

- By anticipating what you can, you can mitigate
- The regulators understand that things happen but as long as you are covered by secure systems when issues do happen, the regulatory risk is ameliorated
- Sponsor companies however, do need to take responsibility and an audit trail proving that is mandatory

Q: Brexit: do we know where we are going?

Ennis Lee of TranScrip picked this up and suggested

- Early communications have given no clarity
- It is unlikely that any significant divergence of UK vs EU rules will happen, not least because the UK wrote many of them
- EMA would likely move, Denmark and Spain have been mentioned
- Qualified Persons for Pharmacovigilance based in the UK may also have to move unless some dispensation is made for a major market (that the UK is, unlike Norway or Switzerland)

Q: Doing things properly and as early as possible adds value but has costs, how to balance?

Proper systematic development with all the accountability trails and decision points covered is now part of any

due diligence process and potential partners and buyers see any shortfall as a risk, because:

- Asset data can unravel later if proper systems have not been applied, Good Clinical Practice, Good Manufacturing Practice-level elements, for instance
- Excluding real-life patients does not de-risk, it simply defers that risk and buyers will see that.
  An actual example of a malaria development for sub-Saharan Africa was mentioned. The development under EMA Article 58 rules where a sponsor tried to limit the label because of perceived liver function tests (LFT) issues, limiting studies to single doses and expecting patients to have pre- and post-dosing LFT testing which is untenable in malaria-ridden country health-care systems. Indeed the need for multiple dosing is endemic in a disease that has resurgences or re-infection, so that eventually had to be done.
  The LFT issue was a non-sequitur, in the event, but delaying real-world data accrual added years to the programme.

The integrity of recorded data is still an issue at the investigator level, so the discussion looked at:

- Risk-based systems to change investigator bias
- Actual risk is an indication-based judgement
- Pre-clinical source data is a risk issue, as is:
  - The clarity of some investigator brochures
  - Sponsors often do not have the expertise to evaluate the data
  - The relationship between sponsor and vendor and the relationship beyond the actual contractual wording is not always sound

Q: Is there real added value in doing things earlier which are not mandated now?

- Do regulators look kindly on going the extra mile?
  Mark Watling, Chris Brearley and Ennis Lee of TranScrip were clear that regulators will always accept more than what is necessary but only react when there is less than required, so a balance needs consideration by people who know the space (Paul Branthwaite of TranScrip added that only asking one individual for such advice runs the risk of incomplete opinion being used at a critical time).
  However, doing more upfront does allow better decision-making overall that can save resources, time and money in the longer-term
- Is the spend-only-when-necessary option a false economy?
  - The consensus was that yes this is risky: This related back to Chris Brearley's presentation proposing starting with the proof of concept design and then developing a programme to support this.
  - A real example of a failure would concentrate minds but until someone has gone to the wall or been caned by the regulator, biotechs do not genuinely see the danger.
  - Far better to look at the best-asset-management argument

If you would like to contribute to the discussion or ask for more information on the topic, please contact Paul Branthwaite, paul.branthwaite@transcrip-partners.com